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APPLICATION NUMBER:

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Summary Review for Regulatory Action

Date	June 30, 2010
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	22-569
Applicant Name	Archimedes Development Limited
Date of Submission	August 30, 2009
PDUFA Goal Date	June 30, 2010
Proprietary Name / Established (USAN) Name	none/ Fentanyl nasal spray
Dosage Forms / Strength	Nasal spray 100 mcg/spray and 400 mcg/spray
Proposed Indication	For the relief of breakthrough pain in opioid-tolerant cancer patients
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Clinical Review	Luke Yip, M.D. (efficacy) Nick Olmos-Lau, M.D. (safety)
Statistical Review	David Petullo, M.S.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Sheldon Markofsky, Ph.D.; Prasad Peri, Ph.D.
Microbiology Review	Steven Fong, Ph.D.; David Hussong, Ph.D.
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DSI	Roy Blay, Ph.D.; Tejashri Purohit-Sheth, M.D.
CDTL Review	Robert B. Shibuya, M.D.
OSE/DMEPA	Loretta Holmes, B.S.N., Pharm.D.; Kristina Arnwine, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	Gita A. Toyserkani, Pharm.D.; Megan Moncur, M.S.; Jeanne Perla, Ph.D.; Claudia Karwoski, Pharm. D.
DDMAC	Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D.
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OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DDMAC=Division of Drug Marketing, Advertising and Communications

1. Introduction

Archimedes Development Limited has submitted this application for a fentanyl nasal spray product intended to treat episodes of breakthrough pain in cancer patients who are already being treated with round-the-clock doses of an opioid analgesic for their background cancer pain. There are three transmucosal fentanyl products already approved for this indication: Actiq, a lozenge on a stick approved in 1998; Fentora, a buccal tablet approved in 2006; and Onsolis, a buccal soluble film approved in 2009. As with the Fentora and Onsolis applications, this is a 505(b)(2) application referencing NDA 20-747 for Actiq, and the evidentiary basis for a finding of efficacy for fentanyl nasal spray is a single, adequate and well-controlled clinical trial of a design based on the original studies performed for Actiq. The major regulatory concerns related to this application have been the development of an adequate Risk Evaluation and Mitigation Strategy (REMS) and concerns related to the spray device, including a large quantity of residual fentanyl after maximal use, potentially unsafe priming procedures, ease of access to the fentanyl solution, and the potential for inadvertent excess dosing and surreptitious abuse due to flaws in the dose-counter mechanism.

2. Background

Fentanyl is an extremely potent opioid (approximately 80 times more potent than morphine) that has the potential to cause serious morbidity and death due to respiratory failure if administered to a non-opioid tolerant person. It is also a highly sought after drug of abuse and sells for a high price on the street when either legitimate product is diverted or illicit product, known as China White, becomes available.

This application represents the fourth NDA for a transmucosal fentanyl formulation, but the first intended for nasal mucosal absorption. Actiq was the first oral transmucosal fentanyl product approved and is a lozenge on a stick that is moved between the gum and the buccal mucosa. Actiq was approved under Subpart H, in large part because of the risk for accidental pediatric exposure due to the similarity in its appearance to a lollipop. A Risk Management Plan (later defined as a RiskMAP) was created to attempt to manage some of the risk associated with that product. In addition to identifying the risk for accidental pediatric exposure and providing some methods to try and minimize that risk, other goals described in the RiskMAP included preventing use in opioid non-tolerant patients and other off-label uses. The only clearly unique adverse event associated with Actiq in post-marketing experience has been the occurrence of dental caries, related to the sugar content in the Actiq lozenge.

Fentora was the second oral transmucosal fentanyl formulation approved and is a tablet that is placed between the buccal mucosa and gum where it dissolves with an element of effervescence. The only adverse event associated with Fentora that differed from Actiq in pre- and post-marketing experience was the occurrence of local ulcers in the mouth at the site of drug exposure. Fentora was approved with a RiskMAP comparable to Actiq. Actiq and Fentora were approved for the same indication sought by the applicant, the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The intended population is already on around-the-clock opioids for pain and has episodes of pain that stand out from their background pain. This indication reflects the need for a specific treatment to meet the needs of cancer patients with breakthrough pain, characterized by a relatively early onset of action, relatively short duration of action and high analgesic potency. Fentanyl is a very potent opioid that can cause respiratory depression in microgram quantities. For this reason, the indication also reflects the need for patients to be opioid tolerant, a physiological state in which patients are able to tolerate higher opioid doses without experiencing the CNS and respiratory depression associated with these drugs.

(b) (4)

Based on the post-marketing history of Actiq, it has become clear that prescribers have found Actiq to be useful in patients without cancer pain, both in the settings of chronic non-cancer pain with episodes of breakthrough pain and other chronic painful conditions not generally associated with breakthrough pain episodes. Of note, use of the term

breakthrough pain in non-cancer pain is somewhat controversial. In the Actiq RiskMAP quarterly reports, the use of Actiq in non-cancer pain has exceeded its use in cancer pain, although it is used primarily in opioid tolerant patients with chronic non-cancer pain.

Fentora has greater bioavailability than Actiq and the formulation is less easily removed from the mouth once dosing has begun. Efforts were made to make the difference in bioavailability clear in the Fentora labeling with specific statements that patients should not be converted from Actiq on a mcg for mcg basis and that Fentora is not a generic version of Actiq. However, post-marketing reports have demonstrated a variety of medication errors that include direct conversion on a mcg for mcg basis by prescribers and product substitution at the pharmacy level, in addition to incorrect dosing instructions. The quarterly RiskMAP reports document the very disturbing trend of a steadily increasing frequency of use in patients who are not opioid tolerant. In the first year of marketing there were two deaths reported in patients prescribed Fentora for headache.

As a result of the post-marketing information from Actiq and Fentora, it appeared that the RiskMAP in place for Actiq and Fentora was not effective in mitigating the risks of these products. During a joint meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees on May 6, 2008, the committee members heard presentations from the FDA, SAMHSA and Cephalon, the NDA holder for Actiq and Fentora, about the risks associated with Fentora and the failure of the RiskMAP to mitigate those risks. The committee recommended a more comprehensive program that included patient and physician registration and improved risk communication.

Onsolis was approved with a REMS, as authorized under the Food and Drug Administration Amendments Act passed in September of 2007. The Onsolis REMS, known as FOCUS (Full Ongoing Commitment to User Safety) calls for dispensing Onsolis via specialty pharmacies. The specialty pharmacies ship Onsolis by traceable courier to enrolled patients only after all of the following criteria have been met:

1) the prescription has been written by an enrolled prescriber for an enrolled patient

2) the prescriber has faxed the prescription to a central or regional pharmacy

3) the FOCUS pharmacy has verified that the prescriber and the patient are both enrolled, that the patient has received a FOCUS program counseling call to review the safe use conditions, and that the prescriber has counseled the patient

An additional component of the FOCUS program include a plan to re-counsel and re-enroll prescribers, patients and pharmacies when substantial changes are made to the program or at an interval of at least every two years. If an enrolled patient transfers to another prescriber, the patient and new prescriber must complete a new FOCUS program patient enrollment form. There is also a distribution and prescription data monitoring plan.

Finally, the plan requires that each FOCUS pharmacy keep a record of delays in patients receiving the drug of greater than 72 hours from the time the prescription was received by the pharmacy. The reasons for the delays are to be investigated and reviewed monthly. There has been limited prescribing of Onsolis since its approval, therefore it is not possible at this time to assess the impact of the FOCUS program on safe use of the product.

Archimedes has submitted a REMS as requested in the Pre-NDA meeting that was held on September 22, 2008. The details of their REMS are discussed below in Section 13. However, the spray device used to deliver the fentanyl to the nasal cavity is inadequately designed to protect the patient, caregivers and other family members, and health care providers from inadvertent exposure to or unintended doses of fentanyl. In addition, the device can be easily separated to remove the fentanyl solution by those intent on abuse and/or diversion, and the residual quantity of fentanyl solution after all primings and actuations is unacceptably high.

3. CMC

This product contains fentanyl citrate in an aqueous solution that includes pectin. When the solution is sprayed into the nasal cavities and upon contact with divalent calcium ions in the nasal mucus the pectin forms a soft gel which purportedly modulates the delivery and absorption of fentanyl through the mucosal tissues and into the systemic circulation. The formulation also contains (b) (4) mannitol, (b) (4). The solution is contained in a glass bottle with a locking screw closure, and with a (b) (4) metered-dose nasal spray pump that incorporates a visual and audible spray counter and an end-of-use lock. There are two formulations: 1.0 mg/mL and 4.0 mg/mL fentanyl base. Each actuation of the pump delivers (b) (4) of solution containing 100 mcg or 400 mcg of fentanyl. After priming, the pump delivers up to 8 sprays and then locks. The fill volume (b) (4) This results in (b) (4) of fentanyl base remaining in the bottles for the low and high concentration products, respectively, after maximal use.

Drs. Markofsky and Peri found the DMF for fentanyl citrate to be adequate to support the NDA. The drug substance specifications were also found to be adequate. While the drug product specifications and the 24-month expiry dating were found to be acceptable, the following concerns led the CMC review team to recommend that the application not be approved at this time:

- The pump system can be unscrewed from the glass container without using any tools, permitting relatively easy access and the potential for inadvertent exposures or frank abuse and diversion.

- There are flaws in the pump assembly that could lead to incorrect priming, dose counting errors, and contact of the fentanyl with the user's hands.

- There is an unacceptably large quantity of residual fentanyl solution remaining after use.

The facilities review and inspection were found to be acceptable. Dr. Fong has concluded that the application should not be approved at this time as the applicant has not provided data to demonstrate that the drug product does not contain Burkholderia cepacia. In addition, they have not provided a validated detection assay. Burkholderia cepacia poses a special threat to individuals with compromised immune systems. It tends to be resistant to preservatives, can survive in nutrient-poor conditions, and has been the cause of several nasal spray recalls.

I concur with the review team that the flaws that are inherent in the current design of this product preclude its approval at this time and that they must complete the microbiological evaluation as per the Agency's prior request.

4. Nonclinical Pharmacology/Toxicology

The applicant submitted 3- and 6-month toxicology studies in rats and a 9-month toxicology study in dogs performed with delivery via the nasal cavity. The histopathological examinations in these studies focused on the nasal cavity, nasopharynx and lung, and found no concerning pathology. The impurity (b) (4) which contained a structural alert for genotoxicity, was adequately qualified and Drs. Bolan and Mellon have concluded that the application could be approved without post-marketing studies.

I concur with the review team that no additional nonclinical pharmacology or toxicology data are necessary for approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the pharmacokinetics of this product (b) (4) was the original trade name proposed by the applicant but it has been found to be unacceptable by DMEPA) has been reproduced from page 3 of Dr. Agarwal's review:

> The relative bioavailability of (b) (4) compared to Actiq® is ~ 120%. Cmax and AUC values for (b) (4) increase with an increase in dose through 100 to 800 mcg and appear dose linear. Median Tmax values range from approximately 15 - 20 min post-dose. A 2 h lapse between two consecutive administrations of (b) (4) is recommended based on lower PK variability (as compared to a 1 h lapse), Tmax range of (b) (4) observed across all the PK studies submitted and frequency of breakthrough pain episodes in the patient population this product is indicated for. (b) (4) absorption in subjects with allergic rhinitis (Active/Untreated) is similar to asymptomatic conditions indicating that presence of rhinitis does not affect absorption of (b) (4). However, (b) (4) absorption in subjects undergoing treatment for allergic rhinitis with oxymetazoline, a vasoconstrictive nasal decongestant, is significantly altered with mean Cmax being significantly lower and mean Tmax being significantly longer as compared to Asymptomatic or Active/Untreated conditions indicating that there exists a possibility of delay in absorption and compromise in efficacy and when a vasoconstrictive nasal agent is co-administered with (b) (4).

The applicant submitted a relative bioavailability study comparing their product to Actiq. That study demonstrated that the fentanyl nasal spray is approximately 20% more bioavailable compared to Actiq at equivalent doses. This will require specific labeling to address the potential for switching from one transmucosal fentanyl product to another. In

general, the nasal spray should always be titrated up from the lowest dose, whether or not the patient is being switched from another transmucosal fentanyl product.

Fentanyl nasal spray is indicated to be used only once per breakthrough cancer pain episode, i.e., it should not be redosed within an episode during either the titration or maintenance phases. The sponsor has recommended a (b) (4) interval between doses during the maintenance phase of treatment. However, based on her review of the pharmacokinetic data, Dr. Agarwal has recommended that a 2-hour dosing interval is acceptable for the maintenance phase. During the titration phase of treatment, if a single dose of fentanyl nasal spray results in inadequate analgesia, patients are to use their customary breakthrough pain therapy (after 30 minutes) as directed by their healthcare provider.

The applicant also studied the effects of allergic rhinitis and concomitant oxymetazoline administration on the absorption of the fentanyl spray. No clinically relevant interactions were noted.

I concur with the review team's conclusion that no additional clinical pharmacology or biopharmaceutics studies are necessary for approval of this application.

6. Clinical Microbiology

There are no clinical microbiology concerns for this application.

7. Clinical/Statistical-Efficacy

Study CP043/06/FCNS enrolled subjects into an open-label, dose-finding period. Dosing was initiated at 100 mcg and increased if an episode of breakthrough pain was inadequately treated. The dose was titrated up from 100 mcg to 200 mcg to 400 mcg to 800 mcg. Subjects were discontinued at any time for intolerable side effects or if they were titrated to 800 mcg without achieving adequate pain control. When a dose level was found to be acceptable, e.g., adequate analgesia and tolerability were achieved, it was repeated for the next episode of pain. If the repeat dose was also successful, that dose was considered to be the subject's titrated dose and the subject was then entered into the double-blind period of the study on that dose.

For the double-blind period, ten doses of study drug were dispensed to each subject; seven were the subject's titrated dose, and three were placebo doses which were randomly assigned to three of the ten breakthrough pain episodes to be treated. Pain intensity was measured on an 11-point numerical rating scale at pre-dose and 5, 10, 15, 30, 25 and 60 minutes post-dose. The primary efficacy endpoint was the SPID30, or summed pain intensity difference from baseline to 30 minutes.

A total of 139 subjects were screened, 114 entered the open-label titration period, and 83 were successfully titrated to a dose of study drug and comprised the intent-to-treat population. Of the 31 subjects who were unable to complete the titration, 6 (5.3%) were unable to tolerate the drug and 7 (6.1%) were unable to achieve an effective level of

analgesia. Other common reasons for discontinuation during the open-label titration period included: did not continue to meet the inclusion/exclusion criteria, 4 (3.5%), and withdrawal of consent, 5 (4.4%). Only 73 subjects completed the study. The explanations for why the 10 subjects discontinued during the double-blind period were varied and did not result in concerns related to the study conduct. The applicant performed their primary efficacy analysis on a modified-ITT population. However, Mr. Petullo performed the analyses on several different populations and found consistent results. The following table, reproduced from page 12 of Dr. Shibuya's review, summarizes Mr. Petullo's analyses:

Table 5: Study 43, FDA's Primary Efficacy Analysis (Applicant's analysis also shown)

Source	Mean $SPID_{30}$ (stdev)			
	Placebo	Fentanyl	Difference	p-value
Applicant, n=73	4.5 (5.5)	6.6 (5.0)	2.1	<0.001
As treated, n=80	4.6 (6.4)	6.0 (6.1)	1.4	<0.001
As randomized, n=80	4.7 (6.2)	6.0 (6.2)	1.3	<0.001

Source: Mr. Petullo's review, page 9/20

The secondary endpoint analyses were supportive of the primary endpoint results. I concur with the clinical and statistical reviewers that the applicant has provided adequate evidence that this product is effective when used according to the proposed labeling.

8. Safety

As with all studies in cancer patients with breakthrough pain, the review of the adverse events for this application was complicated by the fact that the subjects were already quite ill, and many were experiencing significant toxicities related to the treatments for their underlying cancer and the complications associated with the disease. In addition, there were numerous comorbid conditions and, of course, toxicities associated with the subjects' baseline opioid therapy. Finally, since the study design is a 10-period crossover, there is always the potential for some carry-over effect, even with the relatively long dosing intervals. Nevertheless, no unexpected or unusual adverse events were noted in the overall safety database submitted in this application.

There were 88 deaths. Drs. Olmos-Lau and Shibuya concluded that none of these deaths could be clearly attributed to exposure to the study drug. However, it is certainly possible that some of the deaths may have been indirectly related due to the high doses of opioids these patients were being exposed to. Similarly, while many of the non-fatal serious adverse events (which occurred in 70 subjects) and many of the adverse events leading to the discontinuation of 74 subjects may have been exacerbated by exposure to the fentanyl, (e.g., constipation), none appeared to be directly and solely caused by study drug exposure, and the majority appeared to be due to progression of the underlying disease.

The most common adverse events were also, for the most part, those seen with exposure to potent opioids. One exception was pyrexia, which is an event one would nevertheless expect to see in this patient population. Nasal examinations were performed in all of the clinical studies and no significant abnormalities were noted. Adverse events involving the nasal cavities were infrequent and mild.

I concur with the clinical review team that there are no safety concerns specifically related to the proper and labeled use of the product that would preclude approval of this application. However, there are, as noted above, a number of safety concerns related to the design of the product delivery system.

The container-closure system includes a child-resistant outer container for storage when the product is not in use. The drug delivery device itself is, as described above, a spray mechanism that is screwed onto a glass bottle that contains the fentanyl in solution. The plastic spray pump is not glued or crimped to the bottle and the review team found that it could be removed with bare hands by using moderate force. This then permits easy access to a large quantity of fentanyl solution, even after maximal use. On examination of samples provided by the applicant, the review team also found that the device could be easily separated at a point that would allow access to the tubing that accesses the solution, and they observed fluid leaking from the tube when the device was opened in this manner. They also found that the dose-counting mechanism could be easily separated from the spray pump, which could allow for manipulation of the dose counter and then reassembly.

There are additional concerns related to the delivery device as summarized by Dr. Shibuya on page 20 of his review:

> Dr. Olmos-Lau described eleven patients being treated with PecFent who believed that the device either failed to deliver any dose or failed to deliver a full dose. Because of this perception, some patients immediately redosed and one patient suffered a serious adverse event as a consequence. Having seen how the devices work and smelled the product, I believe that adequate patient training and education (to properly actuate the device, to trust the click and counter, and not to redose within two hours) should adequately address the potential for accidental overdose due to confusion about whether the device actuated or not.
>
> While there was a visible plume and an audible click with each actuation, we found that by carefully modulating the force of the actuation, the device could spray without advancing the counter (undercounting). Thus, it is possible for household contacts to use the device undetected by the patient or caretaker.
>
> As noted in Section 2 of this review, the Applicant has been advised on multiple occasions to address the amount of residual remaining in the device after 8 actuations. The Applicant has attempted to optimize the bottle design with a U-shaped cavity to minimize the residual fentanyl solution. According to the Applicant, a fill volume of (b) (4) is optimal to ensure consistent delivery of the desired delivered volume of 100 mcL with a minimal residual volume in the bottle. More than (b) (4) remain in the bottle after full delivery as shown below. In studies of the device, the Applicant found that (b) (4) was recovered.

Activity	Volume dispensed (mL)	Volume remaining (mL)
Full new bottle	(b) (4)	(b) (4)
Priming		
Eight x 100 mcL sprays		

After complete use, each device contains approximately (b) (4) of fentanyl [for the high concentration (4 mg/mL)] solution. Since some patients might use more than one device per day (one device contains as few as 4 doses), a substantial amount of fentanyl could be in the garbage of these patients.

The Applicant proposed to dispose of the fentanyl lost due to priming and any unneeded sprays left in the bottle by (b) (4) This is unacceptable; the chance of transfer of fentanyl to the patient or household contacts is too high. We notified the Applicant of this inadequacy in a 24 March 2010 Discipline Review Letter.

I concur with these concerns. In addition, I think that training and education may not be adequate to assure the safe use of the product by all patients, particularly patients with cognitive impairment and/or mental clouding due to opioid and other drug exposure.

9. Advisory Committee Meeting

The review team determined that an advisory committee meeting was unnecessary for this new formulation of fentanyl as there were no unusual issues related to its safety or efficacy compared to the previously approved products in the class, and there was adequate expertise within the Agency to address the product concerns related to the device and the risk management program.

10. Pediatrics

From page 22 of Dr. Shibuya's review:

> In line with the other "fentanyl for breakthrough cancer pain" products, the ages of birth to 2 years, 11 months may be waived because the numbers of patients available for study are too small. Because the efficacy of opioids may be extrapolated from efficacy in adults, efficacy will not have to be demonstrated in pediatric patients age 3-16 years. However, the Applicant will have to complete a safety and pharmacokinetic study to inform dosing. At the Pediatric Research Committee meeting discussing this NDA, the committee recommended that open-label safety data be collected for a duration of 4-weeks in 30 subjects to adequately address the potential for local irritation.

11. Other Relevant Regulatory Issues

From page 22 of Dr. Shibuya's review:

> The Division of Scientific Investigations (DSI) inspected two sites, both of whom participated in Study 43. While DSI found the data to be acceptable overall, they recommended excluding data from a total of 4 patients because of a lack of documentation of concomitant medications and it was unclear how many doses of study drug one patient administered.

Per their memo dated June 29, 2010, the statistical team reanalyzed the primary endpoint for Study 43, excluding three patients identified by DSI. One of the patients identified by DSI was a screen failure who was not included in the initial analysis. The exclusion of the three patients did not change the interpretation of the study.

12. Labeling

The review team has provided preliminary recommendations regarding changes to the applicant's proposed labeling. However, final labeling discussions will not occur until the applicant addresses the concerns raised during this review cycle in a resubmission.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Complete Response

- Risk Benefit Assessment

  While the applicant has provided adequate evidence to support the efficacy of this product, there are significant design flaws in the delivery device that make its use unsafe for patients, caregivers, family members and health care workers. These flaws include:

  - The device can be opened without an undue amount of effort using only the bare hands, allowing access and possible inadvertent exposure and significant risk for serious adverse consequences.

  - The dose counter can be tampered with allowing for misuse and abuse of the product.

  - An appropriate mechanism for disposal of the residual fentanyl solution after maximal product use has not been delineated.

  The large quantity of residual fentanyl solution after maximal use is particularly concerning due to the high potency of fentanyl and the fact that it is one of the most sought after drugs of abuse. Without the ability to prevent these large quantities of fentanyl solution from gaining access to the community, either inadvertently or by deliberate diversion, the public health risk is considerable. While the applicant's current iteration of their REMS for this product addresses some of the issues related to these risks, it does not adequately address the problems inherent in the product design.

In addition, the applicant has not provided data to assure that the product will not be at risk for contamination with Burkholderia cepacia, a bacterium that could place immune-compromised cancer patients at particularly high risk.

Therefore, the risks associated with the current design of this product and the absence of important data regarding its potential for bacterial contamination outweigh its benefits, particularly in light of the fact that there are three approved OTF products already on the market.

- Required Postmarketing Risk Evaluation and Mitigation Strategy

The applicant did submit a REMS with the NDA, and that REMS included a MedGuide, a Communication Plan, Elements to Assure Safe Use including certification of prescribers and pharmacies, patient registration and documentation of safe use conditions by the pharmacist, and an Implementation System and Timetable for assessments. (b) (4) The applicant was advised of this deficiency in a teleconference on April 16, 2010 and the applicant submitted an amended REMS on May 19, 2010.

As the development of REMS for the OTF products has progressed, several different approaches have been pursued by sponsors. Based on our internal discussions, the approach described by the applicant has been found to be acceptable with the modifications provided. This approach includes prescriber enrollment following completion of the program educational materials, counseling of patients, and pharmacy enrollment and pharmacist training. In response to requests from the Agency, the applicant has amended the program to assure that non opioid-tolerant patients will not receive the product, and to assure that prescribers will counsel their patients and attest to having performed that counseling. Based on the use of electronic pharmacy systems, the product will only be dispensed when an enrolled pharmacy can identify that the patient and his or her health care practitioner have both been enrolled as well.

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
06/30/2010