CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022569Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022569 SUPPL # HFD # 170

Trade Name Lazanda

Generic Name fentanyl

Applicant Name Archimedes Development Ltd

Approval Date, If Known June 30, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☒ NO ☐

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

no

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 019813 Duragesic

NDA# 020747 Actiq

NDA# 022266 Onsolis

NDA# 022510 Abstral

NDA# 021947 Fentora

NDA# 016619 Sublimaze

NDA# 021338 Ionsys

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

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

Lazanda was tested in a single adequate and well-controlled study [Study CP043/06/FCNS] using what has become the standard design for these products. Opioid-tolerant cancer patients with breakthrough pain complete an open-label dose-finding period. If a successful dose (adequate balance between analgesia and tolerability) is found, the patient enters a 10-period, double-blind, placebo-controlled period. Sequential doses (7 active and 3 placebo, distributed randomly) are administered upon the start of an episode of breakthrough pain and the pain intensity is graded at close intervals. Episodes treated with FCNS had a statistically significantly larger difference in the summed pain intensity compared to placebo.

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study CP043/06/FCNS, described above

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

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

Investigation #1		!
		!
IND # 070854	YES ☒	! NO ☐
		! Explain:
Investigation #2		!

IND # YES ☐ ! NO ☐
! Explain:

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

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

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

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Matthew W. Sullivan
Title: Senior Regulatory Project Manager
Date: June 28, 2011

Name of Office/Division Director signing form: Bob A. Rappaport
Title: Director, Division of Anesthesia, Analgesia, and Addiction Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

MATTHEW W SULLIVAN
06/30/2011

BOB A RAPPAPORT
06/30/2011

1.3.3 Debarment certification

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

Signed: ..... Date: 20 August 2010

Mr Michael Clark
Chief Commercial Officer
Archimedes Development Ltd.

Signed: ..... Date: 20 August 2010

Name: Dr Ann Tunstall
US Agent
SciLucent

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022569 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Lazanda Established/Proper Name: fentanyl Dosage Form: nasal spray		Applicant: Archimedes Development, Ltd Agent for Applicant (if applicable): SciLucent
RPM: Matthew Sullivan		Division: Division of Anesthesia, Analgesia, and Addiction Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Actiq NDA 020747

Provide a brief explanation of how this product is different from the listed drug.

New dosage form and route of administration

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 6/30/2011

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is June 30, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR: June 30, 2010

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

REMS: ☒ MedGuide
☐ Communication Plan
☒ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	June 30, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR: June 30, 2010 AP: June 30, 2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	June 30, 2011
• Original applicant-proposed labeling	August 30, 2009
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	June 30, 2011
• Original applicant-proposed labeling	August 30, 2009
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	June 27, 2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	December 16, 2009 April 16, 2010 February 24, 2011 Holmes: December 16, 2009 Holmes: February 24, 2011 Bridges: June 14, 2011
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA Oleszczuk: June 21, 2011 Holmes: April 15, 2011 Holmes: June 14, 2011 Holmes, March 4, 2011 ☒ DRISK March 3, 2011 ☒ DDMAC June 22, 2010 & Feb 22, 2011 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	Sullivan: April 30, 2010 ☐ Not a (b)(2) February 28, 2011 ☐ Not a (b)(2) June 29, 2011
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC April 21, 2010 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Various
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg September 30, 2010
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg September 22, 2008
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg August 24, 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None Rappaport: June 30, 2010 Rappaport: June 30, 2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Shibuya: April 30, 2010 Shibuya: March 7, 2011
PMR/PMC Development Templates *(indicate total number)*	☐ None 1 (PREA) June 29, 2011
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	Yip: April 9, 2010 Olmos-Lau: April 12, 2010 Hertz: March 24, 2010 Yip: March 2, 2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Yip: April 9, 2010
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable Gong: April 29, 2010 Gong: February 22, 2011 Gong: March 22, 2011 Gong: June 17, 2011
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))*	August 30, 2009, February 17, 2010, May 19, 2010, September 30, 2010, January 31, 2011, June 26, 2011, and June 29, 2011.
• REMS Memo(s) and letter(s) *(indicate date(s))*	☐ None Rappaport: June 30, 2010
• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Toyserkani: May 13, 2010 Moncur: March 31, 2010 Moncur: January 27, 2010 Moncur: June 29, 2010 Moncur: March 4, 2011 Auth: April 20, 2011 Toyserkani: June 29, 2011
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Blay: March 10, 2010 (Review)
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None Petullo: April 8, 2010 & June 29, 2010
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Agarwal: April 9, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Bolan: June 20, 2011 April 30, 2010 April 9, 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None Peri: May 25, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Markofsky: April 23, 2010 Markofsky: May 5, 2010 Markofsky: June 25, 2010 Pinto: March 3, 2011
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Fong: May 12, 2010 Fong: March 18, 2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Markofsky: April 23, 2010
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: June 25, 2010 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

MATTHEW W SULLIVAN
07/08/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 022569	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Lazanda Established/Proper Name: fentanyl Dosage Form: nasal spray Strengths: 100 mcg and 400 mcg		
Applicant: Archimedes Development Ltd		
Date of Receipt: August 31, 2009 (initial submission). September 30, 2010 (Class 2 resubmission)		
PDUFA Goal Date: June 30, 2011 (clock extended)	Action Goal Date (if different):	
Proposed Indication(s): Management of breakthrough pain in cancer patients 18 years of age and older who **are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain**.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Actiq (NDA 020747)	Multiple sections of labeling

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Archimedes has conducted clinical pharmacokinetic, efficacy and safety data to support the new route of delivery (nasal), and to compare the bioavailability of fentanyl from Lazanda vs. Actiq.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Actiq	020747	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

Actiq

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides a change in dosage form and route of administration, from transmucosal lozenge to nasal spray.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

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

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

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

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):
Fentora (N 021947), Onsolis (N 022266), and generics for referenced drug, Actiq.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

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

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

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

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

Patent number(s): 4 671 953
4 863 737

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

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

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

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

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

MATTHEW W SULLIVAN
06/29/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, June 23, 2011 10:52 AM
To: Michael Perelman; 'Jackie Mitchell'; Ann Tunstall
Subject: NDA 022569 REMS/PI comments June 23
Attachments: (b) (4)

1. The (b) (4) forms are attached with tracked changes and comments. If there are any questions regarding the changes, please communicate them as soon as possible. If all changes are accepted, we will not need to see these forms again.

2. We are requesting an order change to the material found under (b) (4) program, so that it will match the order in the PI. There is a comment in the document where the change is requested. Please let us know if you need clarification. If the changes are accepted, we will not need to see these forms again.

3. As mentioned briefly yesterday, the edits made to the PI are acceptable.

4. Lastly we also see no issues in the additional WebPages that you have provided.

5. I'm still trying to track down someone in OSE to look at the cartons you've submitted. As soon as I hear, I'll let you know.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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MATTHEW W SULLIVAN
06/23/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, June 15, 2011 12:30 PM
To: Ann Tunstall; 'Michael Perelman'; Jackie Mitchell
Subject: REMS comments, Lazanda NDA 22569
Attachments: [redacted] (b) (4)

Please contact us immediately if you have any questions or concerns regarding the edits. If not, prepare these for submission to the NDA but *please do not* submit until the labeling has been finalized. Also, we have not included the documents which did not require edits from us. They are:

1. [redacted] (b) (4)

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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MATTHEW W SULLIVAN
06/15/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, June 15, 2011 1:31 PM
To: Ann Tunstall; 'Michael Perelman'; Jackie Mitchell
Subject: Carton and container comments, NDA 22569

Please find below several comments regarding your June 1, 2011, submission:

A. General Comments for all container labels and carton labeling

1. The established name lacks prominence. Increase the font weight of the established name and ensure it has a prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features per 21CFR 201.10(g)(2).
2. The statement of strength is not prominent. Increase its prominence by increasing the font weight.

B. Container Labels (100 mcg per spray and 400 mcg per spray)

1. The strengths are not well differentiated. Expand the color bar so that it includes the statement of strength.
2. The "Rx" symbol is too prominent. Unbold the font.
3. The distributor information is too prominent. Decrease the size of the statement "Distributed by Archimedes Pharma".

C. Carton Labeling (100 mcg per spray and 400 mcg per spray), 1-count and 4-count

1. The medication guide statement "Dispense the enclosed Medication Guide to Each patient" is not prominent. Increase the prominence of the medication guide statement by increasing its font weight.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
06/15/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, May 06, 2011 4:47 PM
To: 'Ann Tunstall'; Michael Perelman
Subject: Lazanda REMS Comments

Attachments: 110506 + FDA_REMS SD_ NDA 022569.docx; 110506_Information Needed for Assessments.doc

Good afternoon –

Please find below our latest REMS comments.

Let me know if you have any questions.

Matt

==========

1. **The following documents are attached:**
   a. REMS Supporting Document (received January 31, 2011; Sequence Number: 0032) with FDA comments included

      110506 +
      REMS SD NDA 02

   b. Information Needed for Assessments
      Add this information to the [redacted] (b) (4) " section of your Supporting Document; once agreed upon.

      110506_Informatio
      n Needed for ...

2. **Append the following documents to your REMS document** (i.e. move them from your Supporting Document).

   - [redacted] (b) (4)

a. For documents that have both paper and web versions, append only one version to the REMS, and include the other version in your Supporting Document.

b. Ensure that all documents listed above are also listed in the appropriate section of your REMS document (e.g. list the [redacted] (b) (4)) *Note*:* The [redacted] (b) (4) is part of the [redacted] (b) (4) materials; append it to your REMS, but it does not need to be listed in the REMS.

3. Re-submission Instructions:

a. Once you have made all revisions that we have requested to date, to your REMS, REMS materials and Supporting Document, you should resubmit all your documents via e-mail. We will review the materials to ensure that all revisions have been accurately incorporated, and that revisions you have proposed (if any) are acceptable. We will then notify when you may formally re-submit via the Gateway.

b. Provide the REMS document and Supporting Document as two (2) separate PDF files:

- One file that includes the REMS document and all appended materials (see #2 above)
- One file that includes the REMS Supporting document (and remaining appended materials, as applicable)

c. Provide a clean WORD version of each individual document (provide the REMS and the REMS SD as two separate documents). If you are proposing any revisions to a document, also provide a redlined WORD version of the document that accurately reflects the proposed revisions.

d. Include the name of the document in document's file name (e.g. prescriber overview)

[redacted] 23 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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MATTHEW W SULLIVAN
05/06/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, April 25, 2011 11:59 AM
To: 'Ann Tunstall'; 'Michael Perelman'
Subject: N22569 Package Insert Comments
Attachments: 2d cycle version to Sponsor April 25 2011.doc

Attached are our comments on the PI. For the most part, we accepted your most recent changes.

In a few places, there were a lot of changes, and I left those tracked simply so you could see what all the changes were. Please accept all those you agree with.

Please take a look at the formatting and fix the areas where it needs it.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
04/25/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, April 15, 2011 1:43 PM
To: 'Michael Perelman'; Ann Tunstall
Subject: N 22569 protocol comments

Hello –

Please find below our comments on the labeling comprehension study.

Let me know if you have any questions.

Matt

General Comments for Study Design

1. We acknowledge the study assesses user tasks; however, you did not submit a risk assessment that defined all of the critical user tasks needed for a patient to use Lazanda safely, nor do you define the clinical impact that failure of these user tasks could incur. Ensure a complete risk assessment is included in the study protocol.
2. There is no indication that the Instructions for Use have been screened to determine the literacy level at which they were written. Determine the literacy level at which the IFU is written. The recommended literacy level is sixth to eighth grade.
3. According to the study design, up to 30 adult men and women will be recruited for the study so it is unclear what the intended goal is concerning the number of participants in the study. State the minimum number of participants that will be included in the study to ensure there are enough participants.
4. The study protocol does not state what will be done with the data once it is collected or how it will be used to revise the Instructions for Use. We recommend that revisions be made to the IFU based on the results obtained from the study in order to determine the best presentation of the information to optimize the safe use of Lazanda.
5. Provide the rationale for excluding patients with brain cancer or current use of intrathecal or epidural opioids.

Selection of Participants

6. *Participant Recruitment*: Approximately 5 to 7 participants will be interviewed and a determination made as to whether the interview guide requires revision. If the interview guide is revised for use with the 23 to 25 participants that follow, the data obtained from those 5 to 7 participants should be evaluated separately from the remaining 25 to 27 participants in the study. Additionally, any changes made to the interview guide should be discussed and the rationale provided.
7. The Sociodemographic Form is completed at the end of the interview which may limit the ability to obtain a diverse population sample up front. Determine the sociodemographics up front during the participant selection process in order to ensure there is a diverse population representative of patients who will likely use Lazanda.

Data Collection

8. The Lazanda Use Observation Form does not ask participants what can be done to improve the Instructions for Use or what improvements can be made to the product to make it easier to use. Include this question in the Lazanda Use Observation Form.
9. In the Lazanda Use Observation Form we note that in some of the steps the patient is given the option to “demonstrate or verbalize” the step. Verbalization, rather than demonstration, may not detect potential problems with carrying out that particular step and may hinder the

ability to gather useful data from the study. In all instances where the step can be physically demonstrated, have the participant demonstrate the step.

10. The Clinical Form does not ask how often the potential participant has breakthrough pain. Consider adding this question to the form to help screen potential participants.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
04/15/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, April 15, 2011 9:27 AM
To: 'Ann Tunstall'
Cc: 'Michael Perelman'
Subject: N 22569 MG/IFU Comments
Attachments: fentanyl 22569 MG.doc

Attached is a revised med guide. Also, please note some additional comments below.

1. The Instructions for Use are a part of this Medication Guide and are not intended to be distributed to patients separately from the Medication Guide. For consistency across other products the section title should be "Instructions for Use" rather than (b) (4)
2. The format of the Instructions for Use that is used in performing the use study should be exactly the same as the format of the Instructions for Use as they appear in the MG, which is what patients will receive. The 2-column format is acceptable as long as you plan to use it for the entire MG.
3. (b) (4) Otherwise, all font should be black, without color boxes or borders. Italics should be removed.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
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Phone 301-796-1245
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matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
04/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022569

REVIEW EXTENSION – MAJOR AMENDMENT

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your New Drug Application (NDA) submitted August 30, 2009, received August 31, 2009, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for fentanyl citrate nasal spray, 100 and 400 mcg.

On March 24, 2011, we received your March 24, 2011, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 30, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 16, 2011.

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

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/s/

SARA E STRADLEY
03/29/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, March 25, 2011 1:22 PM
To: 'Michael Perelman'
Cc: Jackie Mitchell; Ann Tunstall
Subject: N22569 Lazanda pouch comments

Below are the comments on the pouch labeling.

Carbon Pouch Labeling

1. For clarity, revise the statement “Disposable Pouch...” to read “Disposable Pouch for use only with Lazanda” or similar verbiage and delete the statement “For exclusive use.” Additionally, increase the prominence of the words “Disposable Pouch”.
2. Provide instructions on the front panel for how to seal the pouch.
3. The company name logo is prominent on the front panel. Decrease its size, relocate it to the back panel, or delete it altogether.

Thanks
Matt

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/s/

MATTHEW W SULLIVAN
03/25/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, March 25, 2011 12:37 PM
To: 'Michael Perelman'
Cc: Jackie Mitchell; Ann Tunstall
Subject: RE: N22569 Lazanda package insert + med guide
Attachments: MG to sponsor 25Mar2011.doc

We have addressed item #3 from your earlier email:

The FDA removed from Section 14 (b) (4)

- (b) (4)

We would appreciate discussing with your perspective on the inclusion (or not) of including that data.

(b) (4)

(b) (4)

We are continuing to review the PI, and we will provide our comments as soon as we can. Also, attached is the updated MG/IFU.

Thanks
Matt

From: Michael Perelman [mailto:michaelperelman@archimedespharma.com]
Sent: Thursday, March 24, 2011 4:49 PM
To: Sullivan, Matthew
Cc: Jackie Mitchell; Ann Tunstall; Michael Perelman
Subject: RE: N22569 Lazanda package insert + med guide

Matt

Thank you very much for these early responses. It is much appreciated.

In addition to the third 'posed-question', there are some proposed changes to the submitted PI that are implicit questions. As we said at yesterday's call (ps thanks for arranging that so promptly – it really helped us), we would appreciate the opportunity to discuss the label and proposed changes.

In parallel we are drafting suggestions for the MG / How to use which we will send to you to help the internal dialogue that Sharon promised to arrange.

Michael Perelman,
- *Phone* : +1 (908) 450-6510
- *Mobile* : (b) (6)
- *eMail* : michaelperelman@archimedespharma.com
- *Assistant* : Kristina Greco kristinagreco@archimedespharma.com +1 (908) 450-6561

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Thursday, March 24, 2011 1:53 PM
To: Jackie Mitchell; Ann Tunstall
Cc: Michael Perelman
Subject: RE: N22569 Lazanda package insert + med guide

You asked us a few questions at the bottom of your email, below.

We have responses to the first two, and are still considering the third.

There are three elements within the PI we would like to discuss, but which we have not changed in the submitted red-line PI

- (b) (4)

(b) (4)

- (b) (4)

I hope to get you some comments on the MG/IFU later today.
Matt

From: Jackie Mitchell [mailto:jackiemitchell@archimedespharma.com]
Sent: Wednesday, March 09, 2011 5:55 PM
To: Sullivan, Matthew; Ann Tunstall
Cc: Michael Perelman
Subject: RE: N22569 Lazanda package insert + med guide
Importance: Low

Dear Mathew
Reference is made to the New Drug Application (NDA 22-569) Archimedes submitted electronically on 31 August 2009 for fentanyl citrate nasal spray, and to the proposed label received from FDA on 4th March. Attached is Archimedes' proposed label (annotated and clean Word versions). Please note the following:

- Your notes in the a-mail below have been taken into account as we have reviewed and prepared the revised PI and Medication Guide (see specific comments in red below each of your points).
- Archimedes has adopted virtually all changes proposed by FDA with the exception of a couple of elements highlighted below (plus some minor rewording/ typographical error corrections, which are tracked):
    - Tradename has been replaced by Lazanda throughout
    - (b) (4)

        2. The recently approved TIRF Abstral does not have a (b) (4)
    - Section 6: we have deleted the reference to the serious adverse reactions described elsewhere in the label as this seems duplicative and is not r (b) (4)
    - (b) (4)

With regard to the comments received on the container and carton labels, also on 4 March 2011, we can confirm that we will be accepting all requested changes and revised pdf files will be submitted shortly.

Please note that the new photographs in the Medication Guide are not in the final position, nor are they necessarily the size, that they will appear in the final printed Medication Guide. In the final version, the relevant picture will be placed adjacent to each corresponding step, as requested by the FDA.

There are three elements within the PI we would like to discuss, but which we have not changed in the submitted red-line PI

- (b) (4)
- (b) (4)

We would appreciate discussing with your perspective on the inclusion (or not) of including that data.

We are requesting a teleconference with you as soon as possible to discuss the above points related to the PI.

Kind regards
Jackie

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: 04 March 2011 01:52
To: Ann Tunstall
Cc: Jackie Mitchell; Michael Perelman
Subject: N22569 Lazanda package insert + med guide

Attached is a copy of the labeling changes for the PI + Med Guide.

A few notes:

1. We tried to use tracked changes, but there is a possibility that some changes were made without it being turned on. You should assume that any deletion/addition made without being tracked is intentional, but you're welcome to ask us if something doesn't make sense.
   We have assumed this
2. As above, we'd like you to use tracked changes in your response(s). Changes in this document that you agree with should be 'accepted' so that the end result is a clean label. It's most helpful if the only tracked changes that we see when we get the label back are the changes you've made (or changes that we have made which you don't agree with).
   We have accepted all changes and made any tracked changes are those that we have made. Reasons for these changes have been given in comments annotated on the document.
3. We spend virtually no time worrying about formatting. Please update the label to ensure that the formatting is correct. (The exception to this is the med guide. We have tried to provide the med guide in the correct formatting.) Additionally, please ensure that all cross-links in the text are correct, and that sections headings all match between the various sections.
   We have corrected formatting and checked for consistency. However, as noted above, the photographs

require proper sizing and alignment in the Medication Guide.

4. Most of our energy is spent on reviewing and editing the full prescribing info (FPI) section. If the FPI is discordant with another section (for example, the warnings are listed in a different order) you should assume that the FPI is correct and make the corresponding change in the highlights and table of contents section.

Done

5. There are some "notes to sponsor" in the label – either as inline text or as a tracked-change balloon comment. If you can easily address the request/comment, you can do so without providing a written response. If you'd like to propose an alternate method of addressing our concern, it's probably best to include that on a separate document so that the label doesn't become too disorganized.

Responses have been given in comments annotated on the document.

6. We've done our best to provide all the changes and comments that we have at the moment, but the label will continue to be reviewed going forward, so additional changes may be necessary.

7. Go ahead and replace the TRADENAME with Lazanda throughout.

Done

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia and
Analgesia Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
03/25/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, March 04, 2011 9:19 PM
To: 'Jackie Mitchell'; Ann Tunstall
Subject: N22569 REMS (b) (4)
Attachments: 110304_LAZANDA REMS (b) (4) .pdf

Ann / Jackie –

As discussed in the March 3, 2011, telecon, we are providing you with a revised Lazanda REMS (b) (4); revised to include more detail, reorganize the flow of information, and the to focus on the key safety messages critical to minimizing the risks of Lazanda. We are providing your (b) (4) (b) (4) as a PowerPoint presentation, however, this format is not a requirement. Your (b) (4) (b) (4) (and all REMS materials) will need to be revised to be consistent with the final agreed-upon PI.

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Reference ID: 2914112

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/s/

MATTHEW W SULLIVAN
03/04/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, March 04, 2011 8:10 PM
To: 'Ann Tunstall'; 'Jackie Mitchell'
Subject: N22569 carton and container comments

Jackie / Ann –

Here are the comments regarding the carton and container labeling:

A. General Comments for the Container Labels and Carton Labeling

1. Ensure the established name (which includes the active ingredient and dosage form) is printed in letters that are at least ½ as large as the letters comprising the proprietary name and that the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].

2. We note the use of "100" and "400" on the container labels and carton labeling, which appear to represent the strength; however, this is an incomplete strength presentation and may be confusing because there is no unit of measure or other indicator of what the numbers represent. Therefore, revise the "100" and "400" to read: "100 mcg per spray" and "400 mcg per spray". These statements may remain in their present locations.

3. The "Rx" portion of the "Rx only" statement is too large and distracting due to its prominence. Decrease the size of the "Rx" portion of the statement.

B. Container Labels

1. As currently presented, the container labels appear crowded. Due to their limited size, ensure that the proprietary name, established name, and strength presentations are the most prominent information displayed. Consider removal of other unnecessary or less important information [see 21CFR 201.10(i)], but retain the statement "Return to child resistant container after use" and consider increasing its prominence since this statement is an important safeguard against accidental exposure.

C. Carton Labeling

1. As currently presented, the (b) (4) on the principle display panel is large and distracting from more important information. We request you remove this (b) (4).

2. Per 21CFR 201.10(d)(1), any statement of the quantity of an ingredient should be expressed per unit (e.g., per spray). The current statement (b) (4) (b) (4) on the principle display panel is incomplete. Additionally, there is already a statement on the side panel that reads "Each 100 microlitre spray contains fentanyl citrate equivalent to 100 mcg fentanyl base." Therefore, remove the statement on the principle display panel. Also change "microlitre" to read "microliter."

3. The statement (b) (4)" is confusing and incomplete. Revise this statement to read, "Each bottle delivers 8 full sprays. Each spray delivers 100 microliters of solution."

4. The top panel of the 4-bottle carton has a statement that reads "See enclosed prescribing information" whereas the 1-bottle carton has a different statement that reads "See enclosed Medication Guide". These statements are inconsistent. Ensure these statements are the same on both carton presentations.

5. Add the Medication Guide statement "Dispense the enclosed Medication Guide to each patient" to the principle display panel.

6. Ensure a minimum of four Medication Guides are enclosed in each of the 4-bottle cartons to ensure that if a single bottle is dispensed from the 4-bottle carton, there will be enough Medication Guides to dispense with each bottle.

7. The usual dosage statement reads [redacted (b) (4)]". The medication guide does not provide the dosage information needed by prescribers. Prescribers should be referred to the insert for dosage information. Therefore, revise the statement to read: Usual dosage: see enclosed prescribing information" or similar verbiage per [21 CFR 201.55].

8. Revise the statement [redacted (b) (4)] "Patients must be tolerant to around-the-clock opioid therapy" since the statement [redacted (b) (4)] may be confusing to healthcare providers.

9. The warning statements "Keep out of reach of children," "Patients must be tolerant to regular opioid therapy *(see comment C-8, above)*," "Do not substitute TRADENAME for other fentanyl products," "Tradename can be harmful or fatal if given to someone for whom it was not prescribed," and "Store the bottle in the child-resistant container..." are on one of the side panels. These statements are important to the correct use of the product and require more prominence and visibility. Relocate these warning statements to the principal display panel and enclose them in a box. Additionally, consider using a graphic (such as a stop sign or triangle) near the word "Warning" in order to draw attention to the boxed statements. Deleting the [redacted (b) (4)] on the principal display panel will allow space for the warning statements. Additionally, consider moving the "Rx Only" statement to the side panel.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
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/s/

MATTHEW W SULLIVAN
03/04/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, March 04, 2011 5:13 PM
To: 'Jackie Mitchell'; Ann Tunstall
Subject: REMS comments N22569
Attachments: Attachment A_110304a_Lazanda REMS Document_redline.pdf

Ann / Jackie –

We refer to the meeting held on October 28, 2010 and to the REMS notification letter for Lazanda dated November 12, 2010. We further refer to the teleconference on February 15, 2011, during which we communicated harmonizing the individual programs to facilitate the implementation of a single, shared system across all TIRF products. We also refer to the teleconference on March 03, 2011, in which we communicated the need for creation of additional REMS materials.

We acknowledge receipt of your proposed REMS for Lazanda included in your submissions dated December 22, 2010, and January 31, 2011. In the Lazanda REMS, you have proposed changes that do not conform with the standardized materials. You have not provided adequate justification for these changes, and in the interest of standardization, we are requesting that you conform the REMS to the template as we requested originally. The attached redline reflects the changes that are needed to conform to the template.

The comments below are based on the preliminary review of the Lazanda REMS and supporting materials. We hope you can provide replies quickly so that we can provide you final input on the REMS, REMS Materials and Supporting Document.

1. The REMS document has been revised to conform with the standardized materials. Please see **Attachment A** for a redlined version of the REMS document. NOTE: FDA has added text to the footer of this document, for document control purposes. This footer (red text) should be deleted in your final document.

2. As discussed in the February 15, 2011, teleconference, your proposed education program and knowledge assessment will require modifications. We will be providing you with specific comments under a separate cover.

3. As discussed in the March 03, 2011, teleconference, Dear Healthcare Provider Letter and Dear Pharmacist Letter distribution has been added to the REMS (under ETASU A and ETASU B, respectively). Refer to the Abstral REMS program 'Dear Healthcare Provider Letter,' 'Dear Outpatient Pharmacy Letter,' and 'Dear Inpatient Pharmacy letter,' create and submit these letters for the Lazanda REMS.

4. As discussed in the March 03, 2011, teleconference, REMS Program Overview materials are needed to inform enrollees about REMS program requirements and operations. Refer to the Abstral REMS program's "Prescriber Program Overview," "Overview for Outpatient Pharmacies," "Overview for Inpatient Pharmacies," and "Overview for Patients & Caregivers," and create and submit these materials for the Lazanda REMS program.

5. As discussed in the February 15, 2011, teleconference, please remove the option for

(b) (4)

6. We recommend that you be mindful of any additional data fields that are being discussed for the single-shared system, and include them in your current program, to facilitate transitioning to the single, shared system.

7. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

8. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

9. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in WORD.

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MATTHEW W SULLIVAN
03/04/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, March 03, 2011 8:52 PM
To: 'Ann Tunstall'
Cc: 'Jackie Mitchell'; 'michaelperelman@archimedespharma.com'
Subject: N22569 Lazanda package insert + med guide
Attachments: 2d cycle version to Sponsor.doc

Attached is a copy of the labeling changes for the PI + Med Guide.

A few notes:

1. We tried to use tracked changes, but there is a possibility that some changes were made without it being turned on. You should assume that any deletion/addition made without being tracked is intentional, but you're welcome to ask us if something doesn't make sense.
2. As above, we'd like you to use tracked changes in your response(s). Changes in this document that you agree with should be 'accepted' so that the end result is a clean label. It's most helpful if the only tracked changes that we see when we get the label back are the changes you've made (or changes that we have made which you don't agree with).
3. We spend virtually no time worrying about formatting. Please update the label to ensure that the formatting is correct. (The exception to this is the med guide. We have tried to provide the med guide in the correct formatting.) Additionally, please ensure that all cross-links in the text are correct, and that sections headings all match between the various sections.
4. Most of our energy is spent on reviewing and editing the full prescribing info (FPI) section. If the FPI is discordant with another section (for example, the warnings are listed in a different order) you should assume that the FPI is correct and make the corresponding change in the highlights and table of contents section.
5. There are some "notes to sponsor" in the label – either as inline text or as a tracked-change balloon comment. If you can easily address the request/comment, you can do so without providing a written response. If you'd like to propose an alternate method of addressing our concern, it's probably best to include that on a separate document so that the label doesn't become too disorganized.
6. We've done our best to provide all the changes and comments that we have at the moment, but the label will continue to be reviewed going forward, so additional changes may be necessary.
7. Go ahead and replace the TRADENAME with Lazanda throughout.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
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MATTHEW W SULLIVAN
03/03/2011

Sullivan, Matthew

From: Sullivan, Matthew

Sent: Thursday, March 03, 2011 4:19 PM

To: 'Ann Tunstall'

Subject: Micro Information Request N22569

Ann –
Some additional microbiology requests. They'd like to get answers, if possible, to these tomorrow. I'm not sure if that's possible, but if you could see what you can do, that would be appreciated.

I should add that our mico reviewer is available for a t-con if necessary to discuss these.

Thanks
Matt

(i) Please briefly describe how the B. cepacia strain used for validation (ATCC 25416) is cultured and maintained prior to being inoculated into 1:10 diluted product.

(ii) Validation SOP 02588 states that testing for B. cepacia may involve a direct inoculation or filter method. (See detailed procedures below questions.) Please indicate which procedure will be used for routine testing.

(iii) For validation the appearance of B. cepacia on OFPBL plates was confirmed by colony morphology (yellow green to blue green colonies with yellow halos). Will additional identification procedures be used during routine testing? Item 8.13.1 (page 15) of SOP 02588 states that verification might be implemented using a Vitek 2 automated identification system.

(iv) The revised drug product specification table (Table 3.2.P.5.1-2) indicates DPT-SOP-00686 as one of the methodologies that will be used for microbial quality testing. Please provide a copy of this SOP or indicate its location in the submission.

Direct Inoculation Method: (1) product is diluted 1:10 (10 mL to 90 mL) in trypticase soy broth (TSB); (2) 10 ml samples are aliquoted into test tubes; (3) the samples are incucated for 18 – 24 hours at 30 – 35^{o}C; (3) samples of incubation mixture from each tube are streaked onto selective OFPBL plates; (4) the OFPBL plates are incubated for 4 – 7 days at 30 – 35^{o}C and examined for B. cepacia colonies.

Filter Method: 10 mL of 1:10 diluted product in TSB is immediately passed through a filter that is then applied to OFPBL plates. The latter are incucated for 4 – 7 days at 30 – 35^{o}C and examined for B. cepacia colonies.

Thanks,
Matt

Matthew W. Sullivan, M.S.
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/s/

MATTHEW W SULLIVAN
03/03/2011

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, February 17, 2011 3:42 PM
To: 'Ann Tunstall'
Subject: NDA 22569 Information Request

Ann –

An information request from OSE:

We have reviewed the revised container closure system and continue to have safety concerns with its use. We note the following:

1. [redacted] (b) (4) Post-marketing surveillance has indicated greater patient comprehension occurs when the device [redacted] (b) (4). This message was conveyed to you in a pre-NDA meeting held on September 22, 2008.

2. It is possible to actuate a partial spray without causing the spray counter to advance. Therefore, patients could potentially deliver multiple sprays without advancing the counter.

3. The carbon pouch must be kept until the bottle is used up. It is not clear how or where the pouch should be stored while the bottle is in use in order to prevent its exposure to children, pets, etc.

We recognize the audible “click” and visual advancement of the counter should help inform patients and caregivers that the dose has been delivered, however, this may not be sufficient for patients or caregivers who are impaired in these areas. Additionally, proper disposal of the priming sprays, unwanted extra sprays and residual fentanyl solution is important in order to protect household contacts from accidental exposure to the fentanyl solution. Therefore, we recommend you address the issues outlined above and then conduct a usability/labeling comprehension study with the revised device to determine if patients and caregivers are able to use and dispose of the product correctly using the instructions provided.

We request that you respond to these issues in a timely manner so that we can continue the review of your application.

Thanks,
Matt

Matthew W. Sullivan, M.S.
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Fax 301-796-9722 / 9723
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/s/

MATTHEW W SULLIVAN
03/01/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022569

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove Street, Suite 300
Herndon, Virginia 20170

ATTENTION: Ann Tunstall, Ph.D.
US agent for Archimedes

Dear Dr.Tunstall:

Please refer to your New Drug Application (NDA) resubmission dated September 30, 2010, received September 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Nasal spray, 100 mcg per spray and 400 mcg per spray

We also refer to your November 29, 2010, correspondence, received November 29, 2010, requesting review of your proposed proprietary name, Lazanda, and your December 10, 2010, amendment to the proprietary name request, received December 10, 2010. We have completed our review of the proposed proprietary name, Lazanda and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your November 29, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abolade (Bola) Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Sullivan at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
02/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022569

PRE-APPROVAL REMS NOTIFICATION

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your August 30, 2009, New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for fentanyl citrate nasal spray, 100 and 400 mcg.

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for fentanyl citrate nasal spray to ensure the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors.

We further refer to the meeting held on October 28, 2010, at the FDA White Oak Campus, at which we discussed that in the interest of public health and to reduce the burden on the healthcare system of having multiple unique REMS programs, we have determined that a single, shared system should be used to implement the REMS for all members of the class. The necessary REMS elements should be implemented across the class of transmucosal immediate release fentanyl (TIRF) products to address the serious risks described above.

We acknowledge receipt of your proposed REMS included in your Class 2 resubmission dated September 30, 2010. At the October 28, 2010 meeting, we informed the sponsors of the TIRF products of our development of standardized REMS materials that could be used in the development of a single shared system to implement the REMS for all TIRF products. At that meeting, we told sponsors that we intend to move rapidly to review and approve REMS for each of the TIRF products that include the standardized program, and we encouraged sponsors to work together to implement a single shared system to reduce the burden on the healthcare system of individual programs. This letter is a follow up to that meeting discussion.

Attachment 1 contains a REMS program that can be implemented as a single shared system across all TIRF products, and we recommend that your proposed REMS be revised to conform to this program. The program will include standardized elements and enrollment forms that can be used by all sponsors of TIRF products and can be implemented using existing pharmacy systems.

Your revised proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that fentanyl citrate nasal spray poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of fentanyl citrate nasal spray. FDA has determined that fentanyl citrate nasal spray is a product for which patient labeling could help prevent serious adverse effects and that has serious risks of which patients should be made aware because information concerning these risks could affect patients' decisions to use, or continue to use fentanyl citrate nasal spray.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed fentanyl citrate nasal spray.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

- Healthcare providers are specially certified or trained
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

The Implementation System must include all elements listed in Attachment 1.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than every six (6) months for the first year following the approval of the fentanyl citrate nasal spray REMS, and annually thereafter. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment.

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

This submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that includes information that we believe is pertinent across the class of TIRF products (see Attachment 1). Additionally, all relevant proposed REMS materials including: enrollment forms, educational, and communication materials should be appended to the proposed REMS. These appended documents should also be standardized across the class of TIRF products, with the exception of the product-specific information that will be included in the training program for prescribers. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Attachment 2).

Before we can continue our evaluation of this supplement NDA, you will need to submit the revised proposed REMS.

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS for NDA 022569**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 022569**." If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

14 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

BOB A RAPPAPORT
11/12/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20857

NDA 022569

MEETING MINUTES

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your New Drug Application (NDA) dated August 30, 2009, received August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for fentanyl citrate nasal spray, 100 and 400 mcg.

We also refer to the August 24, 2010, meeting between representatives of your firm and the FDA. The purpose of the meeting was to discuss our June 30, 2010, Complete Response letter.

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

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes

SPONSOR MEETING MINUTES

MEETING DATE: August 24, 2010

TIME: 12 noon to 1 PM

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: NDA 022569

PRODUCT: Fentanyl nasal spray

INDICATIONS: Management of breakthrough cancer pain in patients with cancer, (b) (4) who are already receiving and who are tolerant to regular opioid therapy for (b) (4)

SPONSOR: Archimedes Development Limited

TYPE OF MEETING: Type A

MEETING CHAIR: Rob Shibuya, MD, Clinical Team Leader, Division of Anesthesia and Analgesia Products (DAAP)

MEETING RECORDER: Matthew Sullivan, MS, Regulatory Project Manager, DAAP

FDA Attendees	Title
Bob A. Rappaport, MD	Division Director, Division of Anesthesia and Analgesia Products (DAAP)
Sharon Hertz, MD	Deputy Division Director, DAAP
Rob Shibuya, MD	Clinical Team Leader, DAAP
Luke Yip, MD	Clinical Reviewer, DAAP
Dionne Price, PhD	Statistical Team Leader, DAAP
David Petullo, PhD	Statistical Reviewer, DAAP
Sheldon Markofsky, PhD	CMC Reviewer, Office of New Drug Quality Assurance (ONDQA)
Matthew Sullivan, MS	Regulatory Project Manager, DAAP
Sponsor Attendees	**Title**
Jackie Mitchell	Director, Regulatory Affairs
Mark Watling	Group Medical Director
Michael Perelman	Chief Scientific Officer
Alan Smith	VP Research and Development
Ann Tunstall	US Regulatory Liason, SciLucent, LLC
Gary Jay	Chief Medical Officer

Background:
The Division's responses to the questions from the August 9, 2010, meeting package were sent to the Sponsor on August 23, 2010.

Presented below are the Division's comments and responses to questions in the background meeting package. The Sponsor's questions are listed in italics, with Agency responses and comments in bold. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

After introductions, the conversation focused on the Division's August 23, 2010, preliminary meeting responses.

PRODUCT QUALITY

Question 1. *The container-closure system is inadequate to prevent accidental exposure to the fentanyl solution by patients, caregivers, and household contacts.*

a. *The* (b) (4) *pump assembly can be removed from the glass bottle with moderate effort and no tools.*

b. *The top of the pump assembly can be easily separated from the bottom of the mechanism, allowing fentanyl solution to leak out.*

- *Can FDA confirm that the modified container-closure system addresses points 1(a) and (b)?*
- *Does the FDA agree that the proposed data package on the modified pump described in Appendix 1 appears adequate to support the change?*

Division Response:
We note the modifications you have made to the device and, on face, the device appears more robust. Whether or not the changes will adequately address the deficiencies will be a review issue. In this vein, as part of your re-submission, provide samples of your re-designed to-be-marketed drug product containing placebo solution, including your proposed disposal pouch and child resistant container, as well as data to support your planned changes.

Discussion:
There was no discussion beyond the Division's initial written response.

Post Meeting CMC Comment:
In addition to data, other relevant information, such as descriptions of design changes (including engineering drawings), should be provided to support modifications of the device.

Question 2. *The container-closure system is inadequate to ensure an accurate accounting of the number of sprays delivered.*

a. *If the top of the pump was removed and then replaced, it could be indexed at various positions along the dose counter and would no longer accurately reflect the number of sprays delivered.*

b. *It is possible to actuate a dose without causing the dose counter to advance.*

- *Does FDA agree that the modifications to the pump assembly described in Appendix 1 addresses both points 2(a) and 2(b) above?*
- *With regard to 2(b), can the FDA confirm the circumstance under which they found it possible to actuate a dose without causing the counter to advance?*

Division Response:
By modulating the force of actuation on the sample device you have provided, we were able to actuate a dose delivery without advancing the counter. We also note that this technique could defeat the purpose of the lock-out mechanism. Also see our response to Question 1.

Discussion:
The Sponsor noted that the amount of drug product that is able to be sprayed out of the device without advancing the dose indicator is less than a full dose. The Sponsor acknowledged that this is not an ideal situation, but they stated that this doesn't cause a safety concern for patients. The Division replied that a partial dose is not a safety concern, but that if the patient realizes that the dose indicator didn't advance, they may subsequently administer a full dose. The Division further noted that in many opioid-tolerant patients this would not be a safety concern, but that it would be an issue for internal discussion when the complete response resubmission was reviewed. The Sponsor noted that since one aspect of the REMS was to ensure that only opioid-tolerant patients were prescribed the product, that a patient receiving a full plus a partial dose should not be a cause for concern.

The Division also stated that the redesigned device appeared sufficiently 'hardened' to prevent inadvertent or accidental opening.

Question 3. *The alternative method of disposal (disposing of priming/unwanted sprays of fentanyl by spraying into an activated carbon cloth pouch), as proposed in Appendix 2, addresses FDA concerns and will protect household members from accidental exposure.*

- *Does the FDA agree in principle that the alternative proposal to dispose of priming/unwanted sprays of fentanyl by spraying into an activated carbon cloth pouch (that irreversibly absorbs the fentanyl) appears adequate to protect patients and household contacts from unintentional exposure?*

- *Does the FDA agree in principle that as a result of the alternative method for disposal of unwanted sprays, in conjunction with the improvements to the container/closure system described above and in Appendix 2, the disposal of the small volume of residual fentanyl left in the bottle by placing it in the CRC and throwing in the trash is adequate to protect patients and household contacts from unintentional exposure?*
- *Does the FDA agree that the proposed data package described in Appendix 2 to demonstrate that the activated carbon pouch is "fit for purpose" will be adequate to support its use?*

Division Response:
We note your proposed disposal method. While the pouch appears to be an improvement over what you proposed in the NDA, whether it is adequate will be a review issue. We suggest that you include at least two carbon cloth pouches per bottle, one pouch for the prime and one pouch for the unwanted sprays. Provide data to support an "expiry" to justify how long the pouch can be used effectively.

The large quantity (b) (4) for the high concentration [4 mg/mL] solution) of residual fentanyl solution after maximal use has not been addressed. While your proposal may address concerns about unintentional exposure of patients and household contacts during priming and disposing of unused doses, it does not address the issue of large quantities of residual fentanyl solution in the community. This problem appears to be inherent in the product design. We recommend that you consider redesigning the device to inactivate the residual fentanyl after the 8th dose.

Discussion:
The Division asked the Sponsor if they would be able to provide two activated carbon cloth pouches with each vial, one for the priming doses, and one for any doses that many need to be discarded at the end of use. The Sponsor stated that they would prefer to provide a single pouch, and ensure that the patients are educated not to discard the pouch until they discard the vial.

The Sponsor stated that the net fill weight per vial can't be lowered below (b) (4), otherwise the amount of drug product delivered in the last dose (dose 8) can't be assured to be the same as the first dose. After 8 sprays, however, a small amount of drug product remains in the vial and in the spray mechanism. The Sponsor proposed that they could remove the current lockout after the 8th dose, and allow a patient to spray the remaining drug product into the pouch. The Division noted that this would not be ideal, since some patients would accidently or intentionally continue to use these diminishing doses. The Sponsor stated that patients could be educated to completely spray out their residual. The Division responded that we would need to be convinced that patients *will* actually do this, rather than patients simply demonstrating that they *can* do this, as would be evidenced in a traditional clinical trial. The Sponsor stated that this education would be an integral part of their provider-patient education.

The Division expressed our concern that having any amount of extra fentanyl in the vial after the 8th use is worrisome. The Division encouraged the Sponsor to continue to investigate the possibilities of chemically inactivating the fentanyl after the last dose.

Question 4. *Archimedes has submitted an assay for detecting Burkholderia cepacia in the drug product in NDA Amendment 19 (submitted on 3 June 2010). Archimedes has also included a specification for the absence of Burkholderia cepacia in the drug product. The data included in Amendment 19 is outlined in Appendix 3 and will be resubmitted with the response to the deficiencies identified in the Complete Response Letter.*

- *Does FDA agree that this is appropriate?*

Division Response:
The revised specification stating absence of *B. cepacia* as well as *P. aeruginosa* and *S. aureus* is appropriate and acceptable.

The proposed *B. cepacia* test method (submission section 3.2.P.5.2.8) in which the bacterium is enriched in tryptic soy broth (TSB) prior to isolation and detection on OFPBL agar plates is appropriate and acceptable. However, TSB may not represent an optimal enrichment medium for strains derived from nutrient-poor environments (see *Carson et al., Appl. Micro. 25(3):476-483; 1973*), and you are encouraged to consider alternative media.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 5. *Archimedes has submitted a commitment to test for Burkholderia cepacia contamination in the Purified Water, USP, used for* (b) (4) *in NDA Amendment 19 (submitted on 3 June 2010). The commitment will be resubmitted with the response to the deficiencies identified in the Complete Response Letter.*

- *Does FDA agree that this is appropriate?*

Division Response:
The commitment to test for *B. cepacia* in the Purified Water USP, utilized for (b) (4) (b) (4) **is acceptable.**

Discussion:
There was no discussion beyond the Division's initial written response.

LABELING

Question 6. *Archimedes seeks clarification from FDA as to why the following language was removed from the clinical section (14):*

a. (b) (4)

b. (b) (4)

c. (b) (4)

- *Can FDA provide comments on the proposed carton and label texts submitted with the NDA?*

Division Response:
A detailed discussion of the labeling is beyond the scope of this meeting. Labeling will be revisited upon submission of your Complete Response. However, we note the following:

1. (b) (4) **This is the standard that is applied to all similar products.**

2. (b) (4)

3. (b) (4)

Discussion:

(b) (4)

REMS

Question 7. *Archimedes is about to initiate the commercial build of the Elements To Assure Safe Use proposed in its REMS. Can FDA identify any areas in the proposed REMS program about which the agency has any remaining concerns and/or major comments?*

Division Response:
This product, as well as all transmucosal immediate-release fentanyl products, will require a Risk Evaluation and Mitigation Strategy (REMS).

We are currently working to create a more standardized REMS for this class of products. In the meantime, your REMS must include the following elements: Medication Guide, Elements to Assure Safe Use, Implementation System and Timetable for Submission of Assessments.

Your REMS must also address proper disposal of residual fentanyl with your product, prescribing to opioid-tolerant patients only, appropriate dosing of these fentanyl products, and surveillance for misuse and abuse.

You must submit a complete REMS at the time of your resubmission. Submit your REMS and REMS Supporting Document with your NDA resubmission as well as all planned materials identified within the proposed REMS that will be necessary to implement your proposal. Education should emphasize the safety messages important for safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

We request that, to the extent possible, you work with the other manufacturers of transmucosal immediate-release fentanyl products. In order to minimize the burden on the healthcare system and its various stakeholders, we recognize the importance of having one shared REMS system for all of these products, not just a REMS for an innovator and its generics.

Discussion:
The Division stated that the burden of REMS on the healthcare system is an Agency concern. Any REMS, taken alone, would likely have a minimal effect on prescribers and pharmacists. However, when the requirements from all approved REMS are taken together, the Agency is concerned that the healthcare system may be completely overburdened. The Division noted that we are trying to standardize REMS to the extent possible, and are interested in a system where prescribers and pharmacists would interact with a single system which would appear very similar for all drugs, but the underlying processes may be implemented differently by Sponsors.

The Division noted that we hope that various forms that are commonly used in REMS programs could be standardized in the next 6 to 12 months.

The Sponsor inquired if the Division had any concern with their proposal to have fentanyl citrate nasal spray available in the retail pharmacy setting. The Division replied that it is acceptable to use retail pharamcies to dispense the product in conjunction with the REMS. The Sponsor then commented that they are concerned with the requirement to administer a knowledge assessment to prescribers after they have completed the training modules. The Division stated that the Sponsor would not be licensing prescribers to practice, but simply ensuring that they understand the FDAAA-mandated training, since the Agency has decided that fentanyl citrate nasal spray requires special skills and training to prescribe.

The Division also remarked that a signed agreement form between the prescriber and patient can be faxed (or otherwise transmitted) to enroll patients, and that the pharmacies don't have to check that the enrollment has occurred before dispensing medication.

CHILD-RESISTANT CONTAINER (CRC)

Question 8. [redacted] (b) (4) *, Archimedes proposes to submit the results of a* [redacted] (b) (4) *post-marketing drug utilization study that is being conducted in the UK to assess:*

a. Practitioners' compliance with the labeled use of the product (such as only opioid-tolerant patients, only cancer patients, use of initial titration of dose, non-switching between products, etc), and

b. The incidence of adverse events, particularly relating to misuse, abuse, diversion /criminal use, off-label use, overdose and accidental exposure.

- *Will the data generated in the DUS and the pharmacovigilance program be sufficient to support a request* [redacted] (b) (4)

Division Response:
We will review your DUS data and data generated in your pharmacovigilance program in support of the [redacted] (b) (4)

Discussion:
There was no discussion beyond the Division's initial written response.

Action Items:

1. The Sponsor will consider additional methods of disposing or inactivating of all residual fentanyl that remains after the final spray.
2. The Sponsor will revise their labelin [redacted] (b) (4)
3. The Sponsor will submit a complete REMS with their resubmission, and will endeavor to work with the Sponsors of other fentanyl products to see if they can work together to combine some REMS aspects.

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/s/

MATTHEW W SULLIVAN
09/30/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022569 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) (proposed) Established/Proper Name: Fentanyl citrate nasal spray (FCNS) Dosage Form: nasal spray Strengths: 100 and 400 mcg		
Applicant: Archimedes Agent for Applicant (if applicable): SciLucent		
Date of Application: August 30, 2009 Date of Receipt: August 31, 2009 Date clock started after UN:		
PDUFA Goal Date: June 30, 2010	Action Goal Date (if different): June 23, 2010	
Filing Date: October 30, 2009	Date of Filing Meeting: October 13, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 070854	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	x			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	x			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		x		
If yes, explain in comment column.			x	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			x	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☒ Paid (July 16, 2009) ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		x		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		x		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	x			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
020747	Actiq	M-63	February 7, 2010
22266	Onsolis	NP	July 16, 2012

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		x		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			x	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: three ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	x			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			x	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**x**			
Index: Does the submission contain an accurate comprehensive index?	**x**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**x**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:* October 7, 2009	**x**			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	x			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	x			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			x	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		x		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	x			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	x			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		x		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	x			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	x			
Is the PI submitted in PLR format?	x			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	x			
REMS consulted to OSE/DRISK?	x			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	x			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		x		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** August 24, 2006 ***If yes, distribute minutes before filing meeting***	x			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 22, 2008 ***If yes, distribute minutes before filing meeting***	x			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		x		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 13, 2009

BLA/NDA/Supp #: 022569

PROPRIETARY NAME: (b) (4) (proposed)

ESTABLISHED/PROPER NAME: fentanyl nasal spray

DOSAGE FORM/STRENGTH: nasal spray, 100 and 400 mcg

APPLICANT: Archimedes

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: 505(B)(2) to actiq. Proposes same indication.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matt Sullivan	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Rob Shibuya		Y
Clinical	Reviewer:	Daniela Vanco (Efficacy) Nick Olmos-Lau (Safety)	Y Y
	TL:	Rob Shibuya Ellen Fields	Y Y

Clinical Pharmacology	Reviewer:	Sheetal Argawal	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	David Petullo	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	N
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Shelly Markofsky	Y
	TL:	Danae Christodoulou	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: none	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: Not first in class

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Genetox studies not submitted. Will notify in 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: (via ONDQA)	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: (via ONDQA)	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob Rappaport **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

MATTHEW W SULLIVAN
04/30/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022569

PROPRIETARY NAME REQUEST
WITHDRAWN

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove Street, Suite 300
Herndon, Virginia 20170

ATTENTION: Ann C. Tunstall, PhD
US Agent to Archimedes

Dear Dr. Tunstall:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Nasal Spray, 100 mcg per spray and 400 mcg per spray.

We acknowledge receipt of your April, 7, 2010 correspondence, on April 10, 2010, notifying us that you are withdrawing your January 21, 2010 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of April 7, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Bola Adeolu, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Sullivan at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

CAROL A HOLQUIST
04/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022569 **INFORMATION REQUEST**

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your New Drug Application (NDA) dated August 30, 2009, received August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fentanyl nasal spray, 100 and 400 mcg.

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

Container Closure System

We have found that the top part of your pump (the nasal spray actuator) could be readily pulled off from the counter ring assembly. In doing so, a small amount of the solution came in contact with our hands. This would be a concern if the solution contained fentanyl. Subsequently, we noted that the actuator could be placed back in different positions relative to the counter ring assembly such that different numbers or colored marking could be seen in the indication window. If this scenario were to occur, the patient might not know how many priming strokes may be needed or the number of doses that have been administered. Accordingly, changes to the device may be necessary to address these concerns.

Additionally, three of our staff members were able to unscrew the pump assembly from three separate glass bottles of your (placebo filled) to-be-marketed drug product. They were able to unscrew the assembly with their bare hands and without the use of any tools. Since opened bottles of your fentanyl solutions are both a safety and abuse concern to the Agency, it may be necessary to modify your drug product so that the pump assembly can not be unscrewed from the bottles.

You are also advised that any changes to the container/closure system, such as discussed above, may require changes to your NDA. For example, specification and spray characteristic changes or additional stability studies may be necessary. In addition, if

modifications are made, you should provide actual samples of the modified to-be-marketed drug product filled with the placebo solution to the Agency for our evaluation.

Methods Validation Data

In accordance with the appropriate sections of ICH Q2A and Q2B, provide the raw data and an adequate description of the methods used to support the validation of your method for the determination of (b) (4) in your drug substance. The raw data is requested to support the conclusions summarized in Table 3.2.S.4.3-1 of the original submission and the LOD and LOQ findings reported in the 2-17-10 amendment.

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

SARA E STRADLEY
04/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022569

DISCIPLINE REVIEW LETTER

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your new drug application (NDA) dated August 30, 2009, received August 31, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Fentanyl nasal spray, 100 and 400 mcg.

Our review of your proposal for disposal of used and partially-used product is complete, and we have identified the following deficiencies:

During our August 24, 2006, and September 22, 2008, meetings, you were instructed to address the proper and safe disposal of the excess fentanyl from your product. The current methods of disposal proposed in your NDA are inadequate to assure the safety of patients, caregivers and household contacts.

The current design calls for four priming sprays and eight sprays intended to deliver the drug to the patient, and each spray is (b) (4) volume. The current fill in this design is (b) (4) After the 12 sprays are delivered, there will be a residual (b) (4) of fentanyl solution in the bottle. As the product is intended to be marketed with either 100 mcg or 400 mcg of fentanyl per 0.1 mL, the amount of residual fentanyl will be (b) (4) mg fentanyl, respectively. After delivery of all 12 sprays, the bottle is intended to be disposed of by placing into the child proof container and placing in the trash.

(b) (4)

The proposed disposal methods for the residual fentanyl in the bottle and the fentanyl (b) (4) is not adequate to protect patients and household contacts from unintentional exposure. The proposed package insert provides the following directions:

[redacted]

with the fentanyl solution potentially places household members at risk from inadvertent exposure to fentanyl, particularly if [redacted] Experience with other fentanyl products that instruct patients to dispose of the product using a specific method has shown that patients and caregivers do not always follow directions [redacted]

Furthermore, it is unclear what additional assistance will be provided by [redacted]

You must provide patients with a method of priming and disposing of partially used and unused bottles that assures the safety of patients, caregivers and household contacts.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final

decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

SARA E STRADLEY
03/24/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-569

INFORMATION REQUEST

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your new drug application (NDA) dated August 30, 2009, received August 31, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Fentanyl nasal spray, 100 and 400 mcg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a commitment to test for *Burkholderia cepacia* in the USP purified water used (b) (4). The commitment should include the testing method.

2. Provide a description of the method for recovering and identifying "objectionable microorganisms" as stated in the revised drug specifications (Table 3.2.P.5.1-2). The methods should include specific procedures for recovery and identification of *B. cepacia*.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

PRASAD PERI
03/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022569

INFORMATION REQUEST

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your New Drug Application (NDA) dated August 30, 2009, received August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fentanyl nasal spray, 100 and 400 mcg.

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

During our August 24, 2006, and September 22, 2008, meetings, you were instructed to address the proper and safe disposal of the excess fentanyl from your product.

In your NDA submission, you propose to have patients (b) (4) This potentially exposes other household members to excessive risk from inadvertent fentanyl absorption.

Propose an alternative method to dispose of the excess fentanyl solution from priming the device and the residual fentanyl solution from a used device.

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

SARA E STRADLEY
02/19/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-569 **INFORMATION REQUEST**

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your new drug application (NDA) dated August 30, 2009, received August 31, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Fentanyl nasal spray, 100 and 400 mcg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For each drug product component (Fentanyl citrate, mannitol, phenyethyl alcohol, propylparaben, HCl, sodium hydroxide, purified water), please provide:
    a. Certificates of analysis;
    b. Microbiological acceptance criteria;
    c. Controls, tests and/or criteria determining absence from *Burkholderia cepacia* contamination.

2. Please amend the Microbial Quality section of the drug product specifications (Table 3.2.P.5.1-2) to include absence of *Burkholderia cepacia*. The specification should include the *B. cepacia* detection method.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

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/s/

PRASAD PERI
01/27/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022569

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Archimedes Development Ltd
c/o SciLucent LLC
585 Grove Street, Suite 300
Herndon, Virginia 20170

ATTENTION: Ann C. Tunstall, Ph.D.
US Agent to Archimedes

Dear Dr. Tunstall:

Please refer to your New Drug Application (NDA) dated August 30, 2009, received August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Nasal Spray, 100 mcg and 400 mcg.

We also refer to your September 16, 2009, correspondence, received September 17, 2009, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable because (b) (4).

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated September 16, 2009. We remind you of our concerns regarding the alternate name, (b) (4), which were expressed during the December 7, 2009 teleconference . (b) (4)

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, HTTP://www.fda.gov/cder/guidance/7935dft.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Bola Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew Sullivan at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

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

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

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/s/

CAROL A HOLQUIST
12/16/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022569

FILING COMMUNICATION

Archimedes Development Limited
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann Tunstall, PhD
Managing Consultant

Dear Dr. Tunstall:

Please refer to your new drug application (NDA) dated August 30, 2009, received August 31, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Fentanyl nasal spray, 100 and 400 mcg.

We also refer to your submissions dated October 14 and 21, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 4, 2010.

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

Your proposed drug product specification for (b) (4) may be inadequate. We note that your justification for the proposed levels of (b) (4) includes a structure-activity assessment which did not reveal the presence of structural alerts for genotoxicity, mutagenicity or carcinogenicity. In contrast, a computational toxicology assessment of (b) (4) conducted internally suggests that (b) (4) may be clastogenic. Provide further justification to support your conclusion that (b) (4) P is not potentially genotoxic or

carcinogenic. In the absence of adequate justification, [redacted] must be regulated to a level of NMT 1.5 mcg/day in the drug substance and drug product.

We recognize that there are literature reports suggesting that [redacted] Significant metabolites are generally deemed adequately qualified for safety. Include in the justification mentioned above a quantitative assessment of [redacted] as a human metabolite at the maximum daily dose of fentanyl for your product. This assessment may include a literature review and copies of referenced citations. The presence of [redacted] as a human metabolite at significant levels could render the need for qualification unnecessary.

Please be advised that as a 505(b)(2) submission, which relies on the Agency's previous findings of safety and efficacy, we can not legally use information contained within a Summary Basis of Approval to support your application unless you have right of reference to the underlying data.

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

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

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/s/

BOB A RAPPAPORT
11/12/2009

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, November 06, 2009 9:45 AM
To: 'Ann Tunstall'
Subject: Clinical Infomation Request, 6 Nov 09

Hi Ann –

Please address:

In the list of study sites for study CP043/06/FCNS attached to the cover letter for the initial NDA submission, there are listings for site 913 (Leung) and 914 (Wallace). However, in the study report for CP043/06/FCNS, there is no site 914 (Wallace), but he is listed as a sub investigator for site 913. Provide clarification for this discrepancy. Also provide the number screened, number of screen failures, number of subjects entering titration, number of subjects randomized, number of premature discontinuations, and number of protocol violations if they are different than those presented in the table.

Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, November 23, 2009 6:36 PM
To: 'Ann Tunstall'
Subject: (b) (4) t IR

Ann –

Thanks for the link you provided earlier today to the table. Please find below an additional request:

- Please provide a table with the frequency of types of cancer in the subjects in study CP 043

Thanks
matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, November 23, 2009 12:17 PM
To: 'Ann Tunstall'
Subject: (b) (4) information request 22569

Ann –

In Section 11.2.2 (Page 66 of the PDF file) of the report for Study CPO43, there is a reference to Section 16.2.4.1. See below:

> **11.2.2 Medical History**
> Past and current medical conditions are listed by patient in Listing 16.2.4.1.

Unfortunately, we can not locate this section in your application. Provide the location of this section so that we can locate the past and current medical conditions of the enrolled subjects, specifically the type of cancer. If this section is not in the submission, submit it as an amendment to the NDA.

Thanks
matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, January 08, 2010 3:54 PM
To: Ann Tunstall
Subject: intranasal fentanyl N022569

Ann –

Here is a CMC info request. Please note that the request for samples (Comment #1) are not a request for addition samples. However, we do request a single disassembled product.

Thanks, and please let me know if you have any questions.

Matt

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA 022569 for your Fentanyl Nasal Spray, and we have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide four actual samples of your proposed drug product filled with placebo solution. In addition, provide the disassembled components of your spray pump.

2. Provide evidence that your proposed drug product is in compliance with (b) (4)

3. In accordance with the FDA Guidance for Industry, related to nasal sprays, provide a specification (range) for the viscosity of your drug product solution to be used for the release of your nasal spray and as part of your post-approval stability protocol. Your proposed range should be justified, and your viscosity procedure should be validated.

4. For your release testing and post-approval stability protocol, provide and justify a range for your gel strength specification.

5. Provide the Limit of Detection (LOD) and the Limit of Quantitation (LOQ) for (b) (4) (b) (4) in your method for the determination of this Related Substance impurity in your fentanyl (drug substance).

6. Provide Appendices A, B, and C for your report entitled "Assay Qualification of the Related Substance Method for (b) (4) in Fentanyl API , P/N 161044, by HPLC".

7. Since particles from your drug product that have a very small particle size can be inhaled into the lungs, reinstitute a validated specification for the percentage of droplets that are less than (b) (4). This specification should be used for the release and stability of your nasal spray and should be part of your post-approval stability protocol. Justify your upper limit (percent) from a safety point of view.

8. Your batch data (e.g. Section 3.2.P.5.4) show a much narrower range for D (max) in your spray patterns than in your proposed specification range (b) (4) Accordingly, narrow

your release and stability acceptance criteria for D (max).

9. Provide and up-date the stability specifications, including acceptance criteria, for the commercial batches that will be monitored according to your post-approval stability protocol.

10. Specify whether or not samples from future commercial batches in your post-approval program will conform to Protocol no. 652001.001.014.

11. Amend your post-approval protocol to include testing for leachables (b) (4)) at all time points.

12. Make your post-approval stability commitment for out-of-specification drug product. Use the following or similar wording for this commitment :

> "Archimedes Development Limited commits to withdraw from the market any lot found to fall outside the approved specifications for Fentanyl Nasal Spray. If the Archimedes has evidence that the deviation is a single occurrence that does not affect the safety or efficacy of the drug product, they will immediately discuss the failure with the FDA and provide justification for the continued distribution of the lot. Change or deterioration in a batch of Fentanyl Nasal Spray will be reported under 21 CFR 314.81(b)(1)(ii)."

Container/Closure

13. 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.

14. 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.

15. Provide a justification for the selection of the mechanical end-of-use lock versus other physical and/or chemical methods to minimize residual fentanyl. You indicated 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.

Labeling

16. The font of the established name on your container and carton labels is too small. This font must be at least one half the size of your proprietary (trade) name.

17. It is preferred that your established name read "(fentanyl) nasal spray" rather than "(fentanyl nasal spray)".

18. Provide the recommended storage conditions of your drug product in the HOW SUPPLIED/STORAGE & HANDLING section (16.1) in your Annotated Draft Labeling text.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, January 28, 2010 2:40 PM
To: 'Ann Tunstall'
Subject: REMS info request N22569

Ann –

These are preliminary REMS comments; as we continue our review, we will likely provide additional comments. Please respond to this request as soon as possible, and no later than February 11, 2010.

1. In order to complete our review, provide copies of the following materials:
   a. Prescriber training program and post-test
   b. Pharmacist training program (if different from above)
   c. All materials that will be enclosed with the letters sent as part of the Communication Plan (e.g. the "Prescribing Information brochure" mentioned in the pharmacist letter).
   d. Website screen shots and copies of all materials that will be available as part of the REMS on the website (as listed in Appendix D). We recommend a link off of the (b) (4) homepage to a REMS landing page. For example, the link could state: "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information." The landing page of the separate REMS link should then contain background information on the REMS, safety information, and the REMS materials. The webpage should not be a means to promote (b) (4) or any other Sponsor product.
2. Address the following questions concerning the (b) (4)

(b) (4)

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Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, February 02, 2010 4:38 PM
To: 'Ann Tunstall'
Subject: Clinical info request N22569

Hi Ann -

Here is a clinical info request:

Study CP043: For patients who discontinued from the study prematurely who were coded as “other” provide further detail with regard to the actual reason(s) for discontinuation.

Also provide the classification for the pain pathophysiology (e.g. neuropathic, nociceptive, or mixed) for the patients studied.

Study CP044: For patients who discontinued from the study prematurely who were coded as “other” provide further detail with regard to the actual reason(s) for discontinuation.

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, February 04, 2010 1:02 PM
To: 'Ann Tunstall'
Subject: FW: NDA 22-569 fentanyl nasal spray IR

Ann –

Please submit race data for the subjects used in the Dose proportionality study # CP04205. The demographic data in the study report does not have that information.

Thanks,
matt

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, February 18, 2010 4:47 PM
To: 'Ann Tunstall'
Subject: Clinical Pharmacology IR N22569

Ann –

Late-breaking request from the Clin Pharm review team:

> Please submit SAS (or Excel) data sets for studies CP04205, CP04707, and CP04807.

We need these rather urgently.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, February 24, 2010 4:28 PM
To: 'Ann Tunstall'
Subject: CMC IR N22569

Ann –

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA 22-569, including your amendment dated February 17, 2010. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The Agency is concerned about the levels of a possible "structural alert" impurity in the drug substance, and we have asked the DMF holder (b) (4) to provide additional information about this potentially genotoxic impurity.

2. DMF (b) (4) has been found **inadequate** to support your NDA, and (b) (4) was, therefore, requested to provide additional information for their type I (b) (4).

3. We previously requested specifications (ranges) for the viscosity and gel strength of your drug product solution to be used for the release of your nasal spray and as part of your post-approval stability protocol. Your updated finished-product specifications, in the February 17, 2010 amendment, did not indicate ranges. You should provide **an upper and lower numerical limit** for the viscosity and gel strength of your drug product solution.

4. Provide an engineering drawing of your Type I glass bottles showing the precise dimensions and the accepted tolerances for these dimensions of the container. In addition, provide a specification for the appropriate inside and outside diameters of the glass rings at the top of the bottle that must fit snugly with the corresponding pump parts; and as part of acceptance testing for your glass bottles, Archimedes should carry out measurements on the appropriate inside and outside diameters of the glass rings to assure that these dimensions are within their accepted limits.

5. Provide a specification for the wall thickness of the thinnest part of the body of the bottle; and acceptance testing for your glass container should include a measurement of the wall thickness of the thinnest part of the body of the bottle to assure that this dimension meets its accepted limits.

6. Provide a copy of the manufacturer's test certificate for the Type I glass bottles in the NDA.

7. Provide engineering drawings of the nasal adapter and counter ring which comprise the end of use lock as well as the precise dimensions and the accepted tolerances for these dimensions for these components.

8. Provide specifications for the appropriate inside and or outside diameters of the nasal actuator, pump insert, and counter ring components that must fit snugly with each other; and as part of your acceptance testing protocols for the nasal actuator, pump insert, and counter ring components, carry out measurements of these diameters to assure that these dimensions are within their accepted limits.

9. Provide copies of the manufacturer's certificates of conformance (or equivalent certificates) for the nasal actuator, pump insert and counter ring in the NDA.

10. Provide data to demonstrate the stability of the various solutions (Working Standard, Working Calibration, and Working Sample solutions) that are used for your Assay and Related Substances method by HPLC.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

MATTHEW W SULLIVAN
06/28/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,854

Archimedes Development, Ltd.
c/o SciLucent, LLC
585 Grove St, Suite 300
Herndon, VA 20170

Attention: Ann C. Tunstall, Ph.D.
U.S. Agent

Dear Dr. Tunstall:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (nasal fentanyl spray).

We also refer to the Pre-NDA meeting between representatives of your firm and FDA on September 22, 2008. The purpose of the meeting was to provide you with feedback on the questions in your August 11, 2008, meeting package related to your preparations for filing your new drug application with your product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: September 22, 2008
Time: 3:00 PM EST
Location: White Oak Conference Room 1315
Application: IND 70,854
Regulatory Status: Active IND
Products: (b) (4) (fentanyl nasal spray)
Proposed Indication: Management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain
Sponsor: Archimedes Development, Ltd
Type of Meeting: Type B- Pre-NDA
Meeting Chair: Sharon Hertz, M.D., Deputy Director
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Minutes Recorder: Kimberly Compton, Project Manager, DAARP

Industry Representatives	**Title**
Barbara Clarke, BSc	Group Regulatory Affairs Director
Jackie Mitchell, MA, DPhil	Director, Regulatory Affairs
Mark Watling, MB ChB, FFPM, MRCGP, DRCOG, Dip Sports Med	Group Medical Director
Tony Fisher, PhD	Early Phase Clinical Director
Alan Smith, B Pharm., MR Pharm S, PhD	VP Research and Development
Peter Watts, PhD, MR Pharm S	Director of Pharmaceutical Development
Michael Hinchcliffe, PhD	Biological Group Head
David Youds, DMS	Director, Strategic Marketing
Heather Wilkins, BSc Hons, MBA	Procurement and Supplies Director,
(b) (4)	(b) (4)
Ann C. Tunstall, PhD	US Regulatory Liaison, SciLucent, LLC
(b) (4)	(b) (4)
FDA	**Title**
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Jane Filie, M.D.	Medical Officer, DAARP
Robert Shibuya, M.D.	Medical Team Leader, DAARP
Elizabeth Bolan, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Adam Wasserman, Ph.D.	Supervisory Pharmacologist, DAARP
Dionne Price, Ph.D.	Statistical Team leader, Division of Biometrics II (DBII)
Jonathan Norton, Ph.D.	Statistical Reviewer, DBII
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Ali Al Hakim, Ph.D.	Chief, Branch II, Division of PreMarketing Assessment 1, Office of New Drug Quality Assessment (ONDQA)
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead (PAL), ONDQA
Kristina Arnwine, Pharm.D.	Team Leader, Office of Surveillance and Epidemiology (OSE)
Jeanine Best, R.N.,	Senior Drug Risk Management, OSE
Afrouz Nayernama, Pharm.D.	Reviewer, OSE
Anne Crandall	Reviewer, OSE
Kim Compton	Regulatory Project Manager, DAARP

Agency Comments and Responses to Questions:

Chemistry Questions (2.4.1)

Question 1
Archimedes will submit data on particle size generated by this (b) (4) method. Does the Agency agree to this proposal?

FDA Response
Your approach to use (b) (4) method rather than the (b) (4) (b) (4) is reasonable. Provide a description of the method and method validation data in the NDA.

Discussion
There was no further discussion of this issue.

Question 2
Does the Agency agree that the proposed product specification adequately controls product quality?

FDA Response
The proposed drug product specifications are reasonable. Include spray content uniformity testing on stability.

Ensure that the spray content uniformity at the end of use for the eight doses (7 days) and end of shelf-life of the drug product.

Discussion
There was no further discussion of this issue.

Question 3
Does the Agency agree that these studies (percentage of droplets below (b) (4) measured by (b) (4), priming/re-priming, amount remaining on actuator tip, tail-off study, effect of dosing orientation on pump performance, robustness-simulated patient use) will ensure adequate characterization of the drug product container closure system?

FDA Response
Yes we agree.

In addition, ensure that the spray rate is consistent for the eight doses at the end of use (7 days) and end of shelf-life of the drug product.

Discussion
There was no further discussion of this issue.

Question 4
Does the Agency agree that this proposed package of data will adequately describe and control the dose-counting nasal spray pump utilized in (b) (4)

FDA Response
Your proposed data for pump assessment is reasonable. Adequacy of the controls for the pump and its components will be determined upon review of the NDA and the supporting container/closure Drug Master File (b) (4)

Discussion
There was no further discussion of this issue.

Question 5
Does the Agency agree that this package of stability data will be adequate to support approval of the product at a (b) (4) *fill volume?*

FDA Response
Include at least 6 months of normal and accelerated storage data for the (b) (4) **at the one-third (clinical/registration) scale for each strength.**

Discussion
There was no further discussion of this issue.

Question 6
Does the agency consider the process validation plan to be acceptable? [2 x 1 mg/mL and 2 x 4 mL or 1 x 1 mg/mL and 3 x 4 mg/mL commercial size batches (b) (4) *)]?*

FDA Response
Provide two validation batches per strength at the commercial scale (b) (4) (b) (4)

Discussion
There was no further discussion of this issue.

Question 7
Does the Agency consider this (manufacture of the confirmation batches post-submission of the NDA, prior to commercial distribution) approach to be acceptable?

FDA Response
This proposal is acceptable.

Discussion
There was no further discussion of this issue.

Chemistry Comments

1. **Provide an accurate estimate of the residual fentanyl for the (b) (4) fills. Include the estimated loss of fentanyl due to priming.**

2. **You have indicated that the (b) (4) still under development. We strongly encourage you to make all possible changes to your device and manufacturing process prior to initiation of Phase 3 trials. We believe that clinical trials are the best validation of the performance of the to-be-marketed device.**

   Discussion
   The sponsor stated that there would be a CRC for each spray bottle for the marketed product, but that for the trials, the CRC would be a canister with a foam liner, noting that neither the prototype sample sent to the Division nor the final CRC would be used in the trials. The sponsor stated that they recognized that the proposed CRC (b) (4) and were working on developing (b) (4) but noted that the spray bottle would stay the same going forward. The sponsor stated that they planned to complete the in-use studies required by the CPSC (in healthy volunteers) to validate the CRC and include that information in the NDA. Dr. Al-Hakim stated that the Agency wants to see information and samples of the new design. Dr. Christodoulou stated that the Agency needs to see performance testing of the device during clinical trials, especially because there are significant differences between the proposed Phase 3 canister and commercial container. She strongly encouraged the sponsor to use one of the proposed commercial prototypes in the remaining clinical trials in an in-use study.

   Dr. Hertz stated that the Agency previously conveyed strong concerns about the safety of this product and now one of the primary safety features (the CRC) will be untested. She noted that a CPSC study in volunteers would not be considered acceptable for FDA purposes. She stated that the firm should get their device far enough along in development to include it in their remaining clinical studies. The Agency will need data to help determine the significant safety concerns that have been discussed have been adequately addressed.

   The sponsor stated that easy removal of the top of the device was not an issue in the trials to date, but noted that they would further examine the force needed to remove the top of the device.

   The sponsor stated that the end-of-use lockout after eight doses is to indicate to the patient that the unit is complete, preventing dose tail-off. They indicated that no patient should use more than one bottle per day even at the highest dose.

   The sponsor stated that while overfill remains in the container after the last dose, the device has a mechanical feature (i.e., a ratchet clip), which activates after the last dose. This feature will be included in the clinical trials spray bottle and the sponsor plans to use it in the commercial product as well. The sponsor stated that they will provide data from a performance test of the ratchet clip feature in the NDA.

   The sponsor noted that they have decreased the residual fentanyl in the device after the last dose from (b) (4) and will include that data in the NDA.

3. **Provide a list of all manufacturing facilities, in alphabetical order, including a statement about their cGMP status and whether they are ready for inspections. For all foreign sites, provide a name contact with telephone number at the site. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may result in non- approval of the NDA.**

4. **We suggest you refer to the following guidance documents as you develop your drug product and your NDA:**

    a. **Guidance for Industry INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information available at http://www.fda.gov/cder/guidance/3619fnl.htm and the 21 CFR 314.23.**

    b. **Guidance for Industry ICH Q3A (R) Impurities in New Drug Substances available at http://www.fda.gov/cder/guidance/4164fnl.htm**

    c. **Guidance for Industry ICH Q3B (R2) Impurities in New Drug Products available at http://www.fda.gov/cder/guidance/7385fnl.htm**

    d. **Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances available at http://www.fda.gov/OHRMS/DOCKETS/98fr/122900d.htm**

    e. **Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation available at http://www.fda.gov/cder/guidance/1714fnl.htm**

    f. **Guidance for Industry Validation of Analytical Procedures: methodology available at http://www.fda.gov/cder/guidance/1320fnl.pdf.**

    g. **Guidance for Industry Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products-Chemistry manufacturing and Controls Documentation available at http://www.fda.gov/cder/guidance/4234fnl.htm.**

Nonclinical Question (2.4.2)

Question 8
Does the Agency agree that the listed nonclinical data are adequate to support submission of a New Drug Application under 505(b)(2), using Actiq (N 20-747) as the referenced drug?

FDA Response
Based on the information provided in the meeting package, your nonclinical program appears to be acceptable to support submission of the NDA. However, final determination of the adequacy of the data will be made upon review of the NDA.

Discussion
There was no further discussion of this issue.

Non-Clinical Comments

1. **Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).**

2. **The fentanyl drug substance may contain residual synthesis intermediates and/or impurities that contain structural alerts for mutagenicity such as: (b) (4) - (b) (4). A specification of NMT 1.5 mcg/day should be set for genotoxic or potentially genotoxic residual intermediates/impurities. The Division recommends that you consult with your DMF holder to decrease the limit of these impurities.**

Discussion
There was no further discussion of this issue.

Clinical Pharmacology Question (2.4.3)

Question 9
Does the Agency concur that the four single- and repeat-dose Pharmacokinetic(PK) studies will provide sufficient information on the pharmacokinetics of (b) (4) in patients, including those with conditions which might potentially alter the absorption of the product to support the NDA for (b) (4)?

FDA Response
Yes.

Discussion
There was no further discussion of this issue.

Packaging Question (2.4.4)

Question 10
Does the Agency agree that the Child-Resistant Container should only be labeled with the product logo in order to facilitate anonimyzed disposal?

FDA Response
We note that you did not submit your proposed logo. Therefore, we do not know if the logo is linked to the drug product or the company. Knowing the appearance of the logo will help determine if there may be an advantage to having the CRC labeled with the drug name and strength for storage purposes

or if disposal of an unlabeled narcotic (i.e. with a company logo only) may prove safer.

Discussion
There was no further discussion of this issue.

Clinical Questions (2.4.5)

Question 11
Does the Agency agree that the proposed single efficacy study is adequate and well controlled, and will support a 505(b)(2) application for (b) (4) *t for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain?*

FDA Response
Yes, one positive, adequate and well-controlled efficacy study will support a 505 (b)(2) application for (b) (4) **for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain.**

Discussion
There was no further discussion of this issue.

Question 12
Can the Agency confirm that the listed safety data would be considered sufficient to support the NDA submission for (b) (4) *t for use in the proposed indication?*

FDA Response
Your proposal is not acceptable.

In the April 26, 2005 Pre-IND meeting, you were told that the total safety database should consist of at least 500 patients, of which at least 150 should be treated for at least 3 months. The majority of the patients should be treated with the highest- to- be- marketed dose. Complete, audited data meeting these specifications must be included in the NDA at the time of submission.

Discussion
There was no further discussion of this issue.

Regulatory Questions (2.4.6)

Question 13
Does the Agency agree that the totality of data proposed in the plan supports a 505(b)(2) application?

FDA Response
Provided you conduct an appropriate patent certification process, the proposed cross-references for the clinical and nonclinical packages appear acceptable.

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/cder/guidance/index.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Discussion
There was no further discussion of this issue.

Question 14
Would FDA consider such deferral/waiver (deferral of data in patients 7 years of age and older, and waiver of data in patients under 7 years of age) of pediatric studies for this product?

FDA Response
Studies in pediatric patients may be deferred until the use of (b) (4) is better understood in adults. Regarding your request for a waiver of PREA in patients under 7 years of age, in the NDA, you will need to provide a strong rationale to support your contention that the proposed indication does not exist in that population. The NDA must contain a pediatric plan at the time of submission.

Discussion
There was no further discussion of this issue.

Question 15
Does the Agency agree that the product is subject to categorical exclusion from the need to provide an environmental impact analysis?

FDA Response
Provide a request for a categorical exclusion from environmental assessment in the NDA, as per 21 CFR 25.31(b), based on the projected first 5-year sales of your product.

Discussion
There was no further discussion of this issue.

Question 16
Is this understanding (that the device will be evaluated as an integral part of the NDA and that CDRH will be consulted if needed) and proposal (to not submit a stand-alone device submission) correct?

FDA Response
Your understanding is correct. The Division of Anesthesia, Analgesia, and Rheumatology will be the lead review division. The Center for Devices and Radiological Health will act as a consultant for the device aspects of your product as needed. A stand-alone device submission is not necessary as it will be evaluated as part of the NDA.

Discussion
There was no further discussion of this issue.

Question 17
Does the Agency agree with this proposal (to submit a paper NDA in CTD format with SAS datasets submitted electronically as transfer files for the IND studies and the ISS)?

FDA Response
Your proposal is acceptable, although electronic submissions are preferable. You must ensure that the table of contents can direct reviewers to the correct page and physical volume, in addition to any reference to NDA section or module.

We remind you that the label must be submitted electronically and in the new physician labeling format (PLR).

Provide all materials related to the abuse potential evaluation of the formulation in a separate volume of the NDA for review. This volume should include primary data, data analysis and a discussion of the following areas, or clearly indicate exactly where in the NDA the following information is located:
- **Chemistry (Final formulation and product information)**
- **Pharmacokinetics and pharmacodynamics**

- **Primary data from any abuse potential study in animals and/or in humans that the Sponsor might have conducted**
- **Adverse events captured in clinical studies related abuse potential**
- **Integrated summaries of safety and efficacy (ISS and ISE)**
- **Assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, overdose and diversion during clinical studies**

Discussion
The sponsor stated that they do plan to submit their ISS in CDISC compliant format, but noted that all of the early data on the product is not in this format. Dr. Hertz stated that the sponsor should summarize what will not be available in CDISC format, state what format it will be in and the Division will review that with our electronic submission/CDISC experts to see if it is acceptable.

Question 18
Does the Agency agree with this proposal (to submit CRFs for deaths, other serious adverse events, withdrawals for AEs and any other adverse events associated with abuse or misuse and supply other CRFs upon request)?

FDA Response
Yes, we agree with your proposal to submit CRFs for deaths, serious adverse events, withdrawals due to AEs and adverse events associated with abuse and misuse. Provide narratives along for these same events.

Provide the following information and data related to abuse, misuse, diversion and overdose:

- **Descriptions of all reports and details, including narratives, of all incidents of abuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies.**

- **Narratives and case report forms for patients that drop out from studies where they were enrolled for reasons that might be coded as "protocol violation", "lack of efficacy" (to capture aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), "lost to follow up", "non-compliance to study medication or procedures," "over compliance" or for "other."**

Discussion
There was no further discussion of this issue.

Risk Management Questions (2.4.7)

Question 19
When would the Agency recommend submitting a full RMP to allow time to incorporate any recommendations in the RiskMAP prior to submission?

FDA Response
This product will require a Risk Evaluation and Mitigation Strategy (REMS). You must submit a complete REMS at the time of initial NDA submission. With regard to specific risk management strategies, we refer you to the Anesthetic and Life Support Drugs Advisory Committee Meeting convened on 6 May 2008 during which the risk management of a similar product was discussed. Your REMS must also address proper disposal of the residual fentanyl remaining in the device after use.

Discussion
The sponsor stated that they are aware of the May 2008 Advisory Committee (AC) meeting and are currently in discussions with experts in the Risk Management field (b) (4) and hope to develop a robust RiskMAP/REMS, but note that the requirements are evolving and requested a separate discussion of this topic with the Agency before submission of their application. Ms. Best stated that the Agency will provide an updated REMS template (see attmt 1), but noted that the Agency is not having individual meetings with firms at this point in time. A Guidance is under development but an issue date is not yet known.

Dr. Hertz stated that the sponsor will need to provide a complete REMS in their NDA, noting that the elements will have to include those discussed at the May 6, 2008 AC meeting. She stated that while surveillance is challenging, the firm is free to employ what's available unless they are able to devise a new system.

Question 20
Does the Agency have any recommendation in this regard (a mechanism to detect inappropriate prescribing early before it leads to harm)?

FDA Response
With regard to specific risk management strategies, we refer you to the Anesthetic and Life Support Drugs Advisory Committee Meeting convened on 6 May 2008 during which the risk management of a similar product was discussed.

Discussion
There was no further discussion of this issue.

Question 21
Does the Agency have any recommendation in this regard (best practice approaches to surveillance for patient misuse, particularly approaches that do not rely on detecting harm)?

FDA Response
See response to Question 20.

Discussion
There was no further discussion of this issue.

Question 22
Does the Agency have any other recommendations on how to minimize off-label prescribing?

FDA Response
See response to Question 20.

Discussion
There was no further discussion of this issue.

Question 23
Does the Agency agree that the choices of utilizing poison control center data, internet, media, pharmacovigilance reports, DAWN-Live!, and AERS are appropriate for monitoring for early signs of emerging abuse of (b) (4)

FDA Response
See response to Question 20.

Discussion
There was no further discussion of this issue.

Question 24
Can FDA provide more detailed recommendations on the appropriate methodology for analyzing and reporting these (events of interest such as misuse, abuse and diversion) events in clinical trials?

FDA Response
We recommend that you set criteria, collect data, and tabulate the abuse, misuse, noncompliance, and diversion cases across the studies and study sites with special attention to aberrant drug behaviors that may be indicative of drug abuse, misuse and diversion.

Important:

- **To prospectively define the criteria for which data will be collected, including the terms addiction, abuse, misuse, overdose, drug diversion/drug**

accountability, discrepancies of study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and "other" reasons for which subjects dropped out of the study.

- **To train clinicians participating in clinical trials in the recognition, assessment and coding of abuse related events to obtain consistent data across study sites**

Discussion
There was no further discussion of this issue.

Question 25
Does FDA have any recommendations on the best approaches to instructing clinicians in this (how to help clinicians screen for risk) regard?

FDA Response
We recommend that you consult with experts in the field of opioid misuse and abuse for information on methods to instruct clinicians in screening patients for risk of abuse and misuse.

Discussion
There was no further discussion of this issue.

Question 26
Please advise if any additional guidance on RMP or similar topics should be consulted or if Archimedes needs to address additional considerations related to REMS legislation introduced recently under FDAAA?

FDA Response
You propose a RiskMAP which is outlined in the briefing package. Any proposal including a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use as described under 505-1(e) of the Food and Drug Administration Amendments Act (FDAAA) should be submitted as a proposed Risk Evaluation and Mitigation Strategy (REMS). However, a complete review of your application will be necessary to determine what components will be essential to assure safe use and to ensure that the benefits of the drug outweigh the risks. Surveillance for patient misuse; prevent off-label prescribing, plans to monitor for emerging signals of abuse, and how to help clinicians screen for risk should all be addressed in your proposed REMS.

For information on the format and content of a REMS, we refer you to the approval letter for Entereg (available at http://www.fda.gov/cder/foi/label/2008/021775REMS.pdf).

Submit your REMS and REMS supporting document with your initial NDA submission and all planned materials identified within the proposed REMS that will be necessary to implement your proposal. Education should emphasize the

safety messages important for safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

If there is any information on product medication errors from the premarketing clinical experience, submit this information with the NDA application.

You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Discussion
The sponsor stated that they will submit another proprietary name as soon as possible, noting that (b) (4) was not acceptable for use (b) (4) and they would like to have a global product name.

Dr. Arnwine stated that the usual turnaround time for feedback on proposed colors and labeling is 60 days, but noted that any feedback may change up until 90 days prior to approval. In addition, she noted that the review time for a proposed proprietary trade name is 180 days during the IND phase. Dr. Hertz stated that while the Agency can comment on problematic items, they cannot guarantee names or color/labeling feedback until a 90-day period before the action.

Question 27
Does the Agency have any additional recommendations on minimizing risk?

FDA Response
The chosen colors, yellow for 100 mcg and blue for 400 mcg, are readily distinguishable from one another. However, the entire label, rather than colors exclusively, is the best indicator of whether errors are likely. Given the limited information regarding the labels, aside from the colors chosen for each strength, we will need to review the full label and labeling information before additional recommendations can be made.

(b) (4)

We recommend that the CRC correspond with the color coding of the product strengths to help prevent confusion with the 100-mcg and 400-mcg strength. Per the pictures in the meeting package, it appears that the CRCs for the 100-mcg strength and the 400-mcg strengths are identical, which may result in confusion if there is no name or strength on the CRC.

(b) (4)

(b) (4)
You will need to address proper product storage in the home in your REMS.

We agree that the appearance (b) (4) to alert the patient that the product must be primed when a new bottle is inserted provides an adequate visual cue; however, (b) (4) does not provide an intuitive signal to prime the device. You will also need to provide overall education, in addition to statements on the labels and labeling and CRC to inform patients, caregivers and providers that the device must be primed.

(b) (4)

(b) (4)

Discussion
The sponsor will change the name of the (b) (4) to reflect that it is actually a spray counter instead.

The sponsor stated that they had considered color-coding the CRC, but felt that it was safer not to color-code it, allowing it to remain unmarked/anonymous. The sponsor stated that all necessary information for proper dispensing will be on the carton, noting that the patient will have to remove the fully-labeled primary bottle from the CRC to administer it. A portion of the training the patient should receive with the product is that they are to carefully examine the label of the product before use. The sponsor stated that most patients will only have one strength in the home at any one time (outside of the titration phase.) The sponsor stated that during the titration phase, the patient use is to be highly supervised and even if an error did occur in this phase, it is likely to be the administration of a lower dose than that intended and so there would not be a clinical danger. If however, the patient does have two strengths in the home at once, they will have to open the CRC and examine the label to determine the strength before using it. Therefore, the sponsor feels that having a blank CRC will force the patient to look at the product label before using it.

Dr. Arnwine stated that OSE found the blank CRC proposal acceptable; however, she noted that if the blank CRC is pursued, the two bottles will need to be **easily** and **readily** distinguishable from on another.

The sponsor stated that they chose the colors provided with the help of expert consultants as these were the most easily distinguishable for those who were color-blind. They indicated that they understood the Agency's concern about (b) (4)

(b) (4), but noted that this product has a different route of administration and believes it will therefore not be as subject to confusion on this point. The sponsor also noted that (b) (4) from that of Fentora, but more like that of Actiq. The sponsor stated that they do not believe the (b) (4) leads to an increased risk, and will provide data to support that contention.

The sponsor stated that they could easily reverse the dose counter as requested, noting that the Guidance document for Metered-Dose Inhalers (MDIs) states that counters which count down are better understood by patients, but this product is different from MDIs, as is the message the sponsor intends to send through the counter—that the patient has taken a dose and should not take too much/more. The firm believes this is best conveyed by counting up and not down. The counter in the Phase 3 trials operates in this fashion and so the sponsor will have data on how this is interpreted by patients. Dr. Arnwine stated that there is evidence to show that it is more intuitive to have a dose counter count down. Dr. Hertz stated that if the sponsor had data to suggest otherwise, and that there is a relevant difference, the sponsor should submit it for the Agency to consider.

Dr. Arnwine indicated that the Agency would try to provide information on where further information on errors, etc, might be found into a Post-Meeting Note.

***POST-MEETING NOTE—
The recommendations discussed in the meeting are based on the March 2003 Guidance for Industry regarding Integration of Dose-Counting Mechanisms into MDI-Drug Products.

In addition, Dr. Hertz directed the company to information from the May 6, 2008 Advisory Committee.

Statistical Questions (2.4.7)

Question 28

(b) (4) *Does the Agency agree with this proposal?*

FDA Response

Your proposal is not acceptable. You will need to provide an integrated summary of safety (ISS), integrating the safety data from all the clinical studies in the development program for your product. Refer to the draft guidance, *Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.*

Discussion
The sponsor stated that they are considering the possibility of an electronic submission or eCTD submission and inquired if they submit electronically, how they

would present a "separate volume" for abuse liability. Dr. Hertz stated that the Division would add a Post Meeting Note to specify in what module the abuse liability section should be placed. If the submission is electronic, the section may just be hyperlinked, it does not need to be duplicated.

***POST-MEETING NOTE –
See Attachment 3 for information on placement of abuse liability materials in an eCTD submission.

The sponsor stated that they will submit a fully integrated summary of safety in Module 5 of their application. Dr. Hertz stated that the Agency expects an ISS to be a full integration of the trial results and any other information the sponsor is relying on for approval of the application. This integration should address how all the pieces together make up the application. The firm is expected to complete an integrated analysis which should address how their product is linked to any item(s) they are referencing, how their product is relevant to any other information on which they are relying, and how they believe this represents a complete application package for their product.

Dr. Hertz stated that the Division views Module 2 as a brief overview or summary, and stated that if the overall material the firm wanted to place there as a summary was small enough, it may be acceptable to present similar information as that in Module 5, but Section 2.7 is intended be a true summary.

Question 29

(b) (4)

FDA Response
Your proposal is not acceptable. You will need to provide an integrated summary of effectiveness (ISE). Refer to the "Guidance for Industry- Integrated Summary of Effectiveness"- http://www.fda.gov/cder/guidance/7694dft.pdf for the content of the ISE other than study data.

Discussion
There was no further discussion of this issue.

Office of Surveillance and Epidemiology (OSE) Comments

1. **Provide the complete description intended to instruct patients how to prime the device, including where the primed spray is to be directed and how much active ingredient is released with each prime.**

2. **Submit all usability studies performed to date.**

Discussion

The sponsor stated that they have usability and functionality data on this and have been focusing on human factors and plan to submit this with their application. Dr. Arnwine stated that if FMEA items are identified, and the firm makes modifications to address them, they will need to retest the revised product with the modifications before submitting the application.

3. **Most nasal products require one to two sprays in each nostril. However, this product is dosed one spray in one nostril which is not intuitive to users of nasal sprays. Provide any information on improper use of this device during clinical studies, e.g. the number of people during the studies who inadvertently sprayed twice if their prescribed dose was one spray.**

The sponsor summarized their understanding of the meeting as follows (includes action items):

1. The sponsor understands that the Agency strongly recommends using the final CRC packaging in their Phase 3 studies and will attempt to accomplish this.

2. The sponsor also understands that the Agency strongly recommends that the firm conduct performance testing and failure testing of the end-of use-lockout and submit these studies with the NDA.

3. For the ISS, the sponsor will submit whatever data it has available in CDISC format, and will provide a summary of format for remaining data in order for the Agency to evaluate how this should be acted upon.

4. Regarding risk management plans, the sponsor is familiar with the May 6, 2008 AC meeting and the points raised there and will attempt to address these issues in their REMS.

5. The Agency will provide a REMS template to the firm (see attachment #2).

6. The sponsor will submit their proposed proprietary name as soon as it is available, with an understanding that the timeline for review of names under INDs is 180 days and under NDAs is 90 days. Dr. Arnwine clarified that if the firm were to submit the name during the IND phase, the review clock would remain at the original 180 days with the NDA submission; the timeline does not accelerate with the submission of an NDA.

7. The sponsor will consider changing the colors of the labeling, but have data on the current colors from their trials.

8. There was agreement between the Agency and the sponsor that the CRC could appear bland and indistinct.

9. The sponsor plans to provide use and medication errors data on their approach to the dose-counter.

10. The sponsor understands that the ISS needs to integrate and present all available data for the product and any product(s) it is referencing. They further understand that if their summary is

concise enough, it may serve as the summary in Module 2 (2.7), but indicated they would re-examine their approach and amend their plans if needed as the Agency sees 2.7 as a true brief summary.

General CLINICAL Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: http://www.fda.gov/cder/mapp/6010.3.pdf.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 5.3 Exposure-Response Relationships - important exposure-response assessments.
3. Section 7.1.6 - Less common adverse events (between 0.1% and 1%).
4. Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.1.8.3.2 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.1.8.3.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.1.9.3. – Standard analyses and explorations of ECG data.
12. Section 7.1.16 – Overdose experience.
13. Section 7.4.2.1 - Explorations for dose dependency for adverse findings.
14. Section 7.4.2.2 - Explorations for time dependency for adverse findings.
15. Section 7.4.2.3 - Explorations for drug-demographic interactions.
16. Section 7.4.2.4 - Explorations for drug-disease interactions.
17. Section 7.4.2.5 - Explorations for drug-drug interactions.
18. Section 8.2 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites
7. Number of protocol violations (Major, minor, definition)

Common PLR Labeling Deficiencies

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).

6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin

mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

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

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

9. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

10. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]

11. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]

12. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

13. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

14. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

15. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

16. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

17. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

18. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.

19. When a subsection is omitted, the numbering does not change.

20. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

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

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

    "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

24. Do not refer to adverse reactions as "adverse events." Refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.

25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]

26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for

the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]

28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.

32. If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.

33. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

34. Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

CDISC Data Requests to Sponsors
Quantitative Safety and Pharmacoepidemiology Group

Safety Analysis Plan

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

Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).
At a minimum the Safety Analysis Plan should address the following components:

a. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment, http://www.fda.gov/CDER/guidance/6357fnl.pdf*).

b. Safety endpoints for Adverse Events of Special Interest (AESI)

c. Definition of Treatment Emergent Adverse Event (TEAE)

d. Expert adjudication process (Expert Clinical Committee Charter)

e. Data/Safety Monitoring Committee (DSMC): (Submit charter for FDA review) by

f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

g. When unanticipated safety issues are identified the Quantitative Safety Analysis Plan may be amended. Amendments should be filed in accordance with FDA regulations.

Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)

2. Domains
    a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, use these domains.
        - (DV) Protocol deviations
        - (DA) Drug Accountability
        - (PC, PP) Pharmacokinetics
        - (MB, MS) Microbiology
        - (CF) Clinical Findings

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

        - Tumor information
        - Imaging Data
        - Complex Inclusion/Exclusion Criteria

3. Variables

    a. All required variables are to be included.

    b. All expected variables must be included in all SDTM datasets.

c. Variables (expected or permissible) for which no values will be submitted must be explicitly stated and discussed with the review division.

d. A list of all Permissible variables that will be included and those that will not be included for each domain must be provided for review and discussed with the review division.

e. A list and description of all variables that will be included in the Supplemental Qualifier dataset must be provided.

f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

4. Specific issues of note:

a. SDTM formatted datasets must not provide replication of core variables (such as treatment arm) across all datasets.

b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.

c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues

1. Specify which ADaM datasets you intend to submit.

2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.

3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.

4. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.

5. Indicate which core variables will be replicated across the different datasets, if any.

6. SDTM and ADaM datasets must use the unique subject ID (USUBJID). Each unique subject identifier must be retained across the entire submission.

General Items

Controlled terminology issues

a. Use a single version of MedDRA for a submission. Does not have to be most recent version

b. We recommend that the WHO drug dictionary be used for concomitant medications.

c. Refer to the CDISC terminology for lab test names.

d. Issues regarding ranges for laboratory measurements must be addressed.

Integrated Summary of Effectiveness

Please refer to the Guidance for Industry located at the following web page http://www.fda.gov/cder/guidance/7694dft.pdf

Dataset Comments

The Division requests the following for the submitted datasets:

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

   The integrated safety dataset that must include the following fields/variables:

   a. A unique patient identifier
   b. Study/protocol number
   c. Patient's treatment assignment
   d. Demographic characteristics, including gender, chronological age (not date of birth), and race
   e. Dosing at time of adverse event
   f. Dosing prior to event (if different)
   g. Duration of event (or start and stop dates)
   h. Days on study drug at time of event
   i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)
   j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
   k. Marker for serious adverse events
   l. Verbatim term

2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT),

and system organ class (SOC) variables. This dataset must also include the Verbatim term taken from the case report form.

3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.

4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.

6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.

9. Also, for the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.

10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.

11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.

12. In every dataset, all dates must be formatted as ISO date format.

13. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.

14. All datasets must contain the following variables/fields (in the same format and coding):
    a. Each subject must have one unique ID across the entire NDA
    b. Study number
    c. Treatment assignment
    d. Demographic characteristics (age, race, gender, etc.)

15. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. Also, a listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.

16. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.

17. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

18. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Attachment 1

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

Attachment 2

RESPONSE TO REQUEST FOR INFORMATION ABOUT SUBMISSION OF PROPOSED REMS

We are providing this information in response to your request for information about how to submit a proposed REMS. We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document."

Attached is a suggested template for the Proposed REMS that you should complete with concise, specific information, as applicable. Additionally, all relevant REMS materials, such as enrollment forms, informed consents, and educational and communication materials should be appended to the Proposed REMS. We recommend that the Timetable for Assessments section specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval. Once FDA reviews the Proposed REMS and finds the content acceptable, we will include this document as an attachment to the approval letter for the REMS. The REMS, once approved, will create enforceable obligations

The second part of the submission should be a REMS Supporting Document that includes a thorough explanation of the rationale for, and supporting information about, the content of the Proposed REMS. This REMS Supporting Document should include the following sections 1. through 5., as well as a table of contents. For section 3., only those elements we have determined are necessary and are required should be included in the Proposed REMS :

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use
    c. Implementation System
    d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

The two parts should be submitted with an original application, as an amendment to an existing original or existing supplemental application, as a new supplemental application or with a new supplemental application. The submission should be prominently identified with the following wording in bold capital letters at the top of the first page of the submission.

When the proposed REMS is submitted as part of an original application:

NEW ORIGINAL APPLICATION FOR <name of drug>
PROPOSED REMS

When the proposed REMS is submitted as an amendment to an existing original or supplemental application:

NDA/BLA/ANDA [assigned #]
PROPOSED REMS

SUPPLEMENT [assigned #]
PROPOSED REMS

When the proposed REMS is submitted as a new supplemental application or with a new supplemental application:

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
PROPOSED REMS
< other applicable content identification >

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA/ANDA [assigned #]
PROPOSED REMS-AMENDMENT

SUPPLEMENT [assigned #]
PROPOSED REMS – AMENDMENT

REMS Template

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:
A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

Attachment 3

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information
1.11.4 Multiple Module Information Amendment
This section should contain:
• A summary, interpretation and discussion of abuse potential data provided in the NDA.
• A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.
• A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries
2.4 Nonclinical Overview
This section should include a brief statement outlining the non-clinical studies performed to assess abuse potential.
2.5 Clinical Overview
This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality
3.2.P.1 Description and Composition of the Drug Product
This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).
3.2.P.2 Description and Composition of the Drug Product
This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports
4.2.1 Pharmacology
4.2.1.1 Primary Pharmacodynamics
These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.
4.2.3.7.4 Dependence
This section should include:
• A complete discussion of the non-clinical data related to abuse potential.
• Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports
5.3.5.4 Other Study Reports
This section should contain complete study reports of all clinical abuse potential studies.
5.3.6.1 Reports of Postmarketing Experience
This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

Linked Applications	Sponsor Name	Drug Name
IND 70854	ARCHIMEDES DEVELOPMENT LTD	FENTANYL CITRATE 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/

KIMBERLY A COMPTON
10/21/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70, 854

Archimedes Development Limited
C/O Custom Regulatory Services
4170 Glen Devon Drive, N.W.
Suite 200
Atlanta, GA 30327-3616

Attention: Virginia O. Ackerman,
U.S. Agent

Dear Ms. Ackerman:

Please refer to your Investigational New Drug Application (IND) for Fentanyl Nasal Spray.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and FDA on August 24, 2006. The purpose of the meeting was to discuss issues related to your Phase 3 studies for your Fentanyl Citrate Nasal Spray (b) (4) 1.0 and 4.0 mg/mL product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: August 24, 2006
Location: White Oak, Building 22, Conference Room 1311
Application: IND 70, 854 Fentanyl Nasal Spray
Sponsor: Archimedes Development Limited
Proposed Indication: Management of breakthrough cancer pain in patients (b) (4) who are already receiving and who are tolerant to opioid therapy (b) (4) (b) (4)

Regulatory Status: Active IND
Type of Meeting: Type B- EOP2
Meeting Chair: Sharon Hertz, M.D., Deputy Division Director
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Minutes Recorder: Kimberly Compton, Project Manager, DAARP

Industry	**Title**
Archimedes Development Limited Representatives	
Virginia Ackerman, M.S.	Consultant and US Agent
Caroline Baird, BSc,	Head of Regulatory Affairs and Pharmacovigilance (Regulatory)
(b) (4)	(b) (4)
Anthony N. Fisher, Ph.D.	Director, Clinical Trials (Clinical)
Michael Hinchcliffe, PhD	Biological Group Head (Preclinical)
Helen Shaw, MD	Medical Director (Clinical / Risk Management)
Alan Smith, Ph.D.	VP Development (Developmental / General)
Peter Watts, Ph.D.	Director, Formulation (CMC /GMP)
Richard Rauch, M.D.	Principal Investigator
FDA	**Title**
Curtis Rosebraugh, M.D.	Deputy Director, ODE II
Robert Meyer, M.D.	Director, ODE II
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Jane Filie, M.D.	Medical Officer, DAARP
Danae Christodoulou, Ph.D.	Chemist, Office of New Drug Quality Assurance (ONDQA)
Mwango Kashoki, M.D.	Medical Team Leader (Pain), DAARP
Adam Wasserman, Ph.D.	Supervisory Pharmacologist, DAARP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader, OCP
Joan Buenconsejo, Ph.D.	Statistics Reviewer, DAARP
Dionne Price, Ph.D.	Statistics Team Leader, DAARP
Kim Compton	Regulatory Project Manager, DAARP
Janice Weiner, J.D.	Office of Regulatory Policy (ORP) (by phone)

Sharon Turner-Rinehardt	Regulatory Project Manager, DAARP
Anjelina Pokrovnichka, M.D.	Medical Officer, DAARP
Keith Burkhart, M.D.	Medical Officer, DAARP
Gita Akhavan-Toyserkani, Pharm.D.	Safety Evaluator, Office of Surveillance and Epidemiology (OSE)
Geoffrey Zeldes, M.D., Pharm.D.	Medical Officer, Controlled Substances Staff (CSS) (by phone)
Deborah Leiderman, M.D.	Director, CSS (by phone)

Meeting Objective: The purpose of the meeting was to respond to the questions posed by the sponsor in their meeting package of July 21, 2006, regarding their Phase 3 studies for their Fentanyl Citrate Nasal Spray (b) (4) 1.0 and 4.0 mg/mL product.

Background:
Presented below are Agency comments related to the sponsor's background material and responses to questions in the background meeting package. The sponsor's questions are listed in *Italics*, with Agency responses in **bold** and discussion that took place at the meeting in normal text following the question it regarded.

On August 22, 2006 (prior to the August 24, 2006 meeting) the Agency forwarded comments and responses to the questions posed by the sponsor. After reviewing the provided material, the sponsor elected to obtain clarification on the responses to Questions 1.1, 4.1, and 4.2.

Meeting:

Question 1.1
Archimedes has updated specifications scaled-up the manufacturing process and is conducting several process and product evaluations. (See section 11.) Does the chemistry, manufacturing and controls (CMC) information summarized in the pre-meeting package adequately cover the aspects that will need addressing to start a Phase 3 study using this route of delivery?

FDA Response
Yes. Provide additional information and clarify the following:

- **IMPURITIES**
  - **The proposed specification fo (b) (4) - (b) (4) is acceptable for the drug substance (b) (4) and the drug product (b) (4). In addition, provide a confirmation that no other related substances/degradants have been identified as structural alerts for mutagenicity.**

- **EXCIPIENTS**
  - **The revised specifications for [redacted]" are acceptable. Provide adequate CMC information on this excipient either in the NDA or in a cross-referenced DMF.**
  - **The use of phenyl-ethyl alcohol is common in nasal sprays and may cause confusion between the fentanyl inhaler and other commercial inhalation products. Provide adequate assurance of distinguishing and tracking this fentanyl product from other nasal sprays.**
- **PROCESS CHANGE**
  - **Introduction of the [redacted] is acceptable. Provide information on the drug [redacted]**
- **DELIVERY DEVICE**
  - **The secondary packaging in an opaque HDPE bottle with CR closure is acceptable.**
  - **The lock-out after the eighth (last) dose does not prevent patient overdose and you should address the safety of dosing frequency – refer to the Clinical comments in 6.2. Provide a description of the lock-out and clarify if it involves a timer, electronic circuit etc.**
- **EXTRACTABLES/LEACHABLES**
  - **The proposed study plans for extractables and leachables from device parts in contact with the drug product are acceptable. Provide information on the identification and quantification of extractables/leachables during Phase 3 and data supporting their safety.**
- **PERFORMANCE OF THE DEVICE**
  - **Patient in-use conditions with the spray used at an angle 30°C from vertical: Explain what the mean values of "83.83" and "81.25" represent in Table Y, page 94.**
- **STABILITY**
  - **Due to the decreasing trend observed for gel viscosity at elevated temperatures, the proposed temperature cycling studies are appropriate.**

Provide information on the temperature cycling studies during Phase 3. Note, that temperature cycling experiments should simulate storage and use conditions.

Discussion of Question 1.1

The sponsor stated that they wished to focus on the suitability of the pump design and its acceptability in the clinical setting as well as the number of sprays per bottle. Dr. Hertz stated that while it is early in development, the sponsor should consider the likelihood the product will be abused and to begin to consider methods to minimize the risk of misuse of this high-potency opioid product.

Any analgesic for breakthrough pain (BTP) takes some time to have an effect and, therefore, a patient who is in pain might use more sprays than originally intended while they are waiting for the product to take effect. Dr. Hertz stated that the sponsor should consider how different approaches can address this issue.

The sponsor stated that they intend for their product to have the following features:

a. thick-walled glass bottle with locked (unremovable) actuator
b. each strength clearly color-coded (in phase 3 trials)
c. simple-to-use device (to help ensure patient compliance)
d. red bars will appear in a window when the device is not ready to use (e.g., priming) and will move to green when the device is ready to use
e. clearly audible click when the product is actuated
f. visible counter so the patient will know when a dose is given
g. odor/sensation when product is dosed.
h. terminal lock after all doses are administered to differentiate the product from a normal inhaler.

The sponsor plans to limit the number of sprays per bottle to eight. The sponsor stated that the total drug in the bottle is appropriate for opioid-tolerant patients. There is about (b) (4) (b) (4) of product left in the bottle after all priming and dosing and the sponsor is working to reduce that amount. The sponsor pointed out that the reservoir cavity design with pointed tip was intended to provide efficient "emptying" of the product. The sponsor stated that each patient in the trials is to be trained in the use of the product using a dummy device and will receive detailed printed information on its use, as well. The sponsor plans to explore the efficacy of these measures in their clinical trials.

The sponsor stated that the nasal cavity cannot retain more than about 200 µL/nostril, and the product is designed to deliver doses of (b) (4) /nostril. The pectin in the product gels in the nasal cavity and, therefore, seems to modulate the C_{max} of the product. Cilia cause the gel to move along in the nasal cavity like mucous. The sponsor stated that, if the patient were to accidentally administer extra sprays, they would not gel with the product already in the cavity and would block the nasal cavity such that any excess product delivered (greater

than 200 µL/nostril) would go down the throat into the GI tract where it is less bioavailable. For these reasons, the sponsor feels their product is safe.

Dr. Hertz stated that the sponsor should perform pharmacokinetic (PK) studies to confirm that the use of more than two sprays per nostril would not result in any increase in exposure to fentanyl. The sponsor stated that they are willing to do so. Dr. Hertz noted that this study would provide information on what can be expected with this novel product, but that there was no absolute criteria to be met. Dr. Doddapaneni stated that performing studies on the 100-mcg strength should be acceptable for the Division to understand how the formulation behaves.

Dr. Rappaport stated that in terms of addressing misuse, abuse and diversion, and for accidental overdose as well, the most important data for the sponsor to submit is that which supports that only a specific amount of product goes into the nasal cavity with the rest going down the GI tract.

Dr. Rappaport stated that it would be useful for the sponsor to conduct an *in vitro* test to support their assumption that the pectin would not gel if the product were given intravenously (intentionally misused). The sponsor agreed to gather that data.

The sponsor confirmed that there are no electronic components to the lock-out mechanism, it is all mechanical.

The sponsor requested clarification on the comment about distinguishing the fentanyl nasal spray from other drug products with similar excipients. Dr. Christodoulou stated that color or appropriate secondary labeling to differentiate the product from other inhalers should be sufficient.

Question 1.2
Is the CMC development plan adequate for generating the appropriate data for the NDA filing?

FDA Response
Yes.

- **The proposed Phase 3 production plans and scale of the registration batches are acceptable for NDA filing.**

- **The proposed testing schedule for pilot-scale clinical/registration batches is acceptable.**

- **12 months of real time, and 6 months of accelerated stability data, are expected at the time of NDA submission.**

- **Provide a detailed pharmaceutical development report highlighting CMC bridging of changes in the formulation, process scale-up, and the device.**

- **Provide information on the additional testing planned, i.e., photostability, temperature cycling, particle size distribution (b) (4) and data on device robustness during Phase 3.**

- **Any new information identified during Phase 3 pertaining to additional testing as indicated above, i.e. characterization of extractables/leachables, performance of the device etc., should be discussed during the pre-NDA meeting.**

There was no further discussion of Question 1.2 beyond that provided in the Agency Response.

Question 2.1
Archimedes believes that the preclinical data package and cited literature are adequate and sufficient for supporting the Phase 3 clinical program and filing an application under 505(b)(2). (See section 12. Also see Appendix 4 – Pectin Safety.) Does the Agency agree the preclinical fentanyl data presented or referenced are acceptable and sufficient to support the proposed Phase 3 clinical program?

FDA Response
The nonclinical studies conducted, as well as information related to the safety of (b) (4) provided in the meeting package, appear sufficient to support the Phase 3 clinical program; however, acceptability of the chronic toxicology studies and the referenced pectin study for support of study CP045/06 will be made upon review of final reports.

You may rely upon studies not conducted by or for you and to which you have not obtained a right of reference of use (i.e., published literature or the Agency's finding of safety and/or effectiveness for a listed drug) to support your nonclinical development program.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/cder/guidance/guidance.htm for further information.

We also note that should a pharmaceutically equivalent product be approved before your application is submitted, such that your proposed product is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

There was no further discussion of Question 2 .1 beyond that provided in the Agency Response.

Question 2.2
Does the Agency agree that the pectin safety data presented or referenced are acceptable and sufficient to support the proposed Phase 3 clinical program?

FDA Response
See response to Question 2.1.

There was no further discussion of Question 2.2 beyond that provided in the Agency Response.

Question 2.3
Are these data acceptable and sufficient for ultimate NDA approval of a product specifically for the indication of breakthrough cancer pain under 505(b)(2)?

FDA Response
Submission of the nonclinical studies described along with information on pectin safety provided in the meeting package would support the submission of the NDA.

Acceptability of studies for support of NDA approval can only be made upon review of the final reports.

There was no further discussion of Question 2.3 beyond that provided in the Agency Response.

Question 3.1
Archimedes believes that the Phase I biopharmaceutics information is adequate and sufficient for supporting the Phase 3 clinical program and filing an application under 505(b)(2). (Refer to section 13.5.) Does the agency agree?

FDA Response
Yes. However, we remind you that you need to collect PK information in patients with rhinitis and rhinitis treated with oxymetazoline.

There was no further discussion of Question 3.1 beyond that provided in the Agency Response.

Question 4.1
Archimedes is developing NASALFENT for use in the restricted indication of breakthrough pain in cancer, the same indication as approved for Actiq®. Archimedes proposes that for the determination of efficacy the clinical development program be comprised of one statistically-powered, well-controlled Phase 3 clinical trial where NASALFENT Nasal Spray is tested against placebo, (similar in design to Actiq® as a 505(b)(2)), with approximately 80 patients to complete, using a cross-over design. See Appendix 5. See section 13 and Appendices 6 and 7 for the Phase 3 safety plans. Does the Agency concur with the design of the proposed pivotal clinical protocol contained in this package?

FDA Response
The design of the proposed pivotal clinical protocol (Study 1) appears adequate to evaluate efficacy.

We strongly recommend that the first dose of fentanyl citrate nasal spray be given in an observed setting in Study 1 and Study 3 given the high bioavailability of the study drug. This is an important type of safety data that is taken into consideration when determining the overall risk/benefit balance of the product.

You also need to provide guidelines (plans) for the management of adverse events, in the event that patients or care providers call with adverse events.

Discussion of Question 4.1
The Division clarified that the request for observation by a healthcare professional of administration of the 1st dose of the product was to provide data to support the safety of continuing dosing at home. It is not necessary to have the patient wait until they have a pain episode, but rather, the first dose could be a test-dose where, after administration, the patient is observed for over-sedation, nasal problems, etc. The sponsor should collect enough data to support that the product can be used safely at home without healthcare oversight. The sponsor stated that they could perform this observation with the 1st dose.

The sponsor verified that it is not a requirement of participation in the study to have a caregiver living with them around the clock.

Dr. Hertz stated that the firm should have instructions containing standard responses prepared for the call center to use in response to any patient or caregiver calls. She also noted that collecting data on drug accountability during Phase 3 studies is very important with this product.

Dr. Hertz stated that it will be very important for approval of the product to have data to demonstrate that the product can be used safely. She went on to say that the sponsor should

have a Risk Minimization Action Plan (RiskMAP) for the product that addresses how to prevent unintended exposures and pediatric exposures, accidental overdose by the patient, etc. A final RiskMAP, to include the tools, surveillance, educational materials, etc. that will be utilized in the plan, is needed at the time of NDA submission.

Dr. Meyer stated that, with a new dosage form, the sponsor should collect data in their Phase 3 trials documenting any problems with the device, and any problems should be noted and thoroughly investigated.

Question 4.2
Does the agency concur with the proposed dosing regimen regarding a) the titration phase, b) the dosing schedule for Study 3?

FDA Response
The dosing regimen for the titration phase seems adequate. The dosing schedule for Study 3 also seems adequate. Clarify the minimum safe interval between dosing for breakthrough pain episodes. This should be based on the pharmacokinetics of the product, the onset of action, and the duration of effect so as to avoid an unintended overdose.

Discussion of Question 4.2
The sponsor stated that they propose a minimum recommended time to re-dose of one hour in the long-term safety study, with a (b) (4) interval in the efficacy study and titration phase. Dr. Rappaport stated that a short interval in the safety study is a good way to demonstrate that a quick repeat-dose is safe, but he noted that the sponsor will need to provide strong support for why they propose to study something different than would be supported by the PK which shows a T_{max} closer to two hours.

(b) (4)
. The sponsor proposed a one-hour interval in the safety trial, to get a better representation of inadvertent patient increases in dose frequency. The sponsor stated that they do not want to prevent patients from taking more medication if they need it, but they have capped the number of BTP episodes in the safety study at not more than four per day.

The sponsor stated that the titration instructions for patients start with a 100-mcg dose and, after ½ hour, if they still have pain, allow them to take their normal rescue medication. For the next BTP episode, if the 100 mcg did not work for the last episode, the patient is to take a 200-mcg dose and keep increasing in that manner until they reach a dose that relieves their BTP. Once the patient finds a dose that works, they are instructed to take the 2nd dose at no more than four-hour intervals as needed for their BTP episodes.

Dr. Rappaport indicated that the Division would need to discuss the proposal internally and provide a decision in a post-meeting note.

***Post-Meeting Note:**

Sufficient data will need to be collected on the safety and efficacy of this product to provide adequate labeling on safe use. The dosing instructions in the package insert must be based on successful (safe and effective) use of the same dosing instructions during clinical studies. If the dosing regimen during the efficacy trial is different than the dosing in the label, the safety study must use the same dosing as the package insert. It would not be considered safe to initiate the safety study with a second dose earlier than four hours after the first until the PK characteristics of any earlier re-dosing have been fully elucidated. If as a result of a re-dose at one hour there is a substantially higher Cmax, patients should have not only the first dose, but a second dose at 1 hour monitored in a clinical setting for safety prior to being permitted to dose at home without medical supervision.

Question 4.3
Does the Agency agree that this study is capable of providing adequate evidence of effectiveness for the indication of breakthrough cancer pain?

FDA Response
Yes.

There was no further discussion of Question 4.3 beyond that provided in the Agency Response.

Question 4.4
Does the Agency agree that this study, if positive, taken with the Agency's prior finding of efficacy for Actiq (NDA 20-747) will be sufficient to demonstrate efficacy for approval under 505(b)(2)?

FDA Response
The proposed study (1) if positive, along with prior findings of efficacy for Actiq, would likely be adequate to support a finding of efficacy for this product.

There was no further discussion of Question 4.4 beyond that provided in the Agency Response.

Question 4.5

As per FDA's pre-IND meeting recommendations, Archimedes proposes a total safety database for the NDA (see section 13.6 and Appendices 6 and 7) of:

- *500 patients exposed to Nasalfent Nasal Spray*
- *a substantial number of patients treated at the highest-to-be-marketed dose.*
- *150 patients treated for at least 3 months.*

The nasal drug delivery system will also be evaluated in subjects with clinical conditions that may potentially alter the absorption of the product:

- *Seasonal/allergic rhinitis*
- *Upper respiratory infections*
- *Side effects of chemotherapy*

Will this be sufficient safety information to support this NDA for this restricted indication?

FDA Response

Your proposed program appears to be suitable to provide substantial support for this application. Additional information will be necessary to support the safety of a multiple-dose vial with a total of eight doses of fentanyl. Specifically, how can inadvertent overdose be avoided given the ease of dosing multiple consecutive sprays quickly?

We strongly recommend that you evaluate the PK of eight consecutive doses to determine the bioavailability of dosing in this manner.

There was no further discussion of Question 4.5 beyond that provided in the Agency Response.

Question 5.1

Archimedes proposes that the pharmacokinetic profile of nasally administered NASALFENT Nasal Spray together with the clinical studies proposed herein, along with the preclinical safety data, will support the submission of a 505(b)(2) application referencing Actiq® (NDA 20-747). Does the Agency concur with the approach as outlined?

FDA Response

A submission of a 505(b)(2) application for this product seems acceptable. However you must clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference. A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.

For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied

on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). (Listed in the Orange Book)

a. **Patent certification should specify the exact patent number(s) and the exact name of the listed drug or other drug even if all relevant patents have expired.**

b. **You must also submit a relative bioavailability study comparing the proposed product to the listed drug(s) (if any).**

There was no further discussion of Question 5.1 beyond that provided in the Agency Response.

Question 5.2
Would these data support the proposed draft labeling? (See Appendix 8)

FDA Response
It is premature to make any labeling determinations for this drug at this time. The adequacy of the content of the label will be determined at the time of the NDA review.

This package insert will need to comply with the format of the Physician Labeling Rule.

This product will require a medication guide rather than a patient package insert.

There was no further discussion of Question 5.2 beyond that provided in the Agency Response.

Question 6.1
Is the proposed draft Risk Management strategy appropriate for the conduct of Phase 3 clinical studies? (See Section 14)

FDA Response
Your draft RMP, which is based on a previous pre-IND discussion with the Agency, seems appropriate for conduct of Phase 3 trials and appears to cover the appropriate topics. We will work with you to further evaluate and expand the plan during the Phase 3 trials.

For the Phase 3 trials, ensure that the 100 mcg-dose and 400 mcg-dose vials are clearly distinguishable to avoid confusion between the vials using color coding and other methods.

The RMP will need to be finalized and submitted as part of the NDA. The final RMP will have to address any risks identified during the clinical studies.

As noted above, one element of risk minimization for this product that must be addressed is how inadvertent overdose will be avoided given the ease of multiple doses in rapid succession.

There was no further discussion of Question 6.1 beyond that provided in the Agency Response.

Question 6.2
Based on current available technologies and practice, Archimedes has incorporated the following into the multidose actuator to minimize the risks of diversion, abuse and accidental overdose

- *to limit the number of doses to a single day's treatment at the maximum recommended dose,*
- *the spray device having a dose counter with an audible click*
- *a lock out mechanism after the maximum daily dose (eight sprays) has been delivered*

Does the Agency agree that this is an adequate actuator design?

FDA Response
No, as designed, there is a possibility that more than 2 sprays, or even all 8 sprays, can be delivered at once. The risk of accidental or unintentional overdose in the patient population exists.

a. Design the device to limit the number of sprays available in a given time.

There was no further discussion of Question 6.2 beyond that provided in the Agency Response.

Question 6.3
Is the tentative proprietary name (b) (4) *acceptable?*

FDA Response
A full proprietary name review will be performed at the time of the NDA submission.

There was no further discussion of Question 6.3 beyond that provided in the Agency Response.

General Comments--

Clinical Comments

Study 2 is an open-label study and, as such, is not considered an adequate and well-controlled study design and would not be considered suitable to support any comparative claims against Actiq. To support any comparative claims, two adequate and well-controlled studies are required.

Statistical Comments

The following comments should be addressed in the statistical analysis plan.

- **During the double-blind treatment phase, patients will be allocated to 10 treatments (7 active, 3 placebo). Specify the possible treatment combinations (sequence).**

- **In the cross-over trial design, patients have observations from each treatment period and these observations are correlated as they originate from the same person. Your analysis should, therefore, use appropriate methodology to analyze dependent observations (i.e. inclusion of subject, period, and/or sequence effects in the model).**

- **Your proposed model may include a term for the "dose number." Clarify what is meant by "dose number."**

- **For the primary analysis (i.e. intent-to-treat population), provide specific details regarding your plan to handle missing data for patients who discontinue from the study and for patients with intermittent missing observations.**

Closing Discussion

Dr. Hertz clarified for the sponsor that the Division is concerned about the risk of administration of inadvertent extra doses resulting in an accidental overdose by the patient, as well as intentional misuse and diversion, indicating that the latter should be addressed in the RiskMAP. Dr. Rappaport stated that, in terms of abuse, the sponsor will need to clearly instruct patients on how to dispose of the product and will need to devise a way to safely dispose of any remaining product (since the top is locked on). The sponsor indicated that they understood the issue and that the outcome of their attempts to change the bottle and decrease the residual product remaining in it after use will have bearing on the disposal issue and instructions.

Dr. Hertz indicated that the sponsor may wish to submit a RiskMAP to their IND and the Division will consult to OSE and CSS and then provide feedback to the sponsor.

The sponsor summarized their understanding of the meeting as follows (includes Action Items):

- The sponsor agreed to complete the PK study on the exposure following repeated doses with the 100-mcg dose in normal volunteers.
- The sponsor will provide data on the nasal cavity capacity.
- The sponsor will complete an *in vitro* study on the gelling of pectin.
- The sponsor will gather data on the 1st dose administration by having the 1st dose being observed by a medical professional. This 1st dose observation may not be necessary for every patient if no safety concerns arise during the efficacy study and during the enrollment during the safety study. .
- The sponsor will provide to the Agency a procedure for the management of adverse events by the study site.
- The RiskMAP will be discussed with the Agency prior to its completion and submission.
- The sponsor will continue to work on improving the product to decrease the risks associated with disposal of the product and to design appropriate disposal methods for the resulting final design.
- The sponsor will look for and investigate device malfunctions.
- The sponsor plans to proceed to Phase 3 studies.
- The sponsor awaits the Division's response on the proposed dosing intervals (one and (b) (4)) in a post-meeting note.

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/s/

Kimberly Compton
9/20/2006 04:32:03 PM