CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209128Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113059

MEETING MINUTES

AcelRx Pharmaceuticals, Inc.
351 Galveston Drive
Redwood City, CA 94063

Attention: Lana Chin
Sr. Director, Regulatory Affairs

Dear Ms. Chin:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food Drug and Cosmetic Act for sufentanil sublingual tablet (ARX-04).

We also refer to the meeting between representatives of your firm and the FDA on December 9, 2015. The purpose of the meeting was to discuss the planned 505(b)(2) NDA submission.

A copy of the official minutes of the meeting is enclosed 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) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type/Category: Type B/Pre-NDA
Meeting Date and Time: December 9, 2015 (3:00 p.m. Eastern Time)
Meeting Location: White Oak Bldg 22, Conference Room 1313
Application Number: IND 113059
Product Name: Sufentanil sublingual tablet (ARX-04)
Proposed Indication: Management of moderate to severe acute pain in a medically supervised setting
Sponsor Name: AcelRx Pharmaceuticals, Inc.

AcelRx Pharmaceuticals, Inc. Representatives	**Title**
Lana Chin	Sr. Manager, Regulatory Affairs
Majella Dooley	Sr. Director, Regulatory Affairs
Pamela Palmer, MD, PhD	Chief Medical Officer
Mike Royal, MD, JD, MBA	Chief, Clinical Affairs
Yu-Kun Chiang, PhD	Statistical Consultant to AcelRx
Mark Evashenk	Vice President, Clinical Operations
Casidy Domingo	Sr. Manager, Engineering
FDA	**Title**
Sharon Hertz, MD	Director, DAAAP, CDER
Ellen Fields, MD	Deputy Director, DAAAP, CDER
Joshua Lloyd, MD	Clinical Team Leader, DAAAP, CDER
Anjelina Pokrovnichka, MD	Medical Officer, DAAAP, CDER
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP, CDER
Elizabeth Bolan, PhD	Pharmacology/Toxicology Reviewer, DAAAP, CDER
Julia Pinto, PhD	Branch Chief, OPQ, CDER
Wei Qiu, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP), CDER
Yun Xu, PhD	Team Leader, OCP, CDER
David Petullo, PhD	Statistical Team Leader, Office of Biostatistics, (OB), CDER
James Hunter, RPh	Reviewer, Controlled Substances Staff (CSS)
Allison Meyer	Sr. Regulatory Project Manager, DAAAP, CDER

1.0 BACKGROUND

The product is sufentanil sublingual microtablet (ARX-04), housed in a single-dose disposable applicator, to be administered by a healthcare provider no more than every hour at a maximum dose of 30 mcg/hour. The Sponsor intends to submit a 505(b)(2) application that will rely on the Agency's previous findings of safety and efficacy for Sufenta (sufentanil citrate) injection, NDA 019050, as well as the safety data in their NDA for Zalviso (sufentanil sublingual microtablet system), (b) (4) via cross reference or integration of that data into the ISS, in addition to studies performed with this formulation. The Sponsor has proposed that the product be indicated for the management of moderate-to-severe acute pain in adult patients in a medically supervised setting for short-term use (up to 24 hours). The system is not intended for outpatient use or for use in children.

2. DISCUSSION

Question 1:
As agreed at the EOP2 meeting, the NDA will contain safety data for at least 500 post-operative and emergency room patients exposed to at least one dose of ARX-04 SST 30 mcg and at least 100 exposed to multiple doses of ARX-04 SST 30 mcg.

Also discussed at the EOP2 meeting was the acceptability of using a portion of the safety database from AcelRx's Zalviso program (b) (4)*. In the EOP2 meeting minutes, the Agency stated that if comparability of Cmax could be demonstrated between a single ARX-04 SST 30 mcg and two doses of Zalviso SST 15 mcg (with 20 minutes elapsed between the first and second doses), then a portion of the Zalviso patients could be considered for incorporation into the ARX-04 safety database.*

Subsequently, AcelRx conducted a pharmacokinetic (PK) study, SAP101, which demonstrated that Cmax and AUC values were comparable between the ARX-04 SST 30 mcg and 2 x SST 15 mcg (with 20 minutes elapsed between the first and second 15 mcg doses). These data were filed in serial submission SN0015 to which the Agency responded in an advice letter dated January 20, 2015 that Zalviso patients who had dosed two 15 mcg tablets 20 minutes apart could be used in the ARX-04 safety database population. In addition, PK modeling supporting the inclusion of Zalviso patients dosing SST 15 mcg up to 25 minutes apart has also been submitted to the Agency.

Most recently, AcelRx submitted SN0027 which contained a compartmental PK model using data from the IV and sublingual arms of the SAP101 study (see Appendix C). The model was shown to be consistent with the SAP101 data and allows projection of concentration-time profiles for alternate SST 15 mcg dosing regimens, comprised of 2 doses spaced at 20 through 25 minute intervals. Adverse coding will be conducted using MedDRA version 11.0.

Does the Agency agree with this proposal to include 323 Zalviso patients who are dosed within 20 to 25 minutes in the ARX-04 overall safety database of 500 patients?

FDA Response:
We agree that, after review of the PK results from Study SAP101 and the PK modeling data, patients who received two 15-mcg doses of Zalviso given 20 to 25 minutes apart can supplement the safety database requirements for the ARX-04 NDA. However, it is not acceptable that the majority of the required safety data for the ARX-04 NDA be comprised of patients exposed to Zalviso, as you proposed, because the safety evaluation of ARX-04 will be based on the overall safety of the drug and device in combination and not just the safety of the systemic drug levels that are achieved. Because the safety data contributed by patients treated with Zalviso and those already treated with ARX-04 may, in part, contribute to the understanding of the safety of ARX-04 in a general patient population, the remainder of your required safety database in patients treated with ARX-04 must also evaluate the potential risks to any other patient populations who may be exposed to the product in the proposed settings, and may be at particular risk for anticipated or unanticipated adverse effects with your product, a potent opioid. For example, vulnerable populations, such as the elderly, patients with hepatic or renal impairment, patients with impaired respiratory function, or patients with other comorbidities often present to an emergency room setting, and the safety of ARX-04 must be evaluated in these populations. As one component of this evaluation, we recommend performing subgroup analyses by ASA class to evaluate the safety of ARX-04 across the high risk or vulnerable populations. Although the safety database for ARX-04 may be comprised of as many patients treated with 15 mcg Zalviso, given 20 to 25 minutes apart as are available, it must include at least 350 subjects exposed to at least one dose of ARX-04 and 100 subjects exposed to multiple doses of ARX-04 over the anticipated duration of use and address the aforementioned issues. These issues may be evaluated in data collected in open-label studies. However, inclusion of an active control may put help to put the safety results for ARX-04 into context. See comments for Study SAP302 under Additional Comments.

Q1 AcelRx Response to Preliminary Comments:
AcelRx would like to confirm that the ARX-04 safety database should include 350 patients exposed to at least one dose of ARX-04, 100 of which should be exposed to multiple doses of ARX-04.

For the studies conducted to date for ARX-04 (SAP202, SAP301 and ongoing study SAP302), we have not limited patient enrollment by age, BMI, or organ impairment. We have only excluded patients dependent on supplemental oxygen as outpatients or patients with sleep apnea diagnosed by a sleep laboratory. However, even with these minimal enrollment limitations, the nature of the SAP202 and SAP301 studies (ambulatory surgeries) have resulted in limited exposure of ARX-04 in elderly patients (≥ 65 years) or patients with comorbidities. The SAP302 ER study is currently averaging 20% of patients ≥ 65 years of age. The Zalviso Phase 3 studies averaged 50% of patients ≥ 65 years of age when enrolling patients after more major surgeries. In the Zalviso Phase 3 studies overall, elderly patients (n= 306 patients) or patients with renal (n=44 patients) or liver impairment (n=46 patients) were shown to not have any significant clinical effect as indicated by the population PK analysis (submitted as SN0007 to (b) (4)) or the typical opioid adverse event rates in Zalviso studies ((b) (4) ISS).

We understand that the Agency is requesting an additional safety study to expose vulnerable populations (e.g., elderly, renally/hepatically impaired, reduced respiratory function, comorbidities) to ARX-04. We propose to satisfy this requirement with an open-label, single-arm, safety study in approximately 100 patients with a study duration of up to 12 hours as a surrogate for the ER setting. It is likely that this study will be conducted in patients immediately following major surgery (PACU setting) in order to enroll the high percentage (~50%) of elderly/comorbidity patients that were enrolled in the Zalviso trials. In addition, we believe that the data from the 323 patients using a second dose of Zalviso SST 15 mcg within 25 minutes of the first dose will provide supportive safety data in at-risk populations, including elderly and organ-impaired patients. Of these 323 patients, 164 were ≥ 65 years of age, 19 had renal impairment and 25 had liver impairment.
Regarding the need for this study to be an active-control safety study, we have previously conducted study IAP309 for our Zalviso program which used IV morphine PCA as an active comparator in comparison to 15 – 45 mcg/hour exposure to sublingual sufentanil. We believe that this study provides context for sublingual sufentanil's adverse event profile relative to a standard of care for moderate-to-severe pain.

Does the Agency agree with the proposed open-label, single-arm, 12-hour safety study design?

Regarding the SAP302 ER study, we did not limit this trial to a single dose for safety reasons. The agreed upon requirement for 100 patients exposed to multiple ARX-04 doses had already been achieved by SAP202 and SAP301. We had also been advised by ER clinical sites that extending the study to multiple doses (and therefore longer evaluation periods) would make this already difficult enrolling study much more onerous. We understand that given this ER population's unique circumstances, the Agency is interested in repeat dosing in this setting. We therefore intend to extend the SAP302 ER study from 40 patients to 100 patients and will begin allowing repeat dosing once this protocol amendment is approved by the Human Research Protection Office of the Department of Defense. Until that time, we will continue to enroll patients under the current protocol.

Does the Agency agree with AcelRx's proposal to extend the SAP302 ER study to allow for repeat dosing?

Overall, the 350 ARX-04 exposures will comprise approximately 100 ER patients (a mixture of single and multiple doses), and approximately 250 patients suffering from either musculoskeletal pain or soft-tissue/visceral pain following either ambulatory or major surgery. Since nurse-administered ARX-04 is likely to be used in medically supervised settings requiring short-term but rapid pain control, such as the ER, ambulatory surgery, and 23-hr stay hospitalized patients, we believe that the clinical trials reflect the patient-use settings and the clinical duration of exposure of the commercial product.

Discussion

The Division confirmed that the ARX-04 safety database should be comprised of at least 350 patients exposed to at least one dose of ARX-04 SST 30 mcg. Of these 350 patients, at least 100 patients should be exposed to multiple doses of ARX-04.

To address the Division's concern about thesafety of ARX-04 in vulnerable populations such as the elderly and those with comorbidities, the Sponsor clarified that although there were minimal limitations in study enrollment criteria for SAP202 and SAP301, the nature of the type of surgical models used in these studies resulted in limited exposure to vulnerable patients (e.g., elderly, renally/hepatically impaired, reduced respiratory function, comorbidities). Based on Phase 3 studies conducted for the Sponsor's Zalviso program, which were conducted in postoperative patients after major orthopedic or abdominal surgeries, a significant number of patients were over the age of 65. Therefore, in order to evaluate the safety of ARX-04 across high risk populations, the Sponsor proposed to include, as a surrogate for the ER setting, an open-label, single-arm, safety study in approximately 100 post-operative patients who have undergone major surgery (SAP303). The study duration proposed is up to 12 hours to mimic the use setting envisioned for this product, such as after ambulatory surgery, in an ER setting, or for 23-hour stays. The Division agreed with conducting the study in approximately 100 patients after major surgery.

The Division clarified that it was a recommendation and not a requirement that an active control be included in open-label safety studies and that, in the absence of an active control, any safety results from an open-label study would be attributed to study drug. The Sponsor explained that they felt they had a good understanding of the safety effects of sufentanil in comparison to an active control, based on data collected in a study conducted as part of the Zalviso (sufentanil sublingual tablet system 15 mcg) program, which included an IV morphine PCA standard of care treatment arm. The Sponsor confirmed that they understood the implication of not using an active control in the safety study.

The Division commented on the Zalviso population PK analysis, in which patients who had mild-to-moderate renal or hepatic impairment were evaluated, and showed no clinically relevant differences. Since most patients were in the mild impairment category and patients with moderate-to-severe impairment of either type were not well represented in the Zalviso studies, the Division recommended that sparse sampling be taken for patients who present with moderate-to-severe renal or hepatic impairment to better understand the effect of ARX-04 in these patient populations. These data should be added to the population PK analysis and evaluated. The Sponsor agreed to take sparse plasma samples for all patients enrolling in the planned ARX-04 open-label safety study, including those with severe renal and hepaticimpairment.

The Sponsor explained that limiting dosing in the SAP302 ER study to a single dose was not due to a safety concern. Instead, it was due to the practicalities of conducting a study in an ER setting, where patients are often transitioned to different areas in the hospital for care after being admitted. Based on the Division's preliminary comments, the Sponsor proposed amending the SAP302 protocol to allow for multiple doses and increasing the size of the study from 40 patients to 100 patients. The Division agreed with this proposal. The Sponsor noted that the SAP302 study is funded by the Department of Defense, and, therefore, the protocol amendment must first be approved by the Human Research and Protection Office, after which it will be submitted to the Division.

Question 2

The Integrated Summary of Safety (ISS) will be generated in accordance with 21 CFR 314.50 (d)(5)(vi) and will include the following:

- *An "All Patient" pool comprised of SAP202, SAP301, SAP302, and relevant patients from Zalviso studies*
- *A "Placebo-Controlled, All Patient" pool including data from ARX-04 placebo-controlled studies SAP202 and SAP301*

- *A "SST 30 mcg Treated Patients" pool (SAP202, SAP301 and SAP302)*

For the above 3 primary ARX-04 patient pools, analysis will include specific adverse events of special interest (AESIs) which will be discussed in detail in separate sections. These AESIs will include respiratory events (such as respiratory depression, hypoxemia, oxygen saturation decreased, and respiratory failure) and central nervous system events (such as delirium, sedation and cognitive dysfunction). In addition, ISS subanalysis of age, gender, weight, concomitant medications, and other relevant cofactors will be assessed for safety. For these ARX-04 studies, no pooling by surgery type is planned in the ISS since each study was conducted on a different surgery type. Safety analysis by surgery type will be discussed in the individual study reports.

- *A "Zalviso patient" pool (relevant patients from Phase 2 and Phase 3 studies) with the following data presented:*
    - *Adverse events (AEs) for entire study duration*
    - *Termination due to AEs*
    - *AEs specifically over 24 hours (for ease of comparison to ARX-04 safety profile)*
    - *All AEs by surgery type*

a: Does the Agency agree with this approach to the ISS?

FDA Response:
We agree with the proposed pooled groups. Additionally, provide pooled analyses for a "combined placebo-controlled" pool that includes patients from ARX-04 and Zalviso placebo-controlled studies and a "Zalviso placebo-controlled" pool that includes the selected patients from the Zalviso placebo-controlled studies that you intend to contribute to the safety database for ARX-04.

b: Does the Agency agree that the (b) (4) *in the draft package insert* (b) (4) (b) (4) *?*

FDA Response:
The acceptability of any proposed labeling will be determined during the NDA review and will be based on review of the totality of the data included in the NDA submission. If there is important safety information that is necessary to communicate to prescribers that is not fully captured by the safety results from the ARX-04 placebo-controlled studies and can only be conveyed by describing the results from open-label studies or from the relevant

analyses for the Zalviso-treated patients, then these safety data may be appropriate for inclusion in labeling.

Discussion: There was no further discussion on this question.

Question 3:
The Integrated Summary of Effectiveness (ISE) for this application primarily will be based on two placebo-controlled studies: SAP301 (multicenter, double-blind, placebo-controlled study following abdominal surgery) and SAP202 (multicenter, double-blind, placebo-controlled study following bunionectomy). Efficacy results from the single-dose, open-label emergency room (ER) study (SAP302) will also be presented. The studies are as follows:

- ***SAP301*** *– A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sublingual Sufentanil Tablet 30 mcg for the Treatment of Post-Operative Pain in Patients after Abdominal Surgery*

- ***SAP202*** *– A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil NanoTab® for the Management of Acute Pain following Bunionectomy Alone or with Hammertoe Repair*

- ***SAP302*** *– A Multicenter, Open-Label Trial to Evaluate the Safety and Efficacy of a Sublingual Sufentanil Tablet 30 mcg for the Treatment of Acute Pain in Patients in Emergency Room Setting*

Efficacy data from SAP301 and SAP202 will be summarized and discussed separately. Subpopulation analyses, including but not limited to age, gender, race and body mass index (BMI), will also be performed across the studies.

Does the Agency agree with this approach for the ISE?

FDA Response:
We agree with presenting the efficacy data for each of the studies separately, including studies SAP202, SAP301, and SAP302. We also agree with conducting both separate subgroup analyses for each study and with conducting a pooled subgroup analysis. However, the single-dose, open-label, emergency room study (SAP 302) is not appropriate for inclusion in the pooled subgroup analyses, as this open-label data will not contribute to the efficacy evaluation and will only be supportive.

Discussion: There was no further discussion on this question.

Question 4:
AcelRx submitted an initial Pediatric Study Plan (PSP) (b) (4)

(b) (4)

(b) (4)

In June 2014, the Agency provided comments to the PSP. (b) (4)

(b) (4)

In accordance with the Pediatric Research Equity Act (PREA), AcelRx presents its revised PSP (see Appendix D) which outlines:

(b) (4)

- *AcelRx believes that the ARX-04 product is not appropriate for the < 6 years age group since children in this age group do not have the cognitive ability to understand and follow the instructions for use of the SST 30 mcg: i.e., that they may not chew or swallow the tablet, and may not eat or drink, and minimize talking, for approximately 10 minutes after each dose administration. If the tablet is swallowed rather than maintained in the sublingual space until it is fully absorbed, bioavailability is significantly reduced and thus will not provide adequate analgesia. Therefore, AcelRx is requesting a waiver for children* (b) (4)

Does the Agency agree that the submission of a pediatric waiver (for children <6 years) and that deferral (b) (4)*?*

FDA Response:
An agreed Pediatric Study Plan (PSP) is required for your NDA submission, and not having one at the time of NDA submission could adversely impact the filing of your NDA. At this time, we do not have an agreed PSP.

You submitted an initial PSP (iPSP) on February 18, 2014, and we provided comments to that plan on June 4, 2014. However, we have not received a formal response to our comments from you. Although we acknowledge that you submitted a version of your PSP as part of this pre-NDA meeting package, it is not clear how this PSP specifically addresses the comments we provided on your iPSP. Submit a revised PSP, in tracked changes (from the version you submitted as your iPSP), that address all of our comments. Once we have reached agreement on your PSP, you will submit your agreed PSP to the IND and this will be discussed at a meeting of the Pediatric Review Committee (PeRC) for final agreement. You will then receive a letter within 30 days stating whether we have reached agreement on your PSP.

Although we will not be able to fully review your PSP in the context of this pre-NDA meeting, we agree that waiving studies in pediatric patients less than six years of age may be acceptable. We also agree that a deferral of studies in pediatric patients 6 to less than 17 years is acceptable until efficacy and safety are established in adults. However, you must ensure that your PSP provides adequate justification for both requests.

Q4 AcelRx Response to Preliminary Comments:
AcelRx plans to submit a redlined PSP addressing the Agency's comments to the Division for review and agreement.

Could the Agency please confirm that the PSP must be approved by both the Division and PeRC prior to NDA submission?

Discussion: The Sponsor stated that the redlined track-changes version of the PSP (or "modified PSP") will be submitted to the Division for review. This version will also include the changes introduced in the Pre-NDA meeting briefing document, (b) (4) (b) (4). The Division stated that these requests appeared acceptable. However, they will need to be reviewed in the context of the entire PSP and will be discussed with the PeRC. The Division stated that, after sponsors receive comments on a PSP, they are encouraged to negotiate the PSP over the following 90-day period to reach agreement on the PSP. Once there is a negotiated version, the Sponsor submits this version to the Division, which will then be reviewed at a meeting of the PeRC. The Division will then respond to the Sponsor within a 30-day period as to whether agreement has been reached on the PSP. The Division clarified that an agreed upon PSP is required for an NDA submission. The Sponsor stated that the target date for the NDA submission is September 2016, based on the need to conduct the open-label safety study.

Question 5: Does the Agency agree that based on the low active substance amount per dosage unit and demonstration of equivalency between 1 g and 10 g of sample for microbiological testing that use of 1 g of finished product each for lot release and stability testing is adequate?

FDA Response:
Include adequate data to justify the proposed sampling plan for microbial testing in the NDA.

Discussion: There was no further discussion on this question.

Question 6: Does the Agency agree the attributes listed in the proposed commercial specification (Table 8) are acceptable for commercial product lot release?

FDA Response:
The proposed drug product testing seems reasonable. However, add a second (b) (4) identification test for the API and a test for (b) (4).

Further, evaluate tablet hardness (b) (4) on the microtablet dispensed from the applicator to ensure the microtablet remains intact when administered. The impurity specifications must be in accordance with ICH Q3B(R2).

Q6 AcelRx Response to Preliminary Comments:

AcelRx agrees to include an attribute (b) (4) *as part of lot release testing.*

Although it was not specifically described in the pre-NDA meeting briefing document, the two identification tests for the API are (b) (4) *methods. These ID methods will be fully described in the NDA.*

With respect to tablet hardness (b) (4) *of the tablet, during pharmaceutical development, there was extensive testing to ensure that tablets are intact after dispensing. In addition, tablet integrity and compatibility with the single-dose applicator (device) has also been evaluated as part of Design Verification Testing, which includes evaluation of the tablets after shipping studies and environmental extremes testing. Currently, the Registration Stability Lots for the ARX-04 SST 30 mcg are tested via a "Tablet Dispense" method where the tablet integrity is visually evaluated for occurrence chips and cracks after being dispensed from the SDA. We intend to continue this testing as part of commercial lot release and stability testing.*

We believe that this adequately addresses the Agency's concern. Does the Agency concur?

Discussion
The Sponsor summarized that (b) (4) attribute will be added to the proposed commercial specification. The Sponsor clarified that the two ID methods submitted in the briefing document are orthogonal and will be described in the NDA.

With respect to the hardness (b) (4) testing, the Sponsor explained that a Tablet Dispense method is used to visually verify that the tablet is intact after it is dispensed from the SDA. This attribute is currently tested on the Registration Stability Lots (RSL) and is an attribute which is tested on the ongoing RSL stability protocol. The Division agreed that visual verification of the dispensed tablet is acceptable.

(b) (4)

The Sponsor proposed adding the Tablet Dispense attribute to the proposed commercial lot release specification and stability protocols. The Division agreed.

Question 7:
AcelRx has developed an outline of the ARX-04 REMS to support the safe and appropriate use of the sufentanil sublingual tablet 30 mcg for the proposed indication of management of moderate-to-severe pain in adult patients in a medically supervised setting. A REMS proposal outlining the main goals and elements of the REMS in provided in Appendix H.
Agency comment on the proposed REMS outline is requested.

FDA Response:
Regarding the REMS, at this point in development, we have insufficient information to determine what the required elements of a REMS for ARX-04 will be. A review of the proposed REMS for your product, in conjunction with the full review of the NDA, will determine if that REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act. Some elements of the REMS for Zalviso may be applicable to the REMS for ARX-04, but it is too early to determine that at this time.

Discussion: There was no further discussion on this question.

Question 8:
The primary container closure system is comprised of ARX-04 SST 30 mcg housed in a SDA and packaged with an oxygen absorber packet; the SDA and oxygen absorber are packaged together in a laminate foil pouch.

Does the Agency agree that all CMC information for the SDA can be placed in Module 3.2.P Drug Product of the eCTD with all device-related information included in 3.2.P.7 Container Closure System?

FDA Response:
Yes, you can place the information for the SDA with all device-related information in Module 3.2.P.7.

Discussion: There was no further discussion on this question.

Question 9: Please refer to the Data Standardization Plan for ARX-04 sufentanil sublingual tablet 30 mcg NDA presented in Appendix I for the list of study data that will be submitted in this NDA. The ISS ADaM datasets will include safety data generated from those selected Zalviso patients identified for the pooled ARX-04 ISS population. The source data in SDTM format submitted previously for Zalviso (b) (4) *studies will not be submitted again.*
Does the Agency agree with this approach?

FDA Response:
We disagree with your proposal. You must submit the source data with the ARX-04 NDA for the patients from the Zalviso studies (Zalviso-treated and placebo-treated) that are contributing to the safety evaluation of ARX-04.

Q9 AcelRx Response to Preliminary Comments:

AcelRx agrees that source data sets in SDTM format of all Zalviso Phase 2 and Phase 3 studies (ARX-C-001, ARX-C-004, ARX-C-005, IAP309, IAP310, and IAP311) will be provided in the NDA. The selected portion of patients from the Zalviso studies (Zalviso-treated and placebo-treated) which contribute to the ARX-04 safety database are included in these data sets.

Discussion: There was no further discussion on this question.

Question 10: It is our understanding that BIMO data listings for the ARX-04 placebo-controlled studies (SAP202 and SAP301) are required for the NDA submission.
Does the Agency agree with this approach?

FDA Response:
Yes, the BIMO data listings should be submitted, as part of the NDA submission, to facilitate the on-site audit of Studies SAP202 and SAP301 at Good Clinical Practice (GCP) inspections of selected clinical study sites.

Discussion: There was no further discussion on this question.

Additional Comments

1. **The following comments pertain to the open-label, single-dose study in an emergency room (ER) setting (SAP302), which you are also proposing to fulfil the requirements for a human factors (HF) study.**

    - **As we stated in our response to your Question 1, the safety of your product must also be investigated in a vulnerable patient population. Therefore, we recommend that you develop a safety protocol, preferably active-controlled, that will provide safety data regarding ARX-04 administration in elderly and patients with other co-morbidities.**

    - **We note that the dosing for the ER study protocol, SAP302, is limited to single-dose administration. Describe why additional dosing in the ER is not safe and how that can be conveyed through labeling so that prescribers will understand the lack of safety and not use the product in an unsafe manner. Alternatively, study ARX-04 in a manner consistent with planned labeling.**

    - **The proposed clinical study (SAP302) will not constitute an adequate HF evaluation.**

2. **We have the following comments on the required Human Factors evaluation:**

    - **We acknowledge that you state in your meeting package submitted November 4, 2015, that you will be conducting formative and summative Human Factors studies on the optimized SDA design and in the appropriate user population with simulated use scenarios. However, prior to conducting your formative and summative human factors studies, we recommend that you first conduct a comprehensive use-related risk analysis. The analysis should include a comprehensive evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your use-related risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use**

for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and if the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the product). The use-related risk analysis can be used to inform the design of a summative human factors study protocol for your product.

If intended end users will utilize the final finished combination product in your clinical trials, then we recommend that your product undergoes human factors (HF) validation testing in a simulated use scenario to ensure that the product has been optimized for safety and that the product is ready to be subjected to the conditions of the clinical study. Highly controlled study conditions may not be sufficient to overcome major design flaws in your product or its user interface that could lead to use error or adverse events during use of the product in a clinical study. Therefore, we recommend that human factors validation testing with at least 15 representative users is performed prior to starting your clinical studies. If the results of such testing indicate that the product can be used safely and effectively by intended users in the clinical study, then you can proceed with your development program without submission of the HF information for prior Agency feedback. This approach carries some risk to you because prospective Agency review is not possible, but this is a business decision for your company.

- **Prior to commencing your HF validation study, we recommend you submit the following items for review and comment by the Agency:**
  - **A summary of your results and analysis from your formative studies;**
  - **A discussion of changes made to your product after the formative studies, including how the results from the formative studies were used to update the user interface and use-risk analysis**
  - **An updated use-related risk analysis for your product;**
  - **Summative human factors study protocol**
  - **Intend-to-market labels and labeling (including editable word version of IFU, if one is proposed) that will be tested in the summative human factors study**
  - **Intend-to-market samples of product that will be used in your summative human factors study**

Note that we will need 120 days to review and provide comments on your risk analysis and protocol under the IND. Plan your development program timeline accordingly.

Guidance on human factors procedures to follow can be found in Medical Product Use-Safety: Incorporating Human Factors Engineering into Risk Management, available at http://www.fda.gov/downloads/MedicalDevices/.../ucm094461.pdf

Note that we recently published three draft guidance documents that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors and product design and labeling:
Applying Human Factors and Usability Engineering to Optimize Medical Product Design, available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf
Safety Considerations for Product Design to Minimize Medication Errors, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf
Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Additional Nonclinical Comments:

1. **(b) (4) is not listed in the CDER Inactive Ingredient Database (IID) or in the Code of Federal Regulations as an acceptable dye for use in oral drug products. Provide a CAS number for this compound or confirm if this compound is FD&C Blue No. 2 (b) (4). If this compound is a new excipient, provide safety justification as per the FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. As noted in the guidance, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration*." (emphasis added).**

2. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:**

    a. **You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome**

aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days duration should be completed for your proposed acute indication.

Refer to
Guidance for Industry: *Q3A(R2) Impurities in New Drug Substances*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

and

Guidance for Industry: *Q3B(R2) Impurities in New Drug Products*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

c. Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.

3. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the

accepted limits established for the stage of drug development in order to mitigate risk.

4. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

5. **Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

6. **We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.**

7. **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds or includes a new excipient that has not been adequately justified for safety.**

AC2 AcelRx Response to Preliminary Comments:

A summative Human Factors protocol will be submitted to the Agency for review and comment. Note that since the Single Dose Applicator is a simple disposable device, a one-page Directions for Use document for the HCP regarding proper sublingual dose administration of the ARX-04 tablet, rather than an Instructions for Use booklet, is planned. This document, as well as the use FMEA will be submitted along with the HF summative protocol, as requested.

Discussion: No further discussion is requested on this topic.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

- In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:
- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study

Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

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 draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.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 that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, 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, in part, 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 or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to 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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions

transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

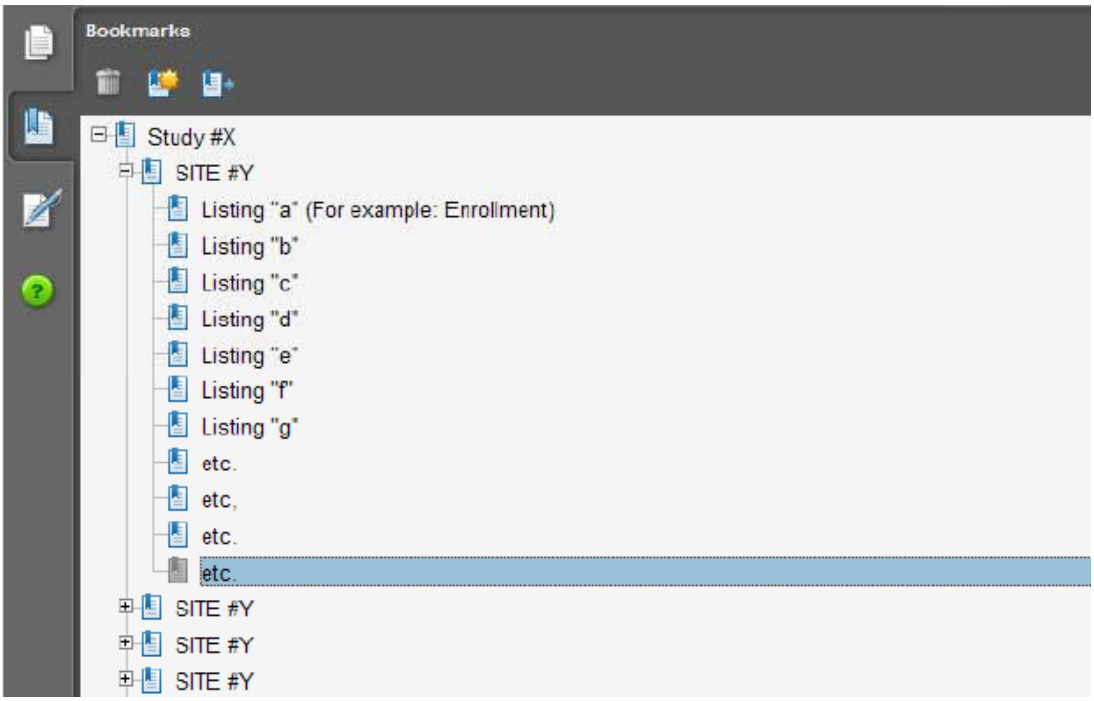
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ACTION ITEMS

1. The Sponsor will conduct an open-label, single-arm, safety study comprised of 100 patients following major surgeries to assess vulnerable populations exposed to ARX-04. The proposed study duration is 12 hours. The Sponsor will add a sampling of patients with severe renal and hepatic impairment for population PK analysis.

2. The Sponsor will amend their SAP302 ER study protocol to allow for multiple dosing of ARX-04 study drug. In addition, the study size will increase from 40 patients to 100 patients. Since the SAP302 study is funded by the Department of Defense, the Sponsor will submit the protocol to the Division after it is approved by the Human Research Protection Office.

3. The Sponsor will submit a redlined Pediatric Study Plan to the Division which addresses comments provided from June 2014 and which will include revisions proposed by the Sponsor in the pre-NDA briefing document.

4. The Sponsor will add (b) (4) to the commercial specification.

5. The Sponsor will add a tablet dispensing attribute to the commercial specification and to the commercial stability protocol.

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

/s/

ALLISON MEYER
01/12/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113059

MEETING MINUTES

AcelRx Pharmaceuticals, Inc.
351 Galveston Drive
Redwood City, CA 94063

Attention: Majella Dooley
Senior Director, Regulatory Affairs

Dear Ms. Dooley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food Drug and Cosmetic Act for sufentanil sublingual microtablet (ARX-04).

We also refer to the End-of-Phase 2 (EOP2) meeting between representatives of your firm and the FDA on December 18, 2013. The purpose of the meeting was to discuss issues related your preparations for Phase 3 studies with your product.

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

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

Sincerely,

{See appended electronic signature page}

Kimberly Compton, RPh
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type/Category: Type B, End-of-Phase 2 (EOP2)
Meeting Date and Time: December 18, at 3:00 PM
Meeting Location: White Oak Bldg 22, Conference Room 1313
Application Number: IND 113059
Product Name: Sufentanil sublingual microtablet (ARX-04)
Regulatory Status: Active IND, EOP2
Proposed Indication: Management of moderate to severe acute pain in a medically supervised setting
Sponsor Name: AcelRx Pharmaceuticals, Inc.
Meeting Chair: Ellen Fields, MD, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), Center for Drug Evaluation and Research (CDER)
Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

AcelRx Pharmaceuticals, Inc. Representatives	**Title**
Lana Chin	Sr. Manager, Regulatory Affairs
Majella Dooley	Sr. Director, Regulatory Affairs
Pamela Palmer, MD, PhD	Chief Medical Officer
Mike Royal, MD, JD, MBA	Chief, Clinical Affairs
Yu-Kun Chiang, PhD	Statistical Consultant to AcelRx
Mark Evashenk	Vice President, Clinical Operations
Casidy Domingo	Sr. Manager, Engineering
FDA	**Title**
Bob A. Rappaport, MD	Director, DAAAP, CDER
Sharon Hertz, MD	Deputy Director, DAAAP, CDER
Anjelina Pokrovnichka, MD	Medical Officer, DAAAP, CDER
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP, CDER
Julia Pinto, PhD	CMC Lead, Office of New Drug Quality Assessment (ONDQA), CDER
Ciby Abraham, PhD	Chemistry Reviewer, ONDQA, CDER
Wei Qiu, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP), CDER
Yun Xu, PhD	Team Leader, OCP, CDER
Janice Derr, PhD	Statistical Team Leader, Office of Biostatistics, (OB), CDER
Irene Chan, PharmD	Team Lead, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE), CDER
James Hunter	Reviewer, Controlled Substances Staff (CSS)
Somya Dunn, MD	Risk Management Analyst, Division of Risk Management (DRISK), OSE, CDER
Kim Lehrfeld, PharmD	Team Leader, DRISK, OSE, CDER
Mark Liberatore, PharmD	Safety Project Manager Team Lead, OSE, CDER
Joan Blair, RN, MPH	Health Communication Analyst, DRISK, OSE, CDER
Kim Compton	Sr. Regulatory Project Manager, DAAAP, CDER

BACKGROUND

The product is sufentanil sublingual microtablet (ARX-04), housed in a single-dose disposable applicator to be administered by a health care provider no more than every 1 hour[1] at a maximum dose of 30 mcg/hour. The Sponsor intends to submit a 505(b)(2) application that will rely on the Agency's previous finding of safety and efficacy for Sufenta (sufentanil citrate) injection, NDA 019050, as well as the safety data in their NDA for Zalviso (sufentanil sublingual microtablet system), (b) (4) via cross reference, in addition to studies performed with this formulation. The Sponsor has proposed that the product be indicated for the management of moderate to severe acute pain in adult patients in a medically supervised setting for short-term use (up to 24 hour). The system is not intended for outpatient use or for use in children.

The Sponsor has stated that their objectives for this Type B, Pre-NDA meeting are as follows:

1. Gain consensus on the proposed non-clinical plan which relies on data from ZALVISO (b) (4) as well as the Sufenta NDA (reference drug) that will support the ARX- 04 sufentanil sublingual microtablet NDA filing

2. Obtain Agency feedback on the proposed dose (30 mcg) for further evaluation in Phase 3, the clinical and statistical design of the Phase 1 and 3 clinical studies, and the overall safety database that will support the ARX-04 SSM NDA filing

3. Confirm proposed trade name strategy and regulatory pathway of a 505(b)(2) NDA filing for ARX-04

The questions from the November 7, 2013, background package are shown below in *italic* font. The Division's responses are shown in **bold** font.

On December 12, 2013, the preliminary responses were issued to the firm. On December 17, 2013, the firm indicated they did not require further discussion on Questions 1, 5, 6, or 7, but would like to discuss Questions 2-4 and the Statistical Comments provided. Their responses, provided via email on December 17, 2013 are included in *italic* font after the question to which they pertain. Discussion that took place at the meeting follows the question to which it pertains in normal text.

DISCUSSION

Nonclinical Questions

Question 1
AcelRx proposes to refer to the Agency's findings of efficacy and safety for Sufenta (NDA# 019050) and to referenced data and published literature available on sufentanil in support of the nonclinical program as part of our ARX-04 NDA submission.

[1] In the Preliminary Comments document, issued on December 12, 2013, the dosing interval for the product was erroneously described as being no more than every four hours, but in actuality the interval is no more than every hour.

As part of the nonclinical program for AcelRx (b) (4) *(ZALVISO™ sufentanil sublingual microtablet system), AcelRx conducted a 4-day hamster cheek pouch irritation study and 7-day and 28-day repeat-dose toxicology studies in hamsters. The 28-day study included a 30 mcg dose and no irritation was observed for the dosages evaluated. The maximum tolerated dose was determined to be 180 mcg/day.*

Does the Agency agree that the Sufenta data along with the 4-day hamster cheek pouch irritation study and the 7-day and 28-day repeat-dose toxicity studies submitted under AcelRx (b) (4) *are sufficient for ARX-04 registration?*

FDA Response

Your proposal to rely upon the Agency's previous finding of safety for the Sufenta drug product (NDA 019050) plus the 4-day hamster cheek pouch irritation study and the 7- and 28-day repeat-dose toxicology studies is acceptable in terms of providing support for an acute indication of up to 24-hours treatment duration.

The following additional nonclinical comments are provided to assist in your preparation of your NDA:

1. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. Unless otherwise justified, adequate qualification must include:**

    a. **Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

    b. **Repeat-dose toxicology study of appropriate duration to support the proposed indication.**

2. **Impurities that are carcinogenic must be reduced to levels in the drug substance or drug product that would limit human exposure to NMT** (b) (4) **mcg/day. Impurities that are genotoxic or contain a structural alert for genotoxicity must be reduced to this same level unless you provide adequate safety qualification. For an impurity with a structural alert for mutagenicity, an adequate safety qualification requires a negative in vitro bacterial reverse mutation (Ames) assay, ideally with the isolated impurity tested to the appropriate highest concentration of the assay as outlined in ICH S2(R1) guidance document entitled "Guideline on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT** (b) (4) **mcg/day, or otherwise justified which may require an assessment for**

carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

3. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

4. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds or contains a structural alert for genotoxicity without adequate safety qualification data.**

5. **Include in your NDA submission a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include in the NDA submission copies of all referenced citations in Module 4. Journal articles that are not in English must be translated into English.**

6. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.**

Discussion
There was no further discussion on this point.

Clinical Pharmacology Questions

Question 2
To confirm previous PK study results as well as Population PK results, we propose a PK registration study in naltrexone-blocked subjects to evaluate single and multiple-dosing of

ARX-04 hourly over 12 hours (refer to protocol synopsis for SAP101, Appendix E). Does the Agency concur with the proposed SAP101 study design?

FDA Response

Based on the study synopsis provided in your meeting package, the study design for SAP101 seems reasonable to assess the single- and multiple-dose PK of your proposed sufentanil sublingual microtablet 30 mcg. In Study SAP101, assess sufentanil clearance following single- and multiple-dose administration, provide a rationale for change in clearance if any, and address clinical implications of any change in clearance and systemic exposure following repeated dosing of your product.

Sponsor Response of December 17, 2013 (received via email)

Based on the Agency's response to Questions 2 to 4, we propose to amend the Phase 1 PK Study SAP101 design to include 4 arms:

- *IV Sufenta 30 mcg*
- *Single dose ARX-04 30 mcg sufentanil microtablet*
- *2 x 15 mcg ZALVISO (dosed 20 minutes apart)*
- *Multiple dose ARX-04 30 mcg sufentanil microtablet*

- *Does the Agency agree with this approach to address the issues raised in the preliminary comments?*

In light of the proposed changes in the PK study design described above, we would like to further discuss the number of safety exposures:

- *For the requested N=500 patients exposed to at least one dose of 30 mcg, please confirm that the N=100 patients exposed to multiple doses of ARX-04 30 mcg microtablet can be addressed with the Phase 3 SAP301 study and that the N=40 patients exposed to multiple doses in the completed Phase 2 Study SAP202 contribute to the overall safety database.*

- *If we obtain PK data showing similar Cmax concentrations between the ARX-04 30 mcg and ZALVISO (2 x 15 mcg dosed 20 minutes apart) products, what reduction in the overall safety database would the Agency consider?*

Discussion

The Sponsor stated that they are planning only one PK study for the development program as outlined in their emailed response above. The Division stated that, if the Sponsor demonstrates that the exposure with the 30 mcg single dose of ARX-04 is lower than that with the two 15 mcg doses of Zalviso given 20 minutes apart (a total dose of 30 mcg), then it may be acceptable to use the same safety exposure data in the Zalviso application. The Sponsor stated that they will conduct a study to demonstrate the comparable C_{max} levels.

Because patients with mucositis can be prescribed another product, the Sponsor is not planning to conduct PK studies in those patients (b) (4) (b) (4). The Division agreed with the approach (b) (4).

The Sponsor proposed to use the same approach as for Zalviso to address the effect of pH and temperature on drug absorption and the Division agreed that this seemed reasonable.

The Division requested that the Sponsor attempt to capture the C_{max} for both dosing paradigms proposed. (b) (4)

(b) (4)

Question 3
Interaction with the CYP3A4 inhibitor ketoconazole, the effect of different routes of administration (oral/swallowed and buccal), and extensive Population PK meta-analyses were already conducted for ZALVISO 15 mcg sufentanil microtablets (refer to Section 11.7 and Population PK report in Appendix D). The formulation (except for dosage and (b) (4) *) and the intended patient population are the same for ARX-04 and ZALVISO. Does the Agency agree that no additional PK studies beyond the single-/multiple-dose PK study SAP101 described above is needed for registration of ARX-04 SSM 30 mcg?*

FDA Response
It appears that you plan to rely on the Agency's previous findings of safety for the Sufenta NDA and cross-reference your data for ZALVISO 15 mcg sufentanil microtablets to support the safety of your proposed 30 mcg sufentanil microtablets. In order to rely on previous Agency findings of safety and efficacy for the Sufenta drug product and cross-reference your data for the ZALVISO 15 mcg drug product, you must establish adequate pharmacokinetic (PK) bridges with each drug you plan to rely upon, e.g., 3-way crossover relative bioavailability study comparing your proposed 30 mcg sufentanil microtablet, ZALVISO 15 mcg sufentanil microtablet, and Sufenta intravenous injection 30 mcg. Also, refer to our response to Question 4 about the potential difference in C_{max} values between your proposed 30 mcg product and 15 mcg ZALVISO, and provide PK data to address it.

Because your product is intended for transmucosal absorption, various degrees of mucositis may affect sufentanil absorption. Either conduct a PK study in patients with mucositis, or provide justification to support that a PK study in patients with mucositis is not necessary. In addition, we suggest you conduct a study to assess PK or provide information on the effects of liquids with high and low temperature on the absorption of your product, e.g., hot coffee, tea, or water; and ice cold water, respectively; or with high and low pH, e.g., baking soda in water, and cola, respectively, on the absorption of your product.

The final to-be-marketed product should be used in the studies to support the NDA. Otherwise, you must provide adequate scientific bridging data between the clinical study formulation and the to-be-marketed formulations.

Discussion
See discussion captured under Question 2 above.

Clinical Questions

Question 4
Does the Agency agree that the proposed ARX-04 clinical development plan (exposure of approximately 140 patients to 30 mcg dose for up to 12 hours), supplemented by the safety data generated under the ZALVISO program (b) (4) *is sufficient for registration of ARX-04 for "management of moderate-to-severe acute pain in a medically supervised setting"?*

FDA Response
We do not agree that the proposed ARX-04 clinical development plan is sufficient for filing an NDA for ARX-04 for the proposed indication.

Your proposed indication for ARX-04 is for the management of moderate-to-severe acute pain in a medically supervised setting. In the briefing document, you state your intention to limit use to 24 hours. You have not provided any explanation for why use of ARX-04 should be limited to 24 hours. In order for us to comment on the proposed indication and the study intended to support the indication, you must clearly define the target population for ARX-04 and the likely duration of use in that population. In addition, you must provide a plan for how the limitation in duration of use would be implemented in the clinical setting. Otherwise, you must provide the appropriate nonclinical data to support the safety of a longer duration of use.

You plan to use data from the ZALVISO NDA to supplement the safety database for ARX-04. The maximum dose given as a single administration in the ZALVISO program was 15 mcg every 20 minutes. The proposed dose for ARX-04 is 30 mcg once per hour. In the absence of actual pharmacokinetic (PK) data comparing ARX-04 to ZALVISO, if the PK profile for the two products is approximately linear, it is expected that a single dose of 30 mcg ARX-04 would result in a higher C_{max} compared to a single dose of 15 mcg ZALVISO and, therefore, potentially result in a different adverse event profile. We have serious concerns regarding the risk for respiratory depression with the higher C_{max} that will be associated with the 30 mcg sufentanil dose. Therefore, the safety database must include at least 500 subjects exposed to at least one dose of ARX-04, and at least 100 exposed to multiple doses. If you obtain PK data comparing the two products that demonstrates similar C_{max} concentrations, we may reconsider the size of the required safety database may.

Sponsor Response of December 17, 2013 (received via email)
We would like to further discuss the definition of our target population for this product and limitation and duration of use to 24 hours.

- *Based on this clarification, does the Agency agree with the primary endpoint of SPID12 for Study SAP301?*

- *Does the Agency have additional comments on the study design for SAP301?*

Discussion
The Sponsor stated that the product is not intended to be used for the maintenance of pain control, but for use in outpatient surgery settings for up to 24 hours, and that this is the population selected for their clinical studies. The Division asked why the product would not be used on an as-needed basis for extended periods. Currently, the clinical safety data do not support longer duration of use and the nonclinical data only support up to 14 days of use. It is necessary for the Sponsor to establish the clinical settings where the product would be used to determine what supportive data are needed for approval.

Regarding the proposed primary efficacy analysis, the Division stated that this must be relevant to the intended use and the currently proposed SPID 12 efficacy analysis does not reflect the proposed 24-hour dosing duration. Furthermore, there is no self-apparent reason for why a prescriber should stop prescribing it beyond 24 hours. The Division stated that findings of either a loss of efficacy after the first 24 hours, or an excess of opioid-related toxicity after 24 hours could support limiting the indication. The Division noted that even though there will be a REMS for this product, a REMS is meant to ensure that the product is not used unsafely, not to prevent off-label use.

The Division stated that, if the study design is very novel, a Special Protocol Assessment (SPA) agreement may not be possible, but the Sponsor may submit the protocol as a SPA, and the Division will provide feedback.

Question 5
The Sponsor requests a deferral for conducting pediatric studies with ARX-04 until after the product has been evaluated in adult patients and the initial two adolescent studies for the ZALVISO program have been conducted. Does the Agency agree?

FDA Response
Your proposal appears reasonable. In conformance with the FDA Safety and Innovation Act (FDASIA), however, you must submit an initial Pediatric Study Plan (iPSP) including requests for waivers and deferrals within 60 days of your EOP2 Meeting. Be advised that final determinations for pediatric plans and deferral requests are made by the FDA Pediatric Review Committee (PeRC). Refer to the PREA comments below for additional information.

Discussion
There was no further discussion on this point.

Statistical Comments
For a confirmatory trial, we emphasize that the National Academy of Sciences (NAS) report on the prevention and treatment of missing data recommends explicit specification of the causal estimand. The report is available at

http://www.nap.edu/catalog.php?record_id=12955. The choice of a causal estimand involves both the outcome measure and population of interest, and the estimand may have important implications for trial design, conduct, and statistical inference. You should propose a clinical relevant estimand and describe how your proposed statistical methodology estimates it. Examples of estimands are provided in the NAS report.

You have proposed the Last Observation Carried Forward (LOCF)/ Worst Observation Carried Forward (WOCF) method as a primary method to impute the missing data in the study. The NAS report does not favor single imputation methods. In your confirmatory study, you must either justify the appropriateness of your current strategy or propose an approach that is more consistent with the NAS recommendations. We continue to favor methods that do not attribute a good score to a patient discontinuing due to an adverse event.

Randomization will be stratified by age (<65 year and ≥ 65 years) at each site. However, none of the proposed analyses appear to incorporate the stratification factor "age." If the concern is that the treatment effect may differ by stratum, then you should conduct a stratified analysis.

Sponsor Response of December 17, 2013 (received via email)
AcelRx would like to further discuss the statistical comments in the Agency's preliminary comments

Discussion
The Sponsor stated that they had minimal missing data in the Zalviso studies and plans to use a similar statistical approach with ARX-04. The Division stated that, while fewer dropouts and discontinuations are seen in hospital settings, the Sponsor would still need to provide a justification of the proposed analysis along with a sensitivity analysis in the SPA protocol they plan to submit.

The Division noted that the Sponsor has proposed using the Worst Observation Carried Forward (WOCF) imputation method to try to address the possibility of an adverse event (AE) being recorded as a favorable event, which could occur using Last Observation Carried Forward (LOCF) imputation method. A single value imputation or the possibility of assigning positive values to dropouts is not acceptable. The Sponsor should address these issues in any proposal they submit.

Regulatory Questions

Question 6
The ARX-04 product differs from ZALVISO (sufentanil sublingual microtablet system) in the following ways:

a. *30 mcg blue microtablet versus 15 mcg* (b) (4) *microtablet (aside from* (b) (4) *and dose, the ZALVISO and ARX-04 commercial formulation and physical dimensions are identical)*

b. *Single-dose, disposable applicator versus* [redacted] (b) (4) *a* [redacted] (b) (4) *Controller (ZALVISO)*

c. *HCP-administered no more frequently than every hour versus patient-controlled administration with a pre-programmed 20-minute lockout*

d. *Intended for use in a medically supervised setting for up to 24 hours versus patient-controlled administration in a hospital setting for multiple days*

e. *Will require a different REMS program than ZALVISO*

We propose that the ARX-04 product should have a different trade name than ZALVISO to avoid potential ordering and prescribing confusion between the two products. Does the Agency concur?

FDA Response

We must conduct a thorough analysis of the risk for medication errors before we make the determination that the ARX-04 product should have a different proprietary name than ZALVISO. The proposed proprietary name submitted for ARX-04 will be evaluated from both a promotional and safety perspective, and requires careful consideration of potential medication errors that may occur during the entire medication use process. The proposed name for ARX-04 will be evaluated for risk of confusion with ZALVISO as well as with other marketed products. These two products, ARX-04 and ZALVISO, have the same active ingredient, same formulation, same dosage form, same indication, overlapping setting of use, and the same manufacturer. They differ by product strength, administration frequency, and delivery device. For the risk of confusion with ZALVISO, we will assess the risk of therapeutic duplication which may result in overdose of sufentanil. We will also assess whether the dose strength and administration frequency can sufficiently differentiate these two products should the name ZALVISO be used for both products.

We encourage you to submit a proposed proprietary name package to the IND to allow for review of these considerations. Along with the request for proprietary name review submission, we request that you to provide a more in-depth rationale and/or analysis to address the risk of therapeutic duplication to support your proposal of a name different from ZALVISO for ARX-04. The appropriate regulatory pathway for a Request for Proprietary Name Review is via a separate submission to your IND/NDA. DMEPA will perform an assessment once we receive a formal request for review. Once our assessment is complete, we will issue a letter with our final determination for your proposed Proprietary Name.

The content requirements for such a submission can be found in the draft guidance for industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names,* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

Regarding the REMS, at this point in development we have insufficient information to determine what the required elements of a REMS for ARX-04 will be. A review of the proposed REMS for your ZALVISO product, in conjunction with the full review of the NDA is ongoing and will determine if that REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act for that product. Some elements of the REMS for ZALVISO may be applicable to the REMS for ARX-04, but it is too early to determine that at this time.

Discussion
There was no further discussion on this point.

Question 7
Assuming the Agency agrees with a trade name for ARX-04 that is different from ZALVISO, we propose to file a 505(b)(2) NDA for ARX-04 referencing Sufenta (NDA# 019050) with a cross-reference to ZALVISO (b) (4) *Does the Agency agree?*

FDA Response
We agree with that a 505(b)(2) NDA is an acceptable regulatory approach for your application. Because your company is the holder of the ZALVISO NDA and owns the data, you do not need to list ZALVISO as a reference drug in your 505(b)(2) application.

Discussion
There was no further discussion on this point.

Device Comments
Regarding manufacturing practice: 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for combination products, we agree with your plan to conduct device performance testing in accordance with 21 CFR 820.30 (briefing document page 20 of 60) and your plan to complete Human Factor (HF) formative and HF validation studies and use the final single-dose applicator design in the Phase 3 study and the definitive PK study (briefing document page 24 of 60). In addition, in future meetings, as appropriate for the stage of development, we urge you to provide information on how you plan to comply with other requirements as provided in 21 CFR Part 4.

Discussion
There was no further discussion on this point.

OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach), any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans,* available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry: *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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 draft guidance for industry: *Applications Covered by Section 505(b)(2)*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.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 that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

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 or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

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) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory

requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would

be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to 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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

SPONSOR SUMMARY OF DISCUSSION (Includes Action Items)

1. Regarding the duration of use and pain settings in which the product will be used, the Sponsor understands that the protocol for the Phase 3 study they plan to conduct should clearly define the intended settings and populations in order to assess efficacy and safety over the intended duration of drug use. The Sponsor is considering submitting the protocol as a SPA, understanding that the Agency is uncertain if agreement on the SPA for a protocol with a novel design can be reached.

2. The Sponsor does not plan to study the product in patients with mucositis, (b) (4) (b) (4).

3. Regarding the effect of pH and temperature on absorption of the product, the Sponsor understands that they may rely on the information in the Zalviso application which addresses this.

4. Regarding the collection of pharmacokinetic data, the Sponsor plans a 4-arm study where one arm tests the characteristics of intravenous sufentanil, one tests 2 x 15 mcg ARX-04 doses administered every 20 minutes, one tests a single 30 mcg ARX-04 dose, and one tests multiple doses. The Sponsor will compare the C_{max} of the two 15 mcg tablets dosed 20 minutes apart and the 30 mcg single-dose arm and, if there are comparable C_{max} levels, they will be able to leverage the Zalviso safety data to support the ARX-04 application. The Sponsor agreed that for the multiple-dose PK study they would try to capture the C_{max} data point as well.

5. The Sponsor will submit a statistical analysis plan as part of the SPA. They plan to propose a method that does not use single imputation and will include WOCF. The Sponsor recognizes that discussion is needed. The Sponsor believes that, with the allowed use of rescue medication, the need for imputed data will decrease.

6. The Division noted that the Sponsor was asked to further define the intended use of and patient population for their product, and include this information in the protocol submission.

ATTACHEMENTS AND HANDOUTS
No handouts or attachments were utilized for this meeting.

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
01/16/2014