CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202880Orig1s000

SUMMARY REVIEW

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

Summary Review for Regulatory Action

Date	October 25, 2013
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	202880
Applicant Name	Zogenix, Inc.
Date of Submission	May 1, 2012
PDUFA Goal Date	March 1, 2013
Proprietary Name / Established (USAN) Name	Zohydro ER Hydrocodone bitartrate extended-release capsules
Dosage Forms / Strength	10 mg, 15, mg, 20 mg, 30 mg, 40 mg, 50 mg capsules
Proposed Indication	Management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Ellen Fields, M.D., M.P.H.
Clinical Review	Robert A. Levin, M.D.
Biostatistics Review	Katherine Meaker, M.S.; Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
ONDQA-CMC/Quality Review	Yong Hu, Ph.D.; Prasad Peri, Ph.D.
Biopharmaceutics Review	Minerva Hughes, Ph.D.; John Duan, Ph.D.
Clinical Pharmacology Review	David J. Lee, Ph.D.; Yun Xu, Ph.D.
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CDRH	James Kane, Ph.D.

OND=Office of New Drugs
OMP: Office of Medical Policy
OMPI=Office of Medical Policy Initiative
OSE= Office of Surveillance and Epidemiology
OPE=Office of Pharmacovigilance and Epidemiology
DMEPA=Division of Medication Error Prevention
DRISK= Division of Riak Management
DEPI-II=Division of Epidemiology II
OPDP= Office of Prescription Drug Promotion
DMPP = Division of Medical Policy Programs
OSI=Office of Scientific Investigations
CDTL=Cross Discipline Team Leader
ONDQA=Office of New Drug Quality Assessment
CMC=Chemistry, Manufacturing, and Controls
CDRH =Center for Devices and Radiological Health

1. Introduction

Zogenix, Inc. submitted their NDA for Zohydro ER, hydrocodone extended-release capsules, on May 1, 2012. This application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, referencing in part the Agency's prior findings of safety and efficacy for Vicoprofen, NDA 20-716. The proposed indication was for the "Management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." If approved, Zohydro ER would be the first approved, indeed the first marketed, single-entity hydrocodone product in the U.S. As a Schedule II drug product under the Controlled Substances Act (CSA), there would be additional restrictions on its prescribing and dispensing compared to the numerous approved hydrocodone combination drug products (e.g., Vicodin, Vicoprofen, multiple generic products) which fall under Schedule III of the CSA.

The CSA was passed into law in 1970. It includes a provision for differential scheduling of hydrocodone single-entity drug products and hydrocodone combination-drug products. This distinction was made based on the hypothesis that lower doses of hydrocodone (must be less than or equal to 15 mg or less than or equal to 300 mg/100 mL per dosage unit) when combined with an additional active pharmaceutical ingredient that at high doses may not be tolerated or may cause serious adverse events (e.g., aspirin, acetaminophen, NSAIDs), would provide some degree of abuse deterrence. However, the combination drug products that contained low doses of oxycodone along with the same types of second analgesics, were placed in Schedule II, perhaps due to the assumption by many physicians and scientists at that time that hydrocodone was inherently less prone to abuse and addiction than oxycodone. Nevertheless, it has become abundantly clear over the past two decades that hydrocodone combination products are being widely abused, with significant and increasing levels of serious outcomes such as addiction, overdose and death.

This product, if approved for marketing, would fall under the recently approved Extended-release and Long-acting Opioid Risk Evaluation and Mitigation Strategy (ER/LA REMS), along with all of the other potent ER and LA opioid drug products. For this application, the applicant has suggested adding additional risk mitigation tools, but these additional tools were not submitted in the NDA; they were noted in the applicant's background information for and presentation to the advisory committee meeting. Due to its inherent risks, and to the current public health crisis of prescription opioid abuse and misuse, this application was presented to the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) on December 7, 2012. While the committee acknowledged that the applicant had provided evidence to support the efficacy

and general safety of Zohydro ER, and that Zohydro ER does not appear to be different from other Schedule II ER/LA opioid analgesics, they nevertheless voted 11 to 2, with 1 abstention, to recommend that the Agency not approve the application due to their concerns about the risks for misuse and abuse of the product and its impact on the public health. A complete description of the committee's deliberations and conclusions is provided below in Section 7.

2. Background

Zohydro ER is a 12-hour, ER formulation of hydrocodone that utilizes Alkermes' patented Spheroidal Drug Absorption System (SODAS®) drug delivery technology. As a 505(b)(2) application referencing an approved Immediate-release (IR) hydrocodone drug, the applicant was required to perform only one adequate and well-controlled clinical trial, essentially to demonstrate that this well-understood analgesic drug remained effective in the new formulation, and that the dosing regimen was appropriate to the pharmacokinetic and pharmacodynamic properties of the product. Alkermes also submitted the data from an open-label safety study with treatment up to 52 weeks. Preclinical toxicology, genotoxicity, and reproductive toxicity studies were also required and performed, as the doses of Zohydro ER exceed those of the referenced combination products. Carcinogenicity studies were required and initiated, but the applicant was permitted to complete and submit those studies in the post-marketing period, based on the extensive use of hydrocodone in the U.S. over many years. A full set of chemistry, manufacturing and controls data was submitted, and inspection of the manufacturing facility was undertaken by Agency field agents. A complete pharmacokinetic and biopharmaceutic data package was also included in this application.

As noted above, the PDUFA goal date for this application was March 1, 2013. This regulatory action was delayed until now because of the Agency's ongoing activities that were undertaken to help ensure the safe and appropriate prescribing, and the safe and effective use of drug products in the ER/LA opioid class. A discussion of these activities can be found in Section 11 of this review.

3. CMC

The following summary of the Chemistry, Manufacturing and Controls data, and the Biopharmaceutics data, submitted in the application has been reproduced from pages 3 and 4 of Dr. Fields' review:

Drug Substance

The Applicant proposes to use the hydrocodone bitartrate drug substance sourced from both (b) (4) (DMF (b) (4) and (b) (4) (DMF (b) (4) however, only the (b) (4) sourced drug product is acceptable because the (b) (4) DMF does not show adequate manufacturing capability and product specification to control impurities below the more stringent ICH qualification threshold for a drug product with > 2 g total daily dose. DAAAP advised the CMC team that the maximum daily dose of hydrocodone bitartrate would be up to 3 grams since the dosing of a single-entity product is not limited by the non-opioid analgesic present in combination hydrocodone products. The drug product manufacturer, Alkermes, has committed to not using the (b) (4) drug substance.

The (b) (4) DMF is adequate. (b) (4) manufactures the drug substance in their (b) (4) or (b) (4) facilities, which have been deemed acceptable by the Office of Compliance. The Applicant has agreed to use only the (b) (4) drug substance.

Drug Product

As stated in Dr. Hu's review:

Hydrocodone bitartrate extended-release (hydrocodone-ER) capsule (also named ELN154088 in some development documentation), is an extended-release capsule product using Alkermes' Spheroidal Oral Drug Absorption System (SODAS®) technology. With this technology the sugar spheres are initially coated with the drug substance and other suitable excipients to form immediate-release (IR) multiparticulates (beads). Sustained-release (SR) multiparticulates (beads) are then prepared by coating the IR beads with a rate-controlling polymer (ammonio methacrylate copolymer (b) (4) . The extended-release product is then achieved by combining IR beads with SR beads in a defined dosage ratio (20:80 w/w) followed by encapsulation to the desired product strength of 10, 15, 20, 30, 40, or 50 mg of hydrocodone bitartrate in hard gelatin capsules. It should be noted that all the capsule strengths (b) (4) The excipients include sugar spheres, hypromellose, silicon dioxide, and talc in addition to the ammonio methacrylate copolymer (b) (4) . The capsule shells contain titanium dioxide, FD&C Blue #1, FD&C Red #40, FDA Yellow iron oxide, FD&C Red #3, FDA Black iron oxide, FDA Red iron oxide, and gelatin. The drug product is manufactured by Alkermes Gaineville LLC (former Elan Holdings) in their Gaineville, Georgia facility, which has been deemed acceptable by the Office of Compliance.

Other CMC information
The Applicant requested a biowaiver for the 15mg strength. The biopharmaceutics reviewer agreed with the CMC team that the biowaiver request is acceptable based (b) (4) and the 15mg showed comparable batch analysis to the other strengths.

The rate-controlling polymer ammonio methacrylate copolymer (b) (4) is soluble in alcohol, therefore the extended-release characteristics of the product may be compromised in the presence of alcohol. This is discussed further in the clinical pharmacology section.

The drug product does not have any abuse-deterrent properties by design. The in vitro abuse liability study demonstrated that (b) (4)

The capsules are supplied in (b) (4) 100-count HDPE bottles with a child-resistant closure. The product is stored at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F). [See USP Controlled Room Temperature]. The proposed (b) (4) expiration dating period (b) (4) 24 months for the 100-count bottles are acceptable.

Of note, on January 25, 2013, the applicant submitted an amendment to the NDA withdrawing DMF (b) (4) for the (b) (4) API manufacturing site, so that only the (b) (4) DMF manufacturing facility will be used for this product.

The applicant submitted an amendment on September 24, 2013, stating that they only intended to market the 100-count bottles (b) (4) They removed all language referring to the (b) (4) bottles from the package insert.

I concur with the review team that there are no outstanding CMC concerns that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The following summary of the nonclinical pharmacology and toxicology data submitted in this application has been reproduced from pages 4 and 5 of Dr. Fields' review:

As stated in Dr. Bolan's review, the excipients, when calculated for the maximum theoretical daily dose of hydrocodone, can all be found in previously approved products and do not present any unique toxicologic concerns. All impurities/degradants in the drug substance and drug product are controlled at acceptable levels. Hydrocodone-related toxicities in acute and repeat-dose

general toxicology studies were consistent with the known toxicities of other opioid agonists.

The standard ICH battery of genetic toxicology studies was conducted. Hydrocodone tested negative in the in vitro bacterial reverse mutation assay, the in vivo mouse micronucleus assay, and the in vitro chromosome aberration assay in the absence of metabolic activation. In contrast, hydrocodone tested positive for clastogenic activity in the in vitro chromosome aberration assay in the presence of metabolic activation. Hydrocodone is considered to have clastogenic potential and a fourth test will be required to be conducted post-marketing. Carcinogenicity assessments in mice and rats with hydrocodone are currently being conducted by the Applicant and will be submitted to the NDA as a post-marketing requirement (PMR). At the time of this review, the results of the two carcinogenicity assessments are not available.

As stated in Dr. Bolan's review, a full battery of developmental and reproductive toxicology studies has been conducted with hydrocodone. Decreases in female fertility were observed at all doses tested in the fertility study. No NOAEL was established for effects on female fertility, the lowest dose tested was two-times the human dose of 100 mg/day on a mg/m^2 basis. However, the changes in fertility observed in the rat may be related to known opioid-mediated effects on prolactin, which is essential for estrous cycling in the rat. The clinical relevance of the fertility finding is not known. No effects of hydrocodone on male fertility parameters were observed (NOAEL is ten-times the human dose of 100 mg/day on a mg/m^2 basis), however, decreased weights of male reproductive organs were observed at all doses. No effects of hydrocodone were seen in a rat embryofetal development study at any dose tested, although hydrocodone-mediated decreases in fertility limited the dosing in the study (NOAEL is approximately two-times the human dose of 100 mg/day on a mg/m^2 basis). In the rabbit embryofetal development study, fetal body weights were significantly decreased in all treated groups. Increases in the number of fetal malformations, including umbilical hernia and various irregularly shaped bones (ulna, femur, tibia, fibula) were observed in the highest dose group. Decreases in the number of ossified hyoid bodies and xiphoid bones, considered a developmental variation, were also observed in the highest dose group. The NOAEL for teratogenicity in the rabbit study is ten-times the human dose of 100 mg/day on a mg/m^2 basis. In the peri- and post-natal study, hydrocodone-mediated decreases on pup body weights, viability and lactation indices were observed (NOAEL is 0.5-times the human dose of 100 mg/day on a mg/m^2 basis). A pregnancy category C is recommended for this product and the relevant results will be described in the label.

The recommendation from the pharmacology/toxicology team is that this NDA be approved with PMRs to conduct an additional fourth tier genetic toxicology study and complete the two ongoing carcinogenicity studies (mouse and rat) with hydrocodone bitartrate. Specific labeling changes proposed by the pharmacology/toxicology team are noted in Dr. Bolan's review.

I concur with the review team that there are no outstanding nonclinical pharmacology or toxicology concerns that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology and biopharmaceutics has been reproduced from pages 5 through 10 of Dr. Fields' review:

Clinical Pharmacology

The clinical pharmacology information in this NDA submission included six Phase 1 studies and two Phase 2 studies. Additionally, the Applicant conducted a population pharmacokinetic (PK) analysis using the information observed from conducted studies to support the hydrocodone dose linearity purpose. The following is a summary of Dr. Lee's review.

Relative Bioavailability (Study ZX002-1102)

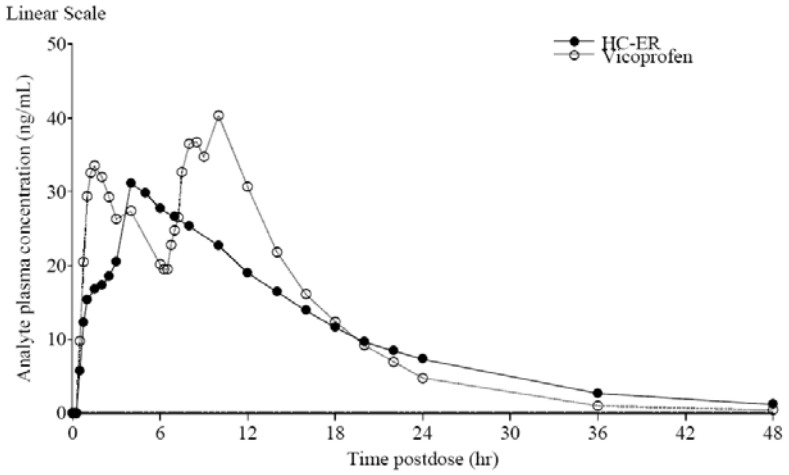
This was a Phase 1, open-label, randomized, two-dose, two-period cross-over study with minimum 5-day washout between treatments. The study was conducted in 15 healthy subjects between 18 and 45 years of age who received a single dose of 30 mg Zohydro ER and two consecutive doses of 2-tablets of Vicoprofen 6 hours apart for a total of 4 tablets. Subjects were fasted appropriately for both treatment groups. All doses were administered with 240 mL of ambient temperature water.

Mean hydrocodone Cmax values were 32 ± 7 and 46 ± 7 ng/mL for Zohydro ER and Vicoprofen treatments, respectively. Mean hydrocodone Cmax were not similar between the two treatments as indicated by the bioequivalence evaluation. Although Zohydro ER has both IR and ER characteristics, it is not surprising that it was not bioequivalent for Cmax when compared to a product with only IR characteristics.

Mean hydrocodone AUC values were 513 ± 92 and 559 ± 122 ng.h/mL for Zohydro ER and Vicoprofen treatments, respectively. The bioequivalence analysis indicated that the AUC values from the two treatments were equivalent.

The following figure taken from page 59 of Dr. Lee's review is a graphic representation of the relative BA results:

Figure 2: Mean Hydrocodone Concentrations at Scheduled Time Points, Stratified by Treatment

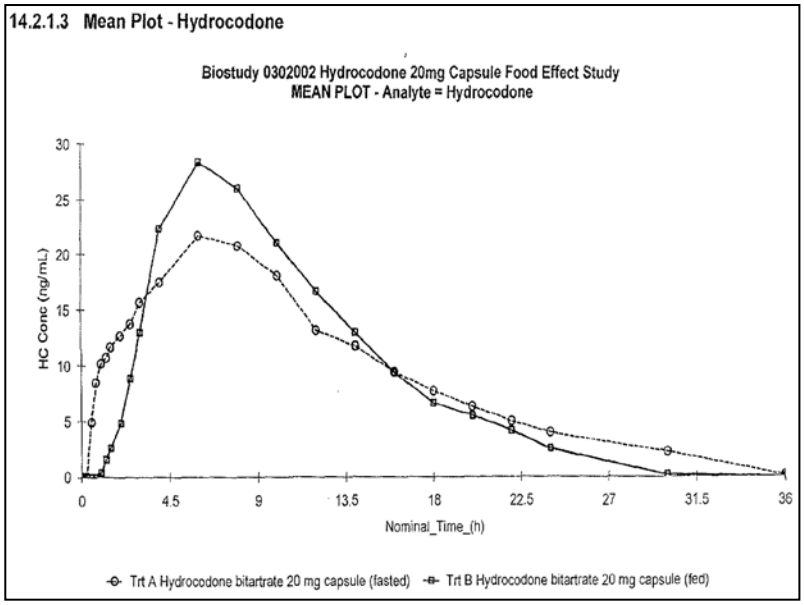


Source: Section 14, Figure 14.2.1-1a

Dose linearity
The Applicant conducted Phase 2 single and multiple-dose studies in bunionectomy and osteoarthritis subjects, respectively. In study ELN154088-201 (bunionectomy patients) linear pharmacokinetics were demonstrated after single doses of 10mg to 40mg. In Study ELN154088-203, multiple-dose PK was obtained on 10, 20, 30, and 40mg BID for 7 days in fed patients. Dose-linear increases in hydrocodone Cmax and AUC values were observed over the 10mg to 40mg dose range after multiple-dose administration.

Food effect
Food effect was assessed in Study 0302-002. Subjects received a single dose of Zohydro ER following a high fat meal compared with a fasting group of subject. Mean hydrocodone Cmax values were 28.8 ± 4.2 ng/mL and 22.7 ± 4.3 ng/mL in fed and fasted states, respectively, after a single dose 20 mg Zohydro ER. Mean hydrocodone Cmax increased approximately 27% in the fed state compared to the fasted state. However, the extent of absorption (AUC) of hydrocodone was similar between fed and fasted (338 ± 55 ng h/mL vs. 345 ± 37 ng.h/mL, respectively). The hydrocodone median Tmax were 6 h and 8 h for fasted and fed, respectively. The hydrocodone half-lives were 4.9 ± 1 h and 6.5 ± 0.9 h for fed and fasted states, respectively.

The relative change in Cmax with food is shown in the graph below from Dr. Lee's review:



Of note, there were two formulations used in clinical studies conducted by the Applicant; the clinical trial formulation ((b) (4) % polymer coated spheres produced at Athlone location) and the to-be-marketed formulation (b) (4) % polymer coated spheres produced at Gainsville location). The only trial that used the Athlone formulation was this food effect study. Although the formulation differs from the to-be-marketed formulation in the percentage of polymer coating, the clinical pharmacology review team has recommended that this study be considered adequate and be included in the label based on the following:

1. The formulations produced at the Athlone and Gainsville(to-be-marketed formulation) manufacturing sites are exactly the same, except for the differences in the polymer coating (b) (4) and (b) (4) %, respectively, and, that the differences are not significant enough to alter the exposure
2. All strengths, 10 to 50 mg, manufactured from the Gainsville manufacturing site were used in clinical studies, including the Phase 3 study, ZX002-0801, such that performance aspects of the formulation are not in question.
3. Comparison of Cmax across Phase 1 studies indicated, with a caveat that this is a cross-study comparison, that Athlone and Gainsville formulations are not drastically different when 'fasted' treatment from the food study is compared to other 'fasted' treatments, or 'fed' treatment from the food study is compared to other 'fed' treatments

Alcohol interaction

Study ZX002-0901 was a Phase 1, open-label, randomized, single-dose, three-period crossover study that assessed the PK of a single dose of 50mg Zohydro ER coingested with orange juice (no alcohol), 20%, and 40% alcohol. Study subjects were appropriately naltrexone blocked.

Mean hydrocodone Cmax values were 109 ± 39, 52 ± 11, and 46 ± 8.6 ng/mL in 40, 20 and 0% alcohol in the fasted state, respectively. Mean hydrocodone Cmax increased approximately 2.4-fold in 40% alcohol compared to the 0% alcohol treatments. The greatest increase in Cmax was observed at 3.9-fold

(Subject #016). Mean hydrocodone Cmax value for 20% alcohol was comparable to 0% alcohol treatment.

Mean hydrocodone AUC values were comparable for all alcohol treatments (1017 ± 217, 900 ± 243, and 846 ± 225 ng.h/mL in 40, 20 and 0% alcohol in fasted state, respectively). Mean hydrocodone AUC was slightly higher for subjects receiving 40% alcohol. The greatest increase in AUC observed was 1.7-fold (Subject #007). This difference was not statistically significant (within bioequivalence range).

Mean hydrocodone Tmax values were 2.4 ± 1.1, 5.4 ± 1.5, and 6.2 ± 2.1 h in 40, 20 and 0% alcohol in fasted state, respectively. Tmax decreased to less than half the time for subjects receiving 40% alcohol in comparison to those receiving 20% or 0% alcohol.

This study demonstrated that the rate of absorption (Cmax) was affected by co-ingestion with 40% alcohol in the fasted state. However, the greatest individual increase in Cmax was comparable or lower than those of the already approved extended-release opioid products. Therefore, the alcohol interaction with the proposed product is not considered as an approvability issue. Warning language on risks with alcohol consumption will be included in the label.

Hepatic impairment
Study ZX002-1001 was a Phase 1, open-label, single-dose, parallel study in subjects with mild or moderate hepatic impairment who received a single 20mg dose of Zohydro ER in a fasted state, compared with control subjects.

Mean hydrocodone Cmax values were 25 ± 5, 24 ± 5, and 22 ± 3.3 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone Cmax values were comparable for all groups.

Mean hydrocodone AUC values were 509 ± 157, 440 ± 124, and 391 ± 74 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone AUC increased approximately 26% for moderately impaired subjects compared to that of normal subjects; this increase in exposure may not be clinically significant and may not warrant a dose adjustment. Severely impaired subjects were not studied. Patients in this population should use a low initial dose and be monitored closely.

Renal impairment
Study ZX002-1002 was a Phase 1, single-dose, parallel study in subjects with mild, moderate, or severe renal impairment per Cockcroft-Gault criteria. Healthy control subjects were matched to renally-impaired subjects. All subjects received a single dose of 20 mg Zohydro ER in a fasted state.

Mean hydrocodone Cmax values were 26 ± 6.0, 28 ± 7.5, 21 ± 5.1 and 19 ± 4.4 ng/mL for severe, moderate, mild renal impaired and normal subjects, respectively. Mean hydrocodone Cmax values were comparable for all groups.

Mean hydrocodone AUC values were 487 ± 123, 547 ± 184, 391 ± 122 and 343 ± 105 ng.h/mL for severe, moderate, mild renal impaired and normal subjects, respectively.

Hydrocodone exposures wee similar in moderate or severe renal impairment. However since hydrocodone plasma levels may be increased in patients with moderate to severe renal impairment, patients in this population should receive low initial doses of Zohydro ER and be monitored closely.

Elderly
No formal studies evaluated differences in hydrocodone PK between young and elderly subjects. However elderly subjects are more likely to have compromised renal function and experience higher hydrocodone exposures compared to younger subjects with normal renal function. Therefore, elderly patients should be started on a low dose of Zohydro ER and monitored closely.

Drug interactions
No drug interaction studies were submitted by the Applicant. It is well known that the formation of norhydrocodone is mediated by CYP3A4, while the formation of hydromorphone is primarily mediated by CYP2D6. Inhibition or induction of these enzymes due to interacting drugs or genetic predisposition is likely to alter the metabolic profile of hydrocodone. Therefore, caution is advised when administering Zohydro ER in combination with CYP3A4 inhibitors or inducers. The extent of drug interaction could be more pronounced with concomitant use of CYP 2D6 and 3A4 inhibitors.

Biopharmaceutics
The biopharmaceutics review team was asked to assess this NDA submission for the following:

- Level A IVIVC model
- Dissolution method and acceptance criteria
- Critical process attributes for drug release
- Formulation development
- Dissolution stability

The following are the conclusions and recommendations as stated in Dr. Hughes' review:

CONCLUSION/RECOMMENDATION:

1. DMF (b) (4) was found adequate, with comments, from the Biopharmaceutics perspective to support NDA approval. An adequate response to the DMF comments is pending; however, based on the outstanding issues noted for the DMF, the following conclusions can be made.

a. The proposed dissolution method and acceptance criteria are acceptable.

Parameter	Criteria
Apparatus	USP 1 (40 mesh baskets)
Paddle Speed	100 rpm
Media	pH 6.8 Phosphate Buffer, 500 mL @ 37°C
Detection	HPLC
Acceptance Criteria	1 hour = (b) (4) 4 hour = 8 hour = 12 hours =

b. A Level A IVIVC model submitted under DMF (b) (4) is adequate to support future post-approval drug product changes in accordance with the SUPAC-MR guidance (see DMF review for additional details). The IVIVC model described in the NDA is not the same IVIVC model accepted for regulatory purposes.

2. A biowaiver is granted for the 15 mg capsule strength.
3. The proposed HC-ER capsule is susceptible to alcohol induced dose dumping in vitro. The safety implication of this finding is assessed by the assigned Clinical Pharmacology and Clinical reviewers.
4. A major formulation change was noted between product used in a PK food effect study and the product used in the clinical efficacy/safety studies. There were insufficient in vitro dissolution data to bridge the formulation changes; however, the to-be-marketed formulation, including the dose used for the food effect study, was used in the clinical safety and efficacy studies, which included PK assessments. Thus, there may be sufficient in vivo PK data on both formulations to support the adequacy of the food-effect study. The acceptability of the in vivo data is not under Biopharmaceutics purview. Refer to the Clinical Pharmacology review for additional details on the acceptability of the food effect study.
5. The in vitro and in vivo data support an extended release claim, from the Biopharmaceutics perspective.

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

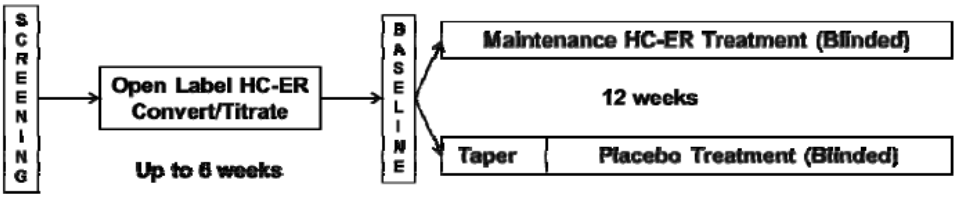
7. Clinical/Statistical-Efficacy

The following summary of the efficacy data for this application has been reproduced from pages 11 through 14 of Dr. Fields' review:

> Hydrocodone in combination with non-narcotic analgesics are the most commonly prescribed analgesic in the US, with approximately 131 million prescriptions dispensed in 2011. Because of its wide use for decades as an analgesic, the Agency stated at a Type B meeting with Zogenix in June, 2008, that for a 505(b)(2) application, one principle efficacy study would be sufficient to demonstrate the efficacy of Zohydro ER in an appropriate population for the

intended indication. Advice was provided to the Applicant regarding the preferred endpoint (change from baseline in average 24-hour pain intensity), duration of double-blind treatment (12-weeks), and the inclusion of COWS and SOWS assessments to evaluate opioid withdrawal during the trial.

The Applicant conducted and submitted the results of Study ZX002-0801 (henceforth Study 801) with this NDA, a multicenter, randomized double-blind, placebo-controlled trial that used an enriched enrollment randomized withdrawal design to evaluate the efficacy, tolerability and safety of hydrocodone bitartrate extended-release capsules in opioid-experienced subjects with moderate to severe chronic low back pain. The following figure from the Applicant's submission illustrates the design of Study 801.



At screening, subjects were eligible to enter the study if they had a clinical diagnosis of moderate to severe CLBP present for at least several hours a day for a minimum of 3 months; were classified as non-neuropathic (Class 1 and 2), neuropathic (Class 3, 4, 5, and 6), or symptomatic for more than 6 months after low back pain surgery (Class 9) based on the Quebec Task Force Classification of Spinal Disorders; required around-the-clock opioid therapy; were taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 45 mg oral morphine equivalents per day (as any immediate or ER opioids); had an average clinic pain score ≥4 on the 11-point (0-10) Numerical Rating
Scale (NRS) for the last 24 hours of the Screening Phase; had stable adjunctive regimens (e.g., physical therapy, biofeedback therapy); were in generally good health; were able to effectively communicate with the study staff and able to complete study procedures; and voluntarily provided written informed consent.

Subjects were excluded from entering the study if they: had any condition that would increase the risk of opioid-related adverse events (e.g., respiratory depression, chronic constipation, and others), had a history of illicit substance or alcohol abuse in the past 5 years or any history of opioid abuse, positive urine drug screen for illicit drugs or non prescribed controlled substances, had severe depression or anxiety, active fibromyalgia or other pain syndrome, spinal or back pathology, condition that would interfere with the assessment of low back pain, were obese, or had allergy to any of the study drugs.

During the open-label conversion/titration phase, subjects were converted to a dosage of Zohydro ER that was approximately 20%-30% less than the conversion dose of Zohydro ER calculated based on their prior opioid treatment, using a conversion table based on approximate equivalent doses of other opioids to hydrocodone. Subject was titrated if needed, in an open-label fashion to achieve adequate analgesia. Rescue medication consisted of up to 4 tablets per day of immediate-release hydrocodone 5mg/APAP 500mg. A stabilized dose was one that subjects tolerated well for at least 7 days with an average 24-hour

daily average pain score of ≤4 on the NRS during the last 7 days prior to Baseline, a reduction of 2 points on the NRS compared to Screening, and no more than 2 tablets of rescue medication on any day. Subjects who did not achieve a stabilized dose, who did not tolerate Zohydro ER treatment due to AEs, who were not compliant with dosing or drug accountability, or who could not complete required study procedures (e.g. study visits, use of the electronic diary) were discontinued from the study.

Subjects were randomized 1:1 to receive either Zohydro ER or placebo if they met the above criteria and had been stabilized on 40 to 200mg per day. The dosage could not be adjusted during the 12-week maintenance period. The initial 14-day supply of study medication contained a tapering dose of Zohydro ER for subjects randomized to placebo, and a mock taper for those randomized to Zohydro ER. Allowed rescue medication was hydrocodone 5mg/APAP 500mg up to two tablets per day. All other opioids, analgesics and other possibly confounding medication were prohibited during the study.

The primary efficacy endpoint of the study was the change from Baseline (randomization) to the end of the double-blind maintenance treatment phase (Day 85 or last visit) in average pain intensity on the 11-point NRS as recorded daily in an electronic diary, comparing Zohydro ER with placebo. Secondary efficacy endpoints included the response rate (with response defined as a 30% improvement from the screening pain intensity score to the Day 85 pain intensity score) and the Subject Global Assessment of Medication, SGAM. Although not specified in the protocol or subsequent protocol amendments, the Statistical Analysis Plan incorporated a hierarchical testing procedure for these endpoints.

Study 801 Results

Of the total 510 subjects enrolled, 302 subjects (59%) completed the conversion/titration (C/T) phase and were randomized to treatment and 208 subjects (41%) discontinued the C/T phase early. Of the 302 subjects randomized, 151 subjects (30%) were randomized to receive Zohydro ER and 151 subjects (30%) were randomized to receive placebo. Forty-one percent of subjects discontinued early from the C/T phase. The most common reasons included protocol violation, noncompliance with study drug, adverse events, and lack of efficacy.

One hundred eighty-three subjects completed the treatment phase, 124 received Zohydro ER and 59 placebo. The most common reasons for discontinuation during this phase in the Zohydro ER group were lack of efficacy (9%), noncompliance with study drug (3%), and adverse event (1%). As would be expected the most common reason for withdrawal from the placebo group was lack of efficacy (42%), followed by noncompliance with study drug (5%) and adverse event related to opioid withdrawal (5%). The large proportion of dropouts from the placebo group was likely due to the small amount of rescue medication allowed during this phase of the trial (a maximum of 2 hydrocodone 5mg/APAP 500mg tablets per day).

In terms of demographics the mean age was approximately 50 years, the percentage of females in the study was slightly greater than males (C/T phase 55% ; Treatment phase: 61% Zohydro ER, 49% placebo), and the majority of subjects were white (77-82% depending on phase and treatment). The average pain score at screening was approximately 7/10 on an 11-point NRS for all

phases, and baseline average pain score (at beginning of treatment phase) was approximately 3/10.

The primary efficacy endpoint for Study 801 was the mean change from Baseline to Day 85 in the Treatment Phase in the average 24-hour pain intensity scores on a 0-10 NRS based on subject diaries. Baseline was defined as the mean of the last 7 days on stabilized dosing of the average pain intensity rating prior to randomization into the maintenance treatment phase. Day 85 was defined as the mean of the last 7 days of the average pain intensity rating prior to Day 85 study visit of the treatment phase.

The primary efficacy analysis population was the Intent-To-Treat (ITT Population), and all 302 randomized subjects were included in the analysis. Missing pain scores were imputed using methods agreed upon between the Applicant and the Agency at the EOP2 meeting: baseline observation carried forward for subjects who discontinued due to opioid withdrawal; screening observation carried forward for subjects who discontinued due to AEs; and last observation carried forward for subjects who discontinued due to lack of efficacy and other reasons.

The primary efficacy analysis used an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline to Day 85. The model included treatment group as a factor and the baseline pain score and screening pain score as covariates. The Zohydro ER and placebo groups were compared at the 5% level of significance The table below from the Applicant's submission shows the results of the primary endpoint analysis.

Table 15: Primary Efficacy Endpoint: Change from Baseline of Average Daily Pain Intensity Score (patient diary), ITT population, Study 801

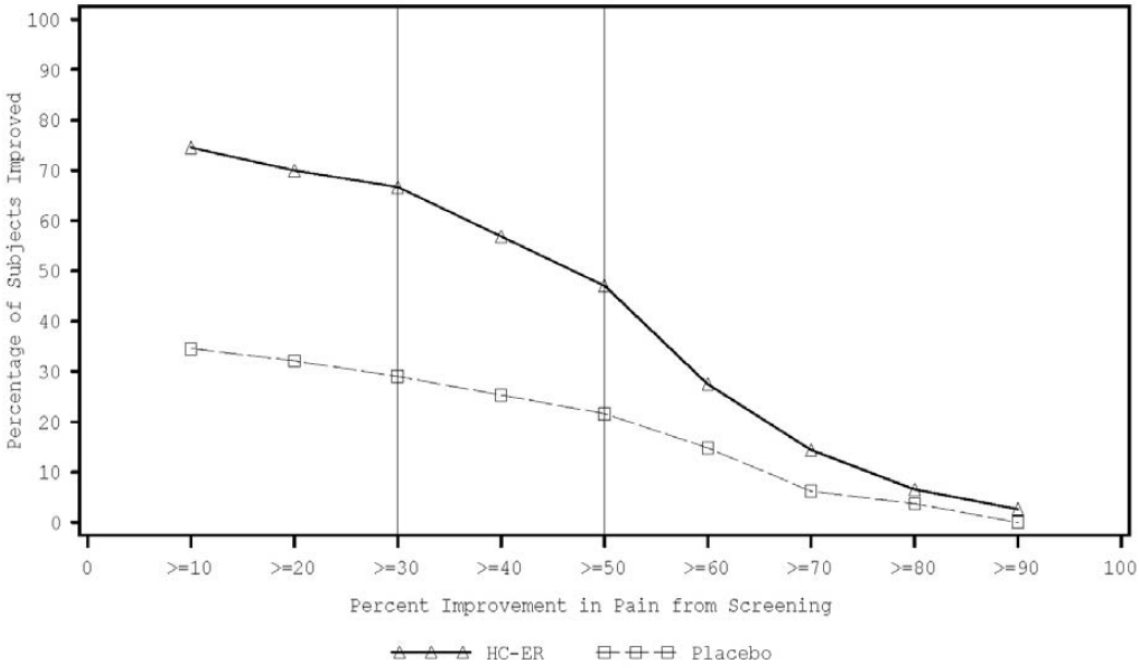
Change from Baseline	HC-ER (N=151)	Placebo (N=151)
Mean (SD)	0.48 (1.563)	0.96 (1.550)
Range	-3.0 – 5.3	-2.4 – 6.7
LS Mean	0.48	0.95
p-value[a]	*0.008*	

[a] Treatment comparison using ANCOVA with treatment group as a fixed effect and screening pain score and baseline pain score as covariates.
ANCOVA = analysis of covariance.

Zohydro ER was superior to placebo in the change from Baseline to the end of study in average daily pain intensity score (p=0.008). The statistical review team was able to replicate the Applicant's analysis of the primary endpoint.

A continuous responder graph was also provided. The graph depicted the percentage of subjects achieving improvement across all possible cut-offs. All patients who discontinued were defined as non-responders. As shown in the figure below from the Applicant's submission, a greater percentage of subjects in the Zohydro ER group compared to placebo group showed improvement in pain across all response rates

Percentage Improvement in Average Pain from Screening to Final Visit



Other secondary endpoints that supported the primary analysis included the Subject Global Assessment of Medication, Worst Pain Intensity, Least Pain Intensity, and Time to Treatment Discontinuation. Analyses of these endpoints were numerically in favor of Zohydro ER.

The results of the analysis of rescue medication use during the double-blind treatment phase were somewhat atypical. Rescue medication during this phase was limited to 2 tablets per day of hydrocodone 5mg/APAP 500mg. The mean total daily dose of rescue for the hydrocodone component only in the Zohydro ER group was 6.0mg mg ± 3.4 mg, with a range from 0.1 mg to 12.5 mg. In the placebo group, the mean TDD of rescue medication was 7.5 mg ± 3.9 mg, with a range from 0.1 mg to 20 mg. The most likely explanation for the small difference between treatment groups in the use of rescue is the relatively low limit on the amount of allowed rescue medication.

I concur with the review team that the study has demonstrated that Zohydro ER is effective for the agreed upon indicated use.

8. Safety

The following summary of the safety data has been reproduced from pages 14 through 19 of Dr. Fields' review:

The Zohydro ER clinical development program consisted of 10 clinical studies: six phase I studies, two phase 2 studies and two phase 3 studies. The Applicant

has provided adequate exposure to assess safety, with a total of 1512 subjects exposed to at least one dose of Zohydro ER, 332 subjects exposed for at least 6 months, and 290 subjects for at least one year. For Study 801, the maximum dose was 200mg/day, however in the open-label study 802, the maximum dose was up to 600mg/day.

There were five deaths among the 575 subjects in the chronic pain population exposed to Zohydro ER. Four deaths occurred during Study 802 as follows: completed suicide (carbon monoxide poisoning), drug toxicity (methadone and oxycodone), lung cancer, and coronary artery disease. The fifth death was an apparent suicide from an overdose of Zohydro ER approximately a year after the end of the study, in a patient who hoarded study medication during Study 802. Dr. Levin reviewed the deaths and concluded that the first four were unlikely related to study medication, and the fifth, while related, occurred a year after the study was completed.

Eighty-one subjects exposed to Zohydro ER reported a total of 118 nonfatal serious adverse events (SAEs). During the C/T phase, 22 subjects reported 32 nonfatal SAEs, and during the treatment phase, 56 subjects reported 83. There were no SAEs reported in the 151 subjects taking placebo, however, most of the SAEs occurred in Study 802 where there was no placebo group. The following table from Dr. Levin's review shows the SAEs observed in more than one subject in the chronic population:

Table 1: Medical Serious Adverse Events Observed in More than One Subject Chronic Population, Treatment Phase

	HC-ER			ZX002-0801
	ZX002-0801	ZX002-0802	Total	Placebo
Preferred term[a]	N=151	N=424	N=575	N=151
Subjects with at least 1 medical SAE	5 (3.3%)	52 (12.0%)	56 (9.7%)	
Chronic obstructive pulmonary disease	0	5 (1.2%)	5 (0.9%)	0
Osteoarthritis	0	4 (0.9%)	4 (0.7%)	0
Pneumonia	0	3 (0.7%)	3 (0.5%)	0
Dehydration	0	2 (0.5%)	2 (0.3%)	0
Small intestinal obstruction	0	2 (0.5%)	2 (0.3%)	0
Intentional overdose	0	2 (0.5%)	2 (0.3%)	0
Hypokalaemia	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Anaemia	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Non-cardiac chest pain	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Depression	1 (0.7%)	1 (0.2%)	2 (0.3%)	0

Percentages are based on the number of subjects in each column.
Subjects were counted once within each preferred term.
[a]All investigator adverse event terms were coded using MedDRA dictionary version 12.1.

Source: ISS (June 14, 2012), p.133

Dr. Levin reviewed the patient narratives for all SAEs. The SAEs he determined to be reasonably related to Zohydro ER are consistent with the known safety profile of extended-release opioids, and include the following: anxiety (1), mental impairment (2), small bowel obstruction (2) and abdominal distension/constipation (3). Dr. Levin reviewed three events coded as SAE due to an overdose and determined that these cases were neither overdoses nor

SAEs. The protocol of the study (Study ELN-154088-203) from which these cases were reported defined an overdose as taking more pills than prescribed whether or not there were any clinical sequelae. Each of these cases took one extra dose of study drug because they forgot whether they had taken their previous dose, and none experienced any adverse event related to the extra dose.

Dr. Levin also reviewed all narratives for subjects discontinuing treatment due to adverse events. The most common adverse events leading to study discontinuation were not unexpected for an opioid and included nausea, somnolence, headache, constipation, vomiting, lethargy, fatigue, and cognitive changes. The following two tables from Dr. Levin's review summarize discontinuation due to adverse events in the C/T Phase and the Treatment Phase of Studies 801 and 802.

Table 2: Adverse Events that Led to Discontinuation of More Than One Subject in the Chronic Population, C/T Phase

	HC-ER		
Preferred term[a]	**ZX002-0801 N=510**	**ZX002-0802 N=638**	**Total N=1148**
Subjects with at least 1 TEAE that led to discontinuation	55 (10.8%)	66 (10.3%)	121 (10.5%)
Nausea	15 (2.9%)	10 (1.6%)	25 (2.2%)
Somnolence	4 (0.8%)	9 (1.4%)	13 (1.1%)
Headache	3 (0.6%)	7 (1.1%)	10 (0.9%)
Constipation	7 (1.4%)	3 (0.5%)	10 (0.9%)
Vomiting	6 (1.2%)	4 (0.6%)	10 (0.9%)
Lethargy	2 (0.4%)	7 (1.1%)	9 (0.8%)
Insomnia	2 (0.4%)	7 (1.1%)	9 (0.8%)
Dizziness	2 (0.4%)	2 (0.3%)	4 (0.3%)
Oedema peripheral	1 (0.2%)	3 (0.5%)	4 (0.3%)
Pruritus allergic	2 (0.4%)	2 (0.3%)	4 (0.3%)
Fatigue	3 (0.6%)	0	3 (0.3%)
Abdominal pain	2 (0.4%)	1 (0.2%)	3 (0.3%)
Agitation	2 (0.4%)	0	2 (0.2%)
Depression	2 (0.4%)	0	2 (0.2%)
Anxiety	1 (0.2%)	1 (0.2%)	2 (0.2%)
Non-cardiac chest pain	1 (0.2%)	1 (0.2%)	2 (0.2%)
Pain in extremity	1 (0.2%)	1 (0.2%)	2 (0.2%)
Haematochezia	1 (0.2%)	1 (0.2%)	2 (0.2%)
Hyperhidrosis	1 (0.2%)	1 (0.2%)	2 (0.2%)
Drug withdrawal syndrome	0	2 (0.3%)	2 (0.2%)
Feeling jittery	0	2 (0.3%)	2 (0.2%)
Irritability	0	2 (0.3%)	2 (0.2%)
Arthralgia	0	2 (0.3%)	2 (0.2%)

Percentages are based on the number of subjects in each column.
Subjects were counted once within each preferred term.
All investigator adverse event terms were coded using MedDRA dictionary version 12.1.
Drug diversion events are not included in this table.

Source: ISS (June 14, 2012), p.137

Table 3: Adverse events that Led to Discontinuation of More than One Subject in the Chronic Population, Treatment Phase

	HC-ER			ZX002-0801 Placebo
	ZX002-0801	ZX002-0802	Total	
Preferred term[a]	N=151	N=424	N=575	N=151
Subjects with at least 1 TEAE that led to discontinuation	3 (2.0%)	34 (8.0%)	37 (6.4%)	16 (10.6%)
Abdominal pain upper	0	2 (0.5%)	2 (0.3%)	0
Constipation	0	2 (0.5%)	2 (0.3%)	0
Cognitive disorder	0	2 (0.5%)	2 (0.3%)	0
Back pain	1 (0.7%)	1 (0.2%)	2 (0.3%)	2 (1.3%)
Withdrawal syndrome	1 (0.7%)	0	1 (0.2%)	6 (4.0%)
Insomnia	0	1 (0.2%)	1 (0.2%)	2 (1.3%)

Percentages are based on the number of subjects in each column.
Subjects were counted once within each preferred term.
All investigator adverse event terms were coded using MedDRA dictionary version 12.1.
Drug diversion events are not included in this table.

Source: ISS (June 14, 2012), p.138

Common adverse events noted in Studies 801 and 802 were consistent with the opioid class of drugs and include constipation, nausea, somnolence, fatigue, headache, and dizziness. The following table from Dr. Levin's review shows adverse events occurring in at least 2% of subjects in Study 801.

Table 4: Adverse Events in ≥2% of Subjects in ZX002-0801

	Open-Label Titration Period	Double-Blind Treatment Period	
	Zohydro	Zohydro	Placebo
Preferred Term	(N = 510)	(n = 151)	(n = 151)
Constipation	56 (11.0%)	12 (7.9%)	0 (0.0%)
Nausea	50 (9.8%)	11 (7.3%)	5 (3.3%)
Somnolence	24 (4.7%)	1 (0.7%)	0 (0.0%)
Fatigue	21 (4.1%)	1 (0.7%)	2 (1.3%)
Headache	19 (3.7%)	0 (0.0%)	2 (0.7%)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Zohydro	Zohydro	Placebo
Preferred Term	**(N = 510)**	**(n = 151)**	**(n = 151)**
Dizziness	17 (3.3%)	3 (2.0%)	1 (0.7%)
Dry Mouth	16 (3.1%)	0 (0.0%)	0 (0.0%)
Vomiting	14 (2.7%)	7 (4.6%)	1 (0.7%)
Pruritus	13 (2.5%)	0 (0.0%)	0 (0.0%)
Abdominal Pain	8 (1.6%)	4 (2.6%)	0 (0%)
Edema peripheral	7 (1.4%)	4 2.6%)	0).0%)
Upper respiratory tract infection	7 (1.4%)	5 (3.3%)	1 (0.7%)
Muscle spasms	6 (1.2%)	4 (2.6%)	2 (1.3%)
Urinary Tract Infection	4 (0.8%)	8 (5.3%)	3 (2.0%)
Back Pain	4 (0.8%)	6 (4.0%)	5 (3.3%)
Tremor	1 (0.2%)	4 (2.6%)	1 (0.7%)

Source: Tables 14.3.9.3.1 and 14.3.9.3.2 in the ISS (June 14, 2012)

In the long-term open-label safety study (ZX002-0802), the common adverse events were reviewed by Dr. Levin and found to be similar to Study 801. The most common adverse events during the C/T Phase Study 802 were: constipation (11.3%), nausea (10.7%), somnolence (7.7%), headache (7.5%), vomiting (4.1%), insomnia (3.8%), fatigue (3.6%), diarrhea (3.1%), dizziness (2.8%), dry mouth (1.9%) and pruritus (1.7%). In the treatment phase the most common adverse events were: constipation (12.5%), back pain (11.1%), nausea (9.9%), vomiting (9.7%), arthralgia (7.8%), headache (6.8%), urinary tract infection (6.6%), upper respiratory tract infection (5.9%), fall (5.9%), anxiety (5.4%), nasopharyngitis (5.7%), sinusitis (5.4%), insomnia (5.0%). Additional adverse events reported that are often associated with opioids included somnolence (4.2%), fatigue (3.5%), confusion (3.3%), and dizziness (3.1%).

There were no clinically meaningful changes in laboratory assessments (hematology and clinical chemistry) in the chronically treated subjects in Studies 801 and 802. Vital signs were monitored at each study visit in the two chronic studies, and no clinically significant unexpected changes in any of the

parameters monitored (blood pressure, pulse, temperature, respiratory rate) were observed. Mild changes in blood pressure were consistent with the hypotensive effect known to occur with opioids.

In Study ELN-154088-201, the single-dose post-bunionectomy study, hypoxia was reported as an adverse event in four subjects and oxygen desaturation was reported in an additional three subjects. The oxygen saturation values for the four subjects reported to have hypoxia were all greater than 90%. Two of the subjects were on Zohydro ER (10 mg and 30 mg), one subject was on 10 mg HC/APAP and one subject was on placebo. There were three subjects with oxygen saturation below 90% (87%, 89% and 89%). Two subjects were on Zohydro ER (10 mg and 20 mg) and one subject on 10 mg HC/APAP. There did not appear to be a dose response with Zohydro ER and hypoxia or desaturation (i.e., no case on the highest dose 40 mg and only one case on the next highest dose, 30 mg). This finding of oxygen desaturation during the post-operative period is not unexpected. The label specifically notes that Zohydro ER is not indicated in the immediate postoperative period.

ECGs were collected at screening and end of study in 159 subjects in four Phase 1 and 2 studies. Data for P-R interval, QRS interval, and QT interval were reviewed and no meaningful changes were identified in theses parameters. Interpretation of the findings is limited because ECGs were not collected at Cmax, and the highest dose administered was 40mg.

Special Safety Issue-audiology assessments

Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this Zohydro ER is higher than the labeled doses from combination products, the Division requested that Zogenix perform audiometry assessments to monitor for potential hearing loss in the principle clinical efficacy trial. Results of the audiometry evaluations performed on 510 subjects in Study 801 were reviewed by James Kane, Ph.D. from the Center for Devices and Radiological Health (CDRH) at the FDA. He concluded that Zohydro ER appears not to affect hearing sensitivity for the dosages studied (maximum Zohydro ER dose allowed in Study ZX002-0801 was 200 mg per day). Details regarding his consult response may be found in Dr. Levin's review.

Misuse, Abuse, and Diversion

The Controlled Substance Staff was consulted to review data regarding misuse, abuse, and diversion of Zohydro ER during the clinical trials; however they have not yet completed their review. The Applicant utilized "diversion events" reported during the Phase 3 trials as a measure of abuse-related events. The Applicant included cases where missing drug was observed, and the study medication could not be 100% accounted for at either the site or subject level. The cases were classified under a number of categories including "administrative serious adverse events". For those considered administrative in nature, the Applicant did not supply narratives, but did provide adverse event report forms.

The Applicant reported 92 diversion-related adverse events in studies 801 and 802. Sixty three possible cases of drug diversion were identified in studies 801 and 802, 13 in Study 801 (2.5%), and 50 in Study 802(7.8%), and six cases of possible abuse. Examples of abuse included tampering with the urine drug

> screen sample, and tampering with the rescue medication to extract hydrocodone, and obtaining prescriptions from more than one prescriber for hydrocodone/acetaminophen.
>
> As a Schedule II opioid analgesic, it is not unexpected that events of misuse, abuse, and diversion would be reported during the clinical trials of Zohydro ER. Hydrocodone is a Schedule II opioid analgesic with abuse liability similar to other drugs its class. In fact, additional in vivo human abuse liability studies were not required for this application since the abuse liability of this drug substance is well known, and the Applicant has made no claims that Zohydro ER is an abuse deterrent formulation.
>
> Safety Summary
> In summary, the safety data provided by the Applicant has demonstrated that during the development of Zohydro ER, the safety profile is consistent with other extended-release opioid analgesics when used as labeled in patients with chronic pain who require treatment with an around-the-clock opioid analgesic. While there were reports of diversion and abuse during the clinical trials, this is not unexpected for a drug in this class. No new or unexpected safety signals were identified during review of this NDA.

I concur with the review team that no new or unexpected safety signals have been demonstrated during this development program.

9. Advisory Committee Meeting

The following summary of the AADPAC meeting held on December 7, 2012 has been reproduced from pages 20 through 22 of Dr. Fields' review:

> The Anesthetic and Analgesic Drug Products Advisory Committee met on December 7, 2012 to discuss this NDA. Although the Division was in agreement with the Applicant that they had provided sufficient evidence that their product is safe and effective when used according to the product labeling and inclusion of Zohydro in the ER/LA REMS, it was determined that it was important to present this application to the advisory committee to obtain their input on the product's potential for abuse and misuse, how this may compare to the already approved products in the ER/LA class, and whether these issues should affect the approvability of Zohydro.
>
> The committee was reminded during Dr. Rappaport's introductory comments that if approved, Zohydro ER will be the first FDA approved and marketed, single-entity hydrocodone analgesic product, and will be available in an extended-release formulation. While combination hydrocodone products are currently controlled under CSA Schedule III, this new single-entity product would be controlled under Schedule II, as are the other single entity ER/LA opioids. In addition, Zohydro ER as a member of the ER/LA opioid class would fall under the ER/LA REMS that was approved in July, 2012. Dr. Rappaport stated that regardless of the existing REMS, it can be anticipated that a single-entity hydrocodone product will contribute to the already critical public health problem of prescription opioid abuse and misuse. And, it is also important to

recognize that this product may be a useful addition to the armamentarium of analgesic drug products that treat chronic pain.

The Agency's presentations during the AC meeting included drug utilization for the combination hydrocodone products by the Office of Safety and Epidemiology (OSE), that stated that the utilization of combination hydrocodone containing analgesics far exceeded all other opioid analgesics analyzed; the Division of Epidemiology within OSE, that discussed the potential risk of abuse of a single entity ER hydrocodone product based on the experience with combination IR oxycodone products and single-entity ER oxycodone. The findings showed that the abuse ratio (ER visits/number of tablets dispensed) of single-ingredient ER oxycodone products is 3-4 fold higher than combination IR oxycodone products (although there are limitations to this analysis as the numerator and denominator data are not linked), which may be predictive of the pattern expected with hydrocodone; and a presentation by Dr. Sharon Walsh who discussed abuse liability studies of hydrocodone conducted in healthy volunteers and opioid abusers that showed the profile for hydrocodone is similar to comparator opioids, including morphine, hydromorphone and oxycodone.

The Applicant presented a summary of their proposed additional risk management tools that they intend to utilize to supplement the ER/LA opioid analgesic REMS. The proposal includes:

1. Commercialize Zohydro ER responsibly (prescriber target audience, pain docs, pain journals, incentivize education,)
2. Augment the ER/LA REMS with their voluntary Zohydro ER Safe-Use initiative that is designed to
   i. Increase and improve participation in training programs and monitor effectiveness
   ii. Uphold safe use among patients
   iii. Implement rigorous utilization surveillance systems
   iv. Take corrective actions if issues are detected

The following is a brief summary of the questions asked of the advisory committee and their votes and discussion.

1. **VOTE**: **Has the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time**?

   Vote: ***Yes= 7*** ***No = 6*** ***Abstain = 1***

   Discussion

   The committee members who voted "Yes" stated that the Applicant had met the efficacy standards set forth by the Agency, and they agreed that the data suggest that Zohydro ER is efficacious, especially given the history of efficacy of combination hydrocodone/acetaminophen products. The committee members who voted "No" and the member who abstained agreed that the length of the 12-week study period was not sufficient to demonstrate efficacy for a chronic use indication

2. **VOTE**: **Has the Applicant demonstrated that Zohydro ER is safe in the intended population?**
3. ***Vote:*** ***Yes= 5*** ***No = 9*** ***Abstain = 0***

Discussion
The committee agreed that the Applicant met the safety standards set forth by the Agency and stated that Zohydro ER is as safe as other long-acting and extended-release opioid analgesics that have previously been approved. However, the majority of the committee did not agree that the Applicant demonstrated that Zohydro ER is safe in the intended population. The committee members who voted "No" shared their concerns about long-term safety risks including risk of addiction. Additionally, these committee members noted that drug diversion and deaths still occurred in clinical trials despite close monitoring, and that frequency of these adverse outcomes would likely be worse in real life clinical practice in the absence of close monitoring.

4. **DISCUSSION**: **Please discuss whether the data presented or discussed suggest that the postmarketing experience concerning abuse with Zohydro ER would be expected to be different from the postmarketing experience associated with other approved Schedule II extended-release opioids.**

Discussion
Some committee members thought that the post-marketing experience concerning abuse would be similar to other ER/LA opioids while others thought that Zohydro ER would be abused more than members of the class. There was concern that since the combination hydrocodone/acetaminophen products are the most widely abused opioid, Zohydro ER would be more likely to be abused due to the absence of acetaminophen.

5. **DISCUSSION: Please discuss whether the data support the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS.**

Discussion
The committee felt that the current ER/LA Opioid Analgesic REMS will at best be modestly effective in addressing the public health issues of opioid abuse and misuse for ER/LA opioids in general, including Zohydro ER. They stated there is a need for additional postmarketing risk mitigation requirements beyond the current REMS for the entire class.

6. **VOTE: Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?**
Vote: ***Yes= 2*** ***No = 11 Abstain = 1***

Discussion:
The committee agreed that standards for opioid product approval should be raised in light of the current public health concerns of abuse and misuse. The committee stated that the FDA should not approve ER/LA opioid analgesics without tamper/abuse-deterrent properties, and that additional risk mitigation features should be adopted to strengthen the current ER/LA Opioid Analgesic REMS.

The following summary of our perspective on the committee's decisions and recommendations has been reproduced from pages 2 and 3 of Dr. Fields' addendum to her review:

> At this meeting, the Office of Surveillance and Epidemiology presented drug utilization data along with data on emergency room visits related to oxycodone use comparing single-entity ER oxycodone with combination IR oxycodone products as one way to explore the potential for abuse following marketing of the first single-entity hydrocodone extended-release product. The findings showed that the proportion of ER visits relative to the number of tablets dispensed (known as the abuse ratio) of single-ingredient ER oxycodone products is three- to four-fold higher than for combination IR oxycodone products. When interpreting this analysis, it is important to note the differences between the current environment for the introduction of Zohydro ER to the marketplace, and the environment that existed when extended-release oxycodone was approved in the mid- 1990's. OxyContin was approved in 1995, which was when the treatment of pain became an important aspect of medical care, and the assessment of pain became the "fifth vital sign." OxyContin was also promoted by industry as less abusable compared to IR oxycodone, which was untrue. In contrast, Zohydro ER will be entering the market during a time of heightened awareness of the risks abuse and misuse of prescription opioids, with more appropriate labeling and the ER/LA class REMS.
>
> After deliberations, the committee agreed that the Applicant met the approval standards set forth by the Agency and stated that Zohydro ER is as safe as other long-acting and extended-release opioid analgesics that have previously been approved. However, the majority of the committee voted that the Zohydro ER NDA should not be approved (11 against approval, two in favor of approval, one abstention) because of the concerns regarding abuse and misuse for Zohydro ER as well as the already approved ER/LA opioid analgesics.
>
> I disagree with the committee's conclusion, in that the benefit risk balance for the already approved non-abuse deterrent opioid analgesics and Zohydro ER remains favorable for patients requiring chronic opioid therapy. The products provide effective and safe treatment options for patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

I concur with Dr. Fields' conclusions.

10. Pediatrics

The Division's current recommendations for pediatric studies for extended-release opioid analgesics under PREA is to waive studies in patients less than 7 years old because there are too few patients with chronic pain in this age group to study. This recommendation is based on an article that was authored by the academic expert participants following their attendance at a 2009 FDA-convened workshop that included thought leaders in pediatric analgesic clinical trials and treatment of pediatric pain. Those authors concluded that the efficacy of certain classes of drugs, including opioids, could be extrapolated from adults to pediatric patients ages 2 years and older. The basis for extrapolation is that

the exposure response to opioids and the mechanism of underlying pain are expected to be similar in children and adults.

The following summary of the pediatric issues related to this application has been reproduced from pages 22 and 23 of Dr. Fields' review:

> The Applicant's initial Pediatric Plan submitted with the NDA was not in line with the [division's] requirements. The Applicant submitted a revised pediatric plan as follows, which appears acceptable. This plan was presented to the Pediatric Research Committee on January 30, 2012, and they concurred with the plan.
>
> The Applicant has requested a waiver for studies in patients less than 7 years of age, and deferral of PK and safety studies in patients 7 to <12 years and 12 to < 17 years. They propose to conduct two separate open-label PK and safety studies with Zohydro ER in opioid-experienced pediatric subjects with chronic pain. The first study will enroll subjects aged
> 12 to < 17 years of age, and the second study will enroll subjects ages 7 to < 12 years.
>
> The Applicant anticipates that some subjects may require doses lower than the current lowest developed dosage strength of Zohydro ER (10 mg). While the six (10, 15, 20, 30, 40, and 50 mg) current dosage strengths of Zohydro ER represen (b) (4) cannot be produced using the current manufacturing process (b) (4). The Applicant proposes to develop (b) (4)
>
> The proposed timeline for the studies is:
>
> **Pediatric Subjects Ages 12 to <17**
>
> - Protocol submitted for review 12 months from NDA approval
> - Study start – 24 months from NDA approval
> - Study stop – 66 months from NDA approval
> - Final report submitted – 72 months from NDA approval
>
> **Pediatric Subjects Ages 7 to <12**
>
> - Protocol submitted for review – 48 months from NDA approval
> - Study start – 60 months from NDA approval
> - Study stop – 96 months from NDA approval
> - Final report submitted – 102 months from NDA approval

11. Other Relevant Regulatory Issues

Due to the increasingly serious public health problem of prescription opioid abuse and misuse, and the consequences including addiction, overdose and death, the Agency determined that increased warnings and a reframing of the

indication were necessary for the labeling of the ER/LA opioid analgesic drug products. This determination was based on extensive review of the available data and related information, as well as public input from a number of sources including citizen petitions, the Zohydro ER Advisory Committee Meeting, and a Part 15 Hearing held on February 7th and 8th of this year on the impact of approved drug labeling on chronic opioid therapy. During a briefing for the CDER Director, Dr. Janet Woodcock, held on February 6, 2013, issues related to the approval of new non-abuse deterrent, extended-release opioids in the environment of the worsening public health problem of prescription opioid misuse and abuse were discussed.

In addition, the Agency determined that certain studies were necessary to better understand the long-term safety and efficacy of the ER/LA opioids. As such, the Agency developed language for a class labeling change for all ER/LA opioid analgesic drug products, and a set of studies which would be postmarketing requirements (PMRs). On September 10, 2013, the Division sent letters to the manufacturers of the ER/LA opioid analgesics that set out the required labeling changes and postmarketing studies. The PMRs will assess the known risks of these drugs in long-term use (including the known serious risks of addiction, abuse, and misuse), the risk of developing opioid-induced hyperalgesia, and the overall risk-benefit profile of long-term use. As a member of the ER/LA opioid analgesic drug class, Zohydro ER will have the same required language in its label and the Applicant will be required to conduct studies to fulfill the PMRs. The Agency has strongly recommended that the ER/LA opioid analgesic drug product NDA holders work collaboratively to design, conduct and analyze these PMR studies, in the interest of saving time and resources, and of collecting a broad-based set of data describing the long-term efficacy and safety of this class of drugs.

The changes to the labeling language that are being required are quite extensive and are discussed in detail in Dr. Fields' review. These changes included additional warnings in the Boxed Warning section that highlight the risks of addiction, abuse and misuse and the potential for overdose and death, as well as a warning regarding the potential for neonatal opioid withdrawal syndrome in infants born to mothers who require opioid therapy during pregnancy. Additional warnings and precautions have been added throughout the rest of the label to accentuate these concerns. The indication has been changed to instruct prescribers to depend less on a categorical scale of moderate to severe pain in choosing to prescribe opioids for a patient, and to rely more on assessing the patient's needs for adequate pain control in light of the patient's previous experience with alternative analgesic treatments, and in balance with the risks specific to the patient, including the risks of developing addiction, and of misuse of the product potentially leading to overdose and death. The previously approved indication for these products was for the "management of

moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." The new indication will be for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."

The Agency has extensively assessed the problem of prescription opioid analgesic misuse and abuse, the impact of the labeling of these products on the problem, and the research gaps that require further study to better define the overall risk-benefit profile for this class of drugs. In doing so, we are attempting to ensure that these products are used as carefully and thoughtfully as possible, and that they remain available for use in patients for whom they are appropriately prescribed.

The CSS review of this application was filed on February 5, 2013. That review stated that the Applicant had not included systematic reporting of abuse, misuse and diversion cases in the clinical trial protocols, and that assessment of the levels of abuse and misuse in the clinical studies was, therefore, not possible. Dr. Love predicted that there would be high levels of abuse, misuse and addiction of Zohydro ER in the community, based on the potency of the drug product, the ease with which it can be abused, and the lack of any abuse-deterrent features to its formulation. I do not dispute the potential for significant abuse of this product. However, all products in this class are associated with serious risks, including addiction, abuse, and misuse. Not withstanding these risks, I have concluded, for the reasons discussed in Section 13, that the benefits of this product outweigh these risks. The Agency has made significant efforts to address the risks associated with these products, and those efforts are expected to reduce the risks of abuse and misuse with Zohydro ER as well as the already approved ER/LA opioid analgesics. In addition, as Dr. Fields notes on page 3 of the September 17 addendum to her review, "The assessment of abuse in the relatively small population of patients who participated in the clinical trials would not likely add useful information to what is already known regarding the abuse of Schedule II opioids, including Zohydro ER."

12. Labeling

The review team and the applicant have reached agreement on all aspects of the product labeling. See Section 11 for a discussion of the changes to the ER/LA opioid class labels that will be incorporated into the Zohydro ER label on initial approval.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The applicant has provided adequate evidence to support that Zohydro ER is safe and effective when used according to the product label for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The approved labeling will include prominent warnings about abuse, including a boxed warning about the known serious risks of addiction, abuse, and misuse. The labeling will also urge prescribers to "assess each patient's risk" before prescribing the drug, and to "monitor all patients regularly for the development of [addiction, abuse, and misuse]." Zohydro will be subject to the ER/LA Opioid Analgesics REMS, which is intended to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse. The REMS requires the distribution of a Medication Guide with each prescription filled, as well as a requirement that training be made available to all those who prescribe ER/LA opioids. However, as part of the risk-benefit assessment, it was essential that we consider how the approval of the first single-entity hydrocodone product might impact the growing problem of misuse and abuse of the ER/LA opioid analgesics.

  Hydrocodone has pharmacologic features that result in its being highly sought after by opioid abusers. The availability up to now of only products that combined hydrocodone with acetaminophen or NSAIDs has appeared to limit the abuse of hydrocodone to some extent. However, while serious adverse outcomes such as overdose and death may have been numerically reduced to some degree, the combination products have still been widely abused and that abuse has not infrequently resulted in addiction, and sometimes overdose and death. Patients who are using these products as prescribed and with appropriate medical oversight to treat pain may also become addicted, although the limited data appear to demonstrate that this is an unusual occurrence in

the absence of other predisposing risk factors. The availability of a high-potency, single-entity hydrocodone product could result in an increase in abuse and addiction. If this did occur, it is not clear whether that increase would be accompanied by a decrease in the abuse of other potent opioids, or whether it would add to the overall levels of abuse, addiction, overdose and death in the U.S.

To mitigate that risk, in addition to requiring adherence to the ER/LA Opioid REMS, the Agency has taken further regulatory actions that will not only apply to Zohydro ER, but to the entire class of ER/LA opioid analgesics. These actions include the additional warning language in the product labeling, the new, reframed indication, and the implementation of PMR studies that will, hopefully, better define the overall risk-benefit of these drugs when used chronically. Nevertheless, these actions are not likely to completely remove the risks associated with the addition of Zohydro ER to the market. However, I firmly believe that the benefits of this product outweigh its risks, for the reasons detailed below.

Pain is the most common symptom accompanying, to some degree, almost every medical condition human beings experience. When it is severe enough, it interferes with a patient's ability to function and with the patient's quality of life. The opioid analgesics are one of a very few classes of analgesic drugs that provide potent efficacy in the relief of pain. The ER/LA opioids, in particular, have been demonstrated to frequently relieve even most types of severe pain. While numerous efforts are underway to find novel, safer, highly effective analgesic drugs, the ER/LA opioids are one of the key components of the current armamentarium. Many patients in the U.S. suffer from untreated or poorly treated chronic pain. Further limiting access to potential treatments is not the answer when new treatments are critically needed. As with many other drug classes, one individual ER/LA opioid is not always effective and/or tolerated by any individual patient. Some patients find that only a single member of this class provides adequate pain relief and/or has a tolerable side effect profile. Some patients are unable to achieve adequate pain relief from, or to tolerate any of the approved products. The addition of an alternative within the class will be potentially beneficial to numerous patients who are currently suffering from undertreated pain.

Even in patients who are currently receiving an ER/LA opioid that is effective for their pain and that is well tolerated, in chronic use opioids have the potential to become less effective, or less well-tolerated, over time. The practice of opioid rotation is common for patients who are being treated for chronic painful conditions. The addition of a new,

high-potency, ER/LA opioid to the armamentarium will likely have an important impact in the treatment of chronic pain for this reason.

For patients with chronic pain who are being treated with one of the combination hydrocodone products, the availability of a single-entity, extended-release hydrocodone product will provide two potential benefits. First, if and when appropriate, a patient would be able to be switched over to Zohydro ER to reduce the number of doses needed per day and, more importantly, to maintain consistent blood levels, which is widely believed to provide better long-term pain control and to reduce the "rush" associated with high blood levels that appears to be sought after by opioid abusers. Second, for patients who have tolerated and generally responded well to hydrocodone in the combination products, but who now need higher doses due to the development of tolerance and/or increased pain due their underlying condition, prescribers would be able to titrate them to higher hydrocodone doses without the potential for the development of the toxicities, particularly the hepatotoxicity which can result in serious morbidity and mortality, associated with the combination product components. This would also help to avoid these patients being switched to analgesics that are either ineffective for them, or that have their own associated serious toxicities.

Ideally, this approval would be for an abuse-deterrent formulation of hydrocodone. However, the technology used to produce abuse-deterrent opioid formulations is still in the nascent stages, and the applicant has not been able to formulate their product with abuse-deterrent features thus far. If and when they, or another manufacturer, are able to create an abuse-deterrent formulation that remains safe and effective for patients, we would certainly give serious consideration to assuring that any non-abuse formulations are removed from the market. Nevertheless, it is important to note that even the currently available abuse-deterrent technologies only limit abuse by routes other than oral administration. The availability of opioid formulations that are not abusable, that are not potentially addictive, and that do not have the potential to cause respiratory depression and death in overdose, is not likely in the near future. Therefore, beyond appropriately educating patients, prescribers and the public about the risks and proper uses of these medications, it would be necessary to severely restrict access to these drugs to limit these unfortunate outcomes. That is not acceptable in the absence of equivalently effective analgesic products.

I highly value the opinions of the members of the Anesthetic and Analgesic Drug Products Advisory Committee. However, for the reasons discussed above, I find that the overall risk-benefit balance for

patients who will be properly, thoughtfully and carefully prescribed Zohydro ER for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, falls firmly on the side of approval of this application.

- Postmarketing Risk Management Activities

  The approved Zohydro ER application must adhere to the requirements of the ER/LA Opioid REMS.

- Postmarketing Study Requirements

  The following summary of the post-marketing study requirements has been reproduced from pages 16 through 19 of Dr. Fields' addendum to her review:

> The following are the post marketing requirements for Zohydro ER, the same as the requirements recently imposed on all ER/LA opioid analgesic sponsors. As these studies further evaluate the known risks of ER/LA opioid analgesics for abuse and misuse and their consequences, no new safety signals arose during the development of Zohydro ER, and considerable data exist on the safety of hydrocodone (used in combination with nonopioid analgesics for pain management for decades), studies to obtain the information described below may be conducted as post marketing studies.
>
> 2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.
>
> These studies should address at a minimum the following specific aims:
>
> a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of

psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: 08/2014
Study Completion: 01/2018
Final Report Submission: 06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated

codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-4 Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

The Agency determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia[3] associated with the class of ER/LA opioids, of which Zohydro ER is a member.

2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Trial Completion: 08/2016
Final Report Submission: 02/2017

Sponsors of the ER/LA opioid analgesic NDAs are encouraged to work together to conduct these studies.

The following are postmarketing requirements for pediatric studies under PREA:

2066-1 Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of hydrocodone extended-release in patients from ages 12 to less than 17 years with moderate-to-severe pain requiring around the clock opioid therapy for an extended period of time.

Final Protocol Submission:
August 31, 2014
Study/Trial Completion:
February 28, 2019
Final Report Submission:
August 31, 2019

2066-2 Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of hydrocodone extended-release in patients from ages 7 to less than 12 years with moderate-to-severe pain requiring around the clock opioid therapy for an extended period of time.

Final Protocol Submission:
August 31, 2017
Study/Trial Completion:
August 31, 2021
Final Report Submission:
February 28, 2022

Non-Clinical PMRs

2066-1 Conduct an in vivo comet assay in liver to evaluate the potential genetic toxicology of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress
Study/Trial Completion: October 1, 2013
Final Report Submission: December 1, 2013

2066-2 Conduct a 2-year bioassay in the rat model to evaluate the carcinogenic potential of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress
Study/Trial Completion: January 15, 2014
Final Report Submission: June 30, 2015

2066-3 Conduct a 2-year bioassay in the mouse model to evaluate the carcinogenic potential of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress

Study/Trial Completion: January 24, 2014
Final Report Submission: June 30, 2015

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

/s/

BOB A RAPPAPORT
10/25/2013