CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA/BLA #	206627/000
Applicant Name	Purdue Pharma L.P.
Date of Submission	April 28, 2014
PDUFA Goal Date	October 28, 2014
Proprietary Name / Established (USAN) Name	Hysingla/ hydrocodone bitartrate extended-release tablets
Dosage Forms / Strength	Tablets 20, 30, 40, 60, 80, 100, and 120 mg
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jacqueline Spaulding, MD
Statistical Review	Yan Zhou, PhD, Janice Derr, PhD
Pharmacology Toxicology Review	Elizabeth Bolan, PhD, R. Dan Mellon, PhD
CMC Review/OBP Review	Xiaobin Shen, PhD, Julia Pinto, PhD Akm Khairuzzaman, PhD, Tapash Ghosh, PhD
CMC Microbiology Review	John Metcalfe, PhD, Bryan Riley, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD, Yun Xu, PhD
OSI	Cynthia Kleppinger, MD, Janice Pohlman, MD, MPH, Kassa Ayalew, MD, MPH
OMPQ/DGMPA	Juandria Williams, PhD, Mahesh Ramanadham, PharmD, MBA, RPH
CDTL Review	Ellen Fields, MD, MHS
OSE/DMEPA	James Schlick, RPh, MBA, Irene Z. Chan, PharmD
OPDP/DCDP	Eunice Chung-Davies, PharmD
OMP/DMPP	Morgan Walker, PharmD, MBA, Barbara Fuller RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN
PMHS Pediatrics PMHS Maternal Health	Donna Snyder MD, Hari Sachs MD, Lynne Yao MD Carol Kasten MD, Melissa Tassinari, PhD
CDRH	Cherish Giusto, AuD, Srinivas Nankumar, Ph.D
CSS	Martin Rusinowitz, MD, James Tolliver, PhD, Silvia Calderon, PhD, Michael Klein, PhD
QT-Interdisciplinary Review Team	Moh Jee Ng, Qianyu Dang, Fang Li, Jiang Liu, Norman Stockbridge MD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs
PMHS=Pediatric and Maternal Health Staff

1. Introduction

Purdue has submitted 505(b)(2) NDA for Hysingla, an oral extended-release formulation of hydrocodone bitartrate with excipients that are intended to confer abuse-deterrent properties. Hysingla ER is formulated in strengths of 20, 30, 40, 60, 80, 100, and 120 mg of hydrocodone per tablet and is intended for q24h dosing. The proposed indication is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative options are inadequate. This NDA, relies in part, on the Agency's prior findings of safety and efficacy for Vicoprofen (NDA 20716). This review will focus on the abuse-deterrent properties of this product and on the choice to file a 505(b)(2) application that relies on the Agency's prior findings of safety and efficacy for Vicoprofen.

2. Background

Hysingla ER consists of hydrocodone bitartrate and excipients intended to provide the extended-release pharmacokinetic characteristics and abuse-deterrent (AD) properties. The product was developed under IND 59175. The value of an AD formulation of extended-release hydrocodone is based on the general problem of prescription opioid abuse, and the fact that this hydrocodone-containing product is listed under Schedule II of the Controlled Substance Act due to the known risk for abuse. Much has been written about the extent of prescription opioid abuse in the US. The frequency of prescription opioid abuse may be greater for immediate-release hydrocodone combination products, perhaps reflective of the greater number of prescriptions, but the consequences of abuse of higher strength single-entity products, particularly extended-release opioids, has been reflected in data from the now defunct Drug Abuse Warning Network and other databases and has led to the creation of the Extended-Release and Long-Acting Opioid Risk Evaluation and Mitigation Strategy (ERLA REMS)[1]. There has been a growing understanding of the need to re-evaluate the manner in which pain is managed in the US and how the approach of managing chronic pain by prescribing medication in place of a coordinated interdisciplinary approach has contributed to the widespread availability of opioids in medicine cabinets across the country.[2] This is important not only for the sake of the patient with chronic pain, but for society as a whole, as the widespread availability of opioids prescribed by healthcare providers is the source for much of the misuse and abuse of opioids in the US.[3]

The primary route of abuse of opioid analgesics is oral, followed by different frequencies of intranasal and intravenous abuse depending on the specific formulation. This is true for both immediate-release and extended-release products. When extended-release products are

[1] http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf

[2] https://prevention.nih.gov/programs-events/pathways-to-prevention/recent-workshop/opioids-chronic-pain/workshop-resources

[3] Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings, 2012. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012. NSDUH Series H-41; HHS publication (SMA) 11-4658.

manipulated to defeat the extended-release characteristics resulting in an earlier peak drug level, whether for oral abuse, or for intranasal or intravenous abuse, the risk for overdose increases. Using PEO, this hydrocodone formulation has been shown in studies to resist efforts to chew and, to some extent, crush the tablet, and when exposed to water, either intact or crushed, forms a viscous gel. The extent of the effect of these properties on the ability to deter abuse has been evaluated to some extent in a variety of in vitro and in vivo studies discussed in detail below. These studies are a best effort to predict whether the abuse-deterrent properties will have an impact on behavior. Additional evaluation of the actual impact on abuse will be required in postmarketing studies also described below. However, for this product, the evaluation will be more difficult than for some other products because there has only been a single-entity extended-release hydrocodone product on the market for approximately one year. There has not been a lot of clinical experience with the first product and only a few reports of abuse have been identified, a result, at least in part, of the limited prescribing so far. This will raise additional questions of how to evaluate the effect of the formulation following approval that the Applicant will need to consider as they address the required postmarketing evaluation.

As a decades-old mu agonist, there is little question that hydrocodone is an analgesic. The Agency met with the Applicant throughout development of Hysingla ER and agreed that, for a 505(b)(2) application, in addition to relying on the Agency's prior findings of efficacy for Vicoprofen, one positive adequate and well-controlled clinical trial would be sufficient to support a finding of efficacy, and serve the purpose of confirming that the once daily dosing was appropriate for the proposed chronic pain indication. It was also agreed that a safety database of at least 300 patients exposed for six months and 100 patients exposed for at least one year would be sufficient to understand if the formulation had any unexpected effects that were not related to hydrocodone. The Division advised the Applicant to monitor hearing during the proposed Phase 3 trials, because hearing loss has been reported in subjects taking hydrocodone/ acetaminophen combination products. The Center for Devices and Radiologic Health (CDRH) was consulted to provide guidance regarding ototoxicity assessments, and multiple interactions occurred between the Applicant and the Division regarding this issue. The Applicant was also told that a thorough QT study would be required for the NDA, or in its absence, rigorous scientific data to justify why it would not be necessary.

The Applicant submitted a full CMC package along with nonclinical studies that assessed the safety pharmacology, general toxicology, genetic toxicology, developmental and reproductive toxicology and the carcinogenic potential of hydrocodone. The Applicant also conducted two Phase 3 studies and 14 Phase 1 studies in support of the application.

3. CMC/Device

The following material represents excerpts from Dr. Shen's review.

> The hydrocodone bitartrate drug substance is manufactured by (b) (4) per DMF (b) (4). The DMF has been last reviewed by this reviewer on 16-Jul-2014 and deemed adequate. There has been no change to the DMF since that review. The drug substance manufacturer site EES status is pending.

Specifications for hydrocodone bitartrate drug substance include both USP and ICH requirements. Collectively they include appearance, identification, specific rotation, pH, assay, impurities, loss on drying, residue on ignition, residual solvents and particle size distribution. The drug substance is packaged in (b) (4) bags inside a (b) (4) drum. The drug substance stability data was referenced to DMF (b) (4), which is adequate to support its use in the NDA. It has a retest date of (b) (4) months.

All excipients are of compendial grades. The magnesium stearate is (b) (4). PEO is used at quantities (b) (4) than used in already approved products. The safety of this excipient is evaluated by the pharm/tox reviewer Dr. Elizabeth Bolan. The tablets are packaged in (b) (4) cc white oblong HDPE bottles at 60 count and closed with a child-resistant closure. Each bottle also contains two oxygen absorbers. The drug product is manufactured and packaged by applicant's site located in (b) (4) The drug product manufacturing and testing sites have satisfactory EES status.

The drug product specifications include appearance, identification, assay, related substances, content uniformity, and dissolution. Microbial limit testing is not included in either release or stability testing. Microbiologist, Dr. John Metcalfe, has been working with the applicant to ensure that adequate control is in place for the final commercial drug product. The drug product primary stability studies were conducted on 3 batches for each strength and packaging configuration combinations. Up to 18 months of stability data is provided for the product stored under long term (25ₒC/60% RH) storage conditions and six months of stability data is provided for the storage under accelerated conditions (40ₒC/75% RH). All tested quality attributes (description, assay, degradation products, and dissolution) results remained relatively stable and showed no trend during the time periods studied for all product strength/packaging configuration combinations and under all storage conditions. Overall, the provided stability data supports the applicant's proposed 24 month product expiry.

In an addendum to the original CMC review dated October 23, 2014, Dr. Shen states the following regarding the inspection of the drug substance manufacture site, (b) (4):

The drug substance manufacturer site inspection was completed on (b) (4). (b) (4) issued Form-483 to the DMF holder post-inspection, and subsequently recommended a "withhold" for this application. On October 16, 2014, Dr. Juandria Williams from Office of Compliance conducted an overall assessment of the inspection findings, listed on the 483, and the firm's response to Form 483 observations. She has recommended a non-concurrence to the (b) (4) recommendation of withhold, based on the firm's responses to the 483. Consequently, the Office of Compliance has given an overall acceptable recommendation for the facilities.

There is an impurity, (b) (4) that has the (b) (4) which carries a structural for genotoxicity. It is controlled to the DMF holder's specification of NMT (b) (4) and *in vivo* toxicology testing for genotoxicity was negative.

This formulation is composed o [redacted] Polyethylene oxide [redacted] functions as release rate-control and provides the abuse-deterrent properties described below. In response to a request, the Applicant added an in process control for monitoring [redacted].

The Applicant was asked to conduct a study to characterize tablet size over time when immersed in water or Simulated Gastric Fluid (SGF) at 37°C (±2°C). The Applicant used the 20 mg and 120 mg strengths and used photographs to evaluate the change in tablet size over time. The swelling was similar for both strengths. After 30 minutes, there was an approximately 20% increase in size in all dimensions. After 10 hours, the increase in size was approximately 80%. This is important in the context of patients with narrowed gastrointestinal lumen due to surgery or disease. There have been reports of formulations containing a large amount of polyethylene oxide causing obstruction as well as sticking to the esophageal mucosa. The rate of increase in size is slow enough not to represent a risk for obstruction while passing into the stomach.

Seven in vitro studies were conducted to evaluate a variety of methods of manipulation for the purpose of abuse.

1. The first study evaluated physical manipulation to increase the rate of release of hydrocodone. Slicing was very difficult. Coffee grinders created small particle sizes but could only be used once due to damage to the grinder. Preheating did not make this any easier. In comparison to OxyContin, Hysingla ER was more difficult to grind.

2. Solvent extraction using a variety of solvents, including water, ethanol, methanol, saline, cola, 40% ethanol, buffers (pH 3, 8, 10), and 0.1N HCl (pH 1). Using a volume of 100 mL with aggressive agitation, the controlled release properties of ground Hysingla ER were substantially reduced small particle size and at high temperatures, with only some degree of controlled release remained. Intact Hysingla ER was resistant to extraction in all solvents even at elevated temperature, releasing only 66% of hydrocodone in 6 hours.

3. Exposure to dry heat and heating in a microwave did not accelerate release of drug from the tablets.

4. Attempts to prepare a solution for injection were not very successful due to the high viscosity of the solution. Milled tablets were able to result in between 3% and 38% release of hydrocodone and the release was increased to 45% with pretreatment with heat.

5. Neither Hysingla ER nor Vicodin were susceptible to vaporizing for smoking.

6. Intact tablets did not release hydrocodone more quickly in various concentrations of alcohol, although following manipulation, release did increase inversely proportionally to particle size.

7. Free base extraction was evaluated, as noted in the following from Dr. Shen's review:

The potential for isolation of hydrocodone base from HYD tablets using pH mediation and organic liquid phase extractions was studied. The water absorption and swelling properties of PEO make it difficult to precipitate hydrocodone free base. The precipitate remains trapped within the viscous solution, therefore separation from the matrix is tedious and time consuming. The resulting free base recovery and purity are low.

Organic liquid phase extraction studies were more successful. The results indicate that with knowledge of chemistry, access to reagents, and willingness to expend significant time and effort, using certain organic solvents which do not dissolve PEO, high purity hydrocodone free base can be extracted. However, the overall total recovery of hydrocodone is compromised. Without knowledge of chemistry and organic separation techniques, specialized equipment, and access to necessary reagents, it will be difficult to isolate hydrocodone free base from HYD tablets.

The biopharmaceutics review noted that hydrocodone is very soluble across relevant pH range of 1.2 to 8. The dissolution method was found to be capable of distinguishing significant changes in composition or manufacturing process.

The CMC microbiology review accepted the Applicant's proposal to waive microbial limits testing for product release.

As noted by Dr. Williams, the Division of Good Manufacturing Practice Assessment has completed a review of the inspection package covering a pre-approval inspection (PAI) and GMP inspection conducted by (b) (4) investigators at (b) (4), the site for manufacturing and release testing of the API hydrocodone bitartrate, along with the firm's written response to the FDA Form-483 observations. The (b) (4) recommended withholding approval of NDA 206627 due to an incomplete cleaning validation of the Hydrocodone API Process (b) (4). DGMPA does not concur with (b) (4) withhold recommendation. The data from a cleaning process development and validation summary report from September 2012 does suggest that they are able to clean the (b) (4) and meet their pre-determined residual threshold. While the firm has been unable to manufacture hydrocodone bitartrate due to DEA restrictions and therefore, unable to perform additional equipment cleaning iterations for hydrocodone bitartrate, DGMPA believes that the data from the 2012 cleaning batch does demonstrate that the firm can clean the (b) (4) such that the potential risk to patient safety from cross-contamination of products in the shared equipment is mitigated. Additionally, the firm does commit to update their summary reports for the development, qualification, verification, and/or validation of cleaning procedures for hydrocodone bitartrate and its intermediates for (b) (4) (b) (4), among other (b) (4), by the end of 2014. DGMPA concluded that the site was acceptable.

I concur with the conclusions reached by the chemistry, microbiology, and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections for the drug substance were found acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted more than the usual amount of nonclinical information for a 505(b)(2) application. There is adequate support for the product based on the information provided. The following is excerpted from Dr. Bolan's review:

> All impurities in the drug substance and drug product are controlled at acceptable levels. Hysingla ER contains excipients that are intended to confer abuse-deterrent properties and resist alcohol-induced dose dumping. The (b) (4) component of the formulation consists of (b) (4) polyethylene oxides (b) (4) With the exception of the PEO, the levels of the excipients in this product, when calculated for the maximum theoretical daily dose of HC, are considered acceptable and do not require qualification. The levels of the PEO (b) (4) levels found in previously approved drugs. To support the safety of the levels of the PEO in this product, the Applicant is referencing MF (b) (4). Master File (b) (4) has been found to be inadequate because (b) (4) These (b) (4) entities could include (b) (4) l and specifications for these impurities in the excipient master file may be required. However, because of the longstanding history of use of PEO in many products which reference (b) (4) this deficiency will not be an approval issue for NDA 206627. The levels of PEO in Hysingla ER when used at the MTDD of hydrocodone are considered acceptable from a pharmacology/toxicology perspective.
>
> The neurobehavioral and respiratory safety pharmacology studies showed results consistent with the known effects of opioids. The cardiac safety pharmacology assessment showed the potential for effects of HC on the heart. Hydrocodone did not show meaningful inhibition of the hERG potassium channel at concentrations >300-fold higher than human exposure at an oral dose of 120 mg. However, the in vitro Purkinje fiber assay showed HC-dependent increases in action potential duration and an in vivo single-dose study in conscious, freely moving telemetered dogs showed increases in RR and QRS interval durations as well as increases in QT and QTc intervals with HC. The findings in dog were seen at C_{max} exposures 0.7-fold the human C_{max} exposure of a 120 mg HC dose. No effects on the heart were observed in the toxicology studies with chronic administration of HC to rat and dog. To address the potential for cardiotoxicity in humans, the Applicant has conducted a clinical study to evaluate the effect of HC on the QT/QTc interval.
>
> The highest available strength for this product will be 120 mg HC and the product is labeled to be used q24h, therefore, the systemic levels at the human dose of 120 mg/day at steady state will be used as the exposure comparison with the toxicology studies described below.
>
> The results of the general toxicology studies in rat and dog were typical of an opioid agonist and no clinically-relevant toxicities unique to HC were demonstrated. No target organs were identified in either species. No adverse findings were identified in the dog

study; therefore, the NOAEL in dog was greater than the highest dose tested. The highest dose tested yielded exposure margins in male and female dogs of 0.9-fold and 0.8-fold, respectively, the human systemic exposure of a 120 mg HC dose (based on AUC comparisons). No adverse findings were identified in the rat study; therefore, the NOAEL in rat is greater than the highest dose tested. The highest dose tested yielded exposure margins in male and female rats of 0.2-fold and 0.1-fold, respectively, the human systemic exposure of a 120 mg HC dose (AUC).

The standard ICH battery of genetic toxicology studies was conducted with HC and the weight-of-evidence suggests that HC does not have mutagenic or clastogenic potential. Additionally, two-year carcinogenic assessments were conducted in rat and mouse and no HC-related neoplasms were observed. Exposure margins for the highest dose tested in male and female rats were 0.2- fold and 0.1-fold, respectively, the systemic levels at the human dose of 120 mg/day (AUC). Exposure margins for the highest dose tested in male and female mice were 3.5-fold and 3.1-fold, respectively, the systemic levels at the human dose of 120 mg/day (AUC).

A full reproductive and developmental toxicology battery was conducted with HC. No embryotoxicity, teratogenicity or effects on fertility were observed in rats at exposures 0.1-fold the human HC dose of 120 mg/day based on exposure (AUC) comparisons. However, the embryofetal development studies in rat and rabbit showed reduced pup survival rates and reduced fetal/pup body weights. A pre- and post-natal development study in rat showed decreases in pup viability, pup survival indices, litter size, and pup body weight. These effects in rat and rabbit were seen at exposures approximately 0.1 and 0.3-fold, respectively, the human HC dose of 120 mg/day based on exposure comparisons (AUC). The observed toxicities in the reproductive and developmental toxicology battery are consistent with a Pregnancy Category C designation and the findings will be described in the label.

The pharmacologic effects of opioids limit the dosing in nonclinical species and typically multiples of human clinical exposures are not achieved. Although the mouse carcinogenicity study provided exposure margins of ~3-fold at the NOAEL, all of the rat and dog exposures of HC in the studies conducted are below the systemic exposure in humans at the dose of 120 mg.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. There are remaining deficiencies associated with Master File (b) (4), and I concur with the pharmacology and toxicology team that these are not sufficient to preclude approval. However, four postmarketing requirements will be issued to address these deficiencies and to get better characterization of the low molecular weight entities in the polymer and to establish specifications for impurities as needed.

5. Clinical Pharmacology

Fifteen studies examining the pharmacokinetic characteristics of Hysingla ER were reviewed by Dr. Nallani. The following are excerpts from his review.

> **Absorption**
> After a single dose administration of 20, 40, 60, 80 and 120 mg Hysingla ER tablets, Hysingla ER yields a gradual increase in plasma hydrocodone concentrations with median Tmax ranging from 14 to 18 hours after single and multiple dosing. Systemic exposure (AUC and Cmax) increased linearly with doses from 20 to 120 mg. Both Cmax and AUC increased slightly more than dose proportionally. Mean plasma concentrations of hydrocodone increased slowly after oral administration of Hysingla ER extended-release tablets and reached a maximum concentration at 14 to 16 hours post-dose at all dose levels. However, it should be noted that in some individuals peak plasma levels were noted at 24 hour or up to 30 hours following single dose of Hysingla ER administration.
>
> *Food-effect:* Hydrocodone Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, hydrocodone AUC with Hysingla ER 120 mg tablets was only 20% higher when coadministered with a high fat meal. Both Cmax and AUC of hydrocodone with Hysingla ER 120 mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). Upon consumption with high-fat meal the inter-individual variability (AUC %CV = 24%) of Hysingla ER Cmax and AUC decreased compared to fasting condition (AUC %CV = 37%). This observation suggests factors affecting GI transit, such as high-fat meal consumption, could affect Hysingla ER bioavailability. Four individuals (1021, 1034, 1074, 1085) had very low bioavailability under fasting condition compared to the rest of the subjects in the study, possibly due to emesis (1 subject 1021 documented and three not reported); while their plasma hydrocodone levels were higher after high-fat treatment and comparable to the rest of the subjects. Amongst these individuals, two subjects had 8-fold higher Cmax after high-fat meal compared to the low plasma levels noted under fasting condition. The magnitude of AUC increase after high-fat meal was similar to that of Cmax, and the Tmax values were delayed after high-fat meal in these four subjects, which indicates the PK changes observed were due to increased bioavailability under fed status.

Dr. Nallani recommends that food consumption be consistent for the individual when dosing with Hysingla ER.

The evaluation of dose proportionality consisted of a comparison of four 20 mg tablets and one 80 mg tablet, and found comparable exposure.

As noted by Dr. Nallani:

> **Distribution:** Following administration of hydrocodone to healthy subjects, the mean apparent volume of central compartment (Vc/F) was 402 L, suggesting extensive tissue

distribution. The extent of in vivo binding of hydrocodone to human plasma proteins was minimal with a mean percent bound of 36%.

Metabolism: Hydrocodone exhibits extensive metabolism, including CYP3A4, CYP2D6 and 6-keto reduction. CYP3A4 mediated N-demethylation yields norhydrocodone (major metabolite) and CYP2D6 mediated O-demethylation yields hydromorphone (minor metabolite) and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy metabolites. Some extent of CYP2B6 and CYP2C19 involvement was also noted in the formation of norhydrocodone and hydromorphone. Taken together, multiple hepatic metabolic enzymes appear to be involved in clearing hydrocodone in to different metabolites.

Elimination: Approximately 6.5% of the administered oral dose of hydrocodone administered as HYD is excreted as unchanged hydrocodone in urine. The mean terminal half-life (t1/2) was similar for all HYD dose strengths ranging from approximately 7 to 9 hours in healthy subjects across the range of doses. Steady state of plasma hydrocodone concentrations were attained by day 2 of once-daily dosing of HYD. The extent of accumulation of systemic exposure was low (1.3 fold). The mean t1/2 at steady state was 7 hours.

An evaluation of the relative bioavailability of Hysingla ER compared to Vicoprofen found comparable exposure at steady state dosing after 3 days of Hysingla ER 30 mg every 24 hours and Vicoprofen 7.5 mg/200 mg every 6 hours.

Dr. Nallani reviewed data from Study HYD1016 on the difference between peak and trough concentration within one dosing interval at steady state, or fluctuation. He found that the percentage fluctuation (range of plasma concentration values during steady state relative to $C_{ss,avg}$) and percentage swing (the range of plasma concentration values during steady state relative to Css,min) was relatively high for Hysingla, a once daily extended-release formulation. As noted in the following tables, the first from page 8 and the second modified from a table on page 9 of Dr. Nallani's review, the fluctuation for Vicoprofen, an immediate-release product, was higher than for the 30 mg Hysingla ER. The percent fluctuation and the percent swing were higher for the higher strengths of Hysingla, but would be expected to be higher for higher strengths of an immediate-release formulation as well.

Table 1: Percentage fluctuation for Hysingla ER 30 mg compared to Vicoprofen IR tablets at steady-state from Study HYD1016.

Metric (Unit)	HYD (30 mg q24h for 3 days) N = 22	Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg) (1 tablet q6h for 3 days) N = 23
%Fluctuation		
Mean	60.490[a]	96.331
SD	30.1864	26.7992
%CV	49.9	27.8
Minimum, Maximum	6.43, 112.73	55.87, 193.02

Table 2 Summary Steady State PK Data, Study HYD1009

	AUC0-24,ss (hr*ng/mL)	Cmax,ss (ng/mL)	Tmax,ss (hr)	Cmin,ss (ng/mL)	Cavg,ss (ng/mL)	%Fluctu-ation	%Swing
Hysingla ER 80 mg Day 9 (HYD1009) N=77							
Mean	1252.49	82.62	14.96	28.21	52.19	105.20	245
Maximum	2358.64	175.00	23.92	59.90	98.28	213.80	1875
Hysingla ER 120 mg Day 12 (HYD1009) N=75							
Mean	1844.10	122.12	14.51	43.51	76.84	102.72	220
Maximum	3358.29	312.00	23.97	94.10	139.93	185.67	2073*
Hysingla ER 160 mg Day 15 (HYD1009) N=73							
Mean	2380.47	151.05	14.67	57.79	99.19	94.56	222.56
Maximum	4764.17	337.00	23.92	132.00	198.51	185.20	1299

Studies were conducted to evaluate the effect of age, hepatic and renal impairment. The effect of age was evaluated in a study comparing elderly subjects to young subjects and found 1 16% increase in Cmax and 15% increase in AUC for patients over 65 relative to those under 45. In an evaluation of exposure in patients with hepatic impairment, the use of lactulose to manage hepatic encephalopathy by four patients complicated interpretation as these patients had lower systemic exposures than the four patients who did not receive lactulose. Taking the use of lactulose into consideration, Dr. Nallani found an increase in AUC and Cmax of 50% in patients with severe hepatic impairment. The use of lactulose had no effect on exposures in patients with mild hepatic impairment, a small effect in patients with moderate hepatic impairment and decreased mean hydrocodone concentration by more than half in patients with severe hepatic impairment. In a study of patients with mild, moderate, and severe renal impairment and with end-stage renal disease on dialysis, hydrocodone Cmax values were higher by 14%, 23%, 11%, and lower by 13% and AUC values were higher by 13%, 61%, 57%, and 4% in patients compared with patients with normal renal function.

Hydrocodone exposure increased by 2-fold when coadministered with ketoconazole, a strong CYP 3A4 inhibitor, and did not change with coadministration of paroxetine, a strong CYP 2D6 inhibitor. An in vitro assessment demonstrated that hydrocodone does not inhibit major CYP enzymes.

Dr. Nallani reviewed the human abuse potential studies, HYD1013 and HYD1014. These studies are discussed below in Section 11.

Dr. Nallani has recommended labeling regarding the following issues. Refer to his review and the final label for details:

- Because the peak plasma levels of hydrocodone may occur more than 14-16 hours following administration of Hysingla, patients should be made aware that plasma levels may be high enough after 24 hours to impair activities that require alertness. Additionally, Hysingla ER should be taken at a consistent time each day to maintain 24-hour dosing interval.
- Patients should following the prescriber's titration instructions, and not attempt to increase Hysingla ER dose on their own.
- Patients with any degree of renal impairment and severe hepatic impairment should be started on a low dose of Hysingla ER and monitored closely for adverse events.
- Patients taking CYP3A4 inhibitors may require lower doses of Hysingla ER and should be monitored for adverse events
- The effect of lactulose on the Hysingla ER PK should be described in the label

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The efficacy of Hysingla ER for the intended population was demonstrated in one adequate and well-controlled study of 12 weeks duration in patients with chronic low back pain. For this 505(b)(2) application, the Applicant was told that one clinical trial was adequate in addition to their reliance on the Agency's prior findings for Vicoprofen. The purpose of a clinical trial for efficacy of an old mu agonist opioid, reformulated as a once daily product is to determine whether the strengths and dosing regimen are appropriate to support efficacy for the intended population, not to reestablish that hydrocodone is an analgesic. Also, as Vicoprofen was not studied in chronic pain, and Hysingla ER is intended for use in patients with chronic pain, the design of the study was appropriate for supporting the proposed indication.

The study design and results of Study HYD3002 have been carefully reviewed and described by Drs. Spaulding and Fields. In short, HYD3002 was double-blinded, placebo-controlled, randomized withdrawal study in patients with chronic low back pain for at least three months. Patients were either previously on opioids, are due to inadequate response to other analgesics, considered appropriate for initiating an around-the-clock opioid. A total of 905 patients entered the run-in period characterized by titration onto Hysingla, starting with a conversion if on prior opioid. At Day 45, subjects who tolerated Hysingla ER and achieved adequate analgesia were randomized to remain on Hysingla ER or to begin a blinded taper to placebo.

A total of 592 patients (65%) met the criteria for randomization. Of the 312 patients not randomized, 33% discontinued due to an adverse event, 19% failed to have adequate analgesia, 7% were suspected or confirmed as diverting study drug, 19% did not qualify, 6% were removed for administrative reasons, 6% were lost to follow up and 9% was due to subject choice. It is highly likely that the 15% of subjects choosing not to continue or failing to return to follow up experienced either a lack of adequate response or adverse events as a reason for not participating, so that the 33% and 19% figures are likely under reporting the actual occurrence. The criteria for did not qualify included meeting ECG criteria, achieving a stable Hysingla ER dose that would be in the double-blind period, forgoing all analgesic medications, not using use of any prohibited concomitant medication specified by protocol and not having results meeting the American Society of Hearing Audiology (ASHA) criteria. Results must be reviewed by medical monitor before subject randomization. Of the 588 patients randomized (four received no study drug), 17% discontinued early as shown in the following table from page 16 of Dr. Fields review. This is a relatively low number for a randomized 12-week period with placebo, and is likely due to screening out nonresponders and those with adverse events they are unwilling to tolerate during the open-label titration, and the use of rescue medication.

Table 3 Revised Summary Table, Subject Disposition and Reasons for Discontinuation from Study Drug and Study Simultaneously during Double-Blind Period

DOUBLE- BLIND PERIOD (NN= 588)			
	Placebo (NN=292)	**HYD (NN=296)**	**Overall (NN=588)**
Discontinued Study Drug and Study Simultaneously n (%)	51 (17)	46 (16)	97 (17)
Adverse Event	10 (3)	9 (3)	19 (3)
ASHA-Related Event	0	1 (<1)	1 (<1)
Subject's Choice	6 (2)	12 (4)	18 (3)
Lost to Follow-Up	3 (1)	5 (2)	8 (2)
Lack of Therapeutic Effect	24 (8)	7 (3)	31 (5)
Confirmed or Suspected Diversion	3 (1)	3 (1)	6 (1)
Administrative	6 (2)	8 (3)	14 (2)

Source: NDA 202627, CSR, Study HYD3002, Table 18 pg. 177 of 6082 and Applicant Response to IR #2

The primary efficacy outcome was the change from baseline at randomization to the end of the 12 weeks of double-blind treatment. Dr. Zhou was able confirm the primary efficacy analysis and the support from the sensitivity analyses. Because of deficiencies found at two study sites for the efficacy study, the result were reanalyzed omitting the data from these sites. Dr. Zhou found the results were the same for the reanalysis.

The primary efficacy analysis as conducted by the Applicant and replicated by Dr. Zhou is shown below.

Table 4. Primary Efficacy Analysis

Table 6: Primary efficacy analysis

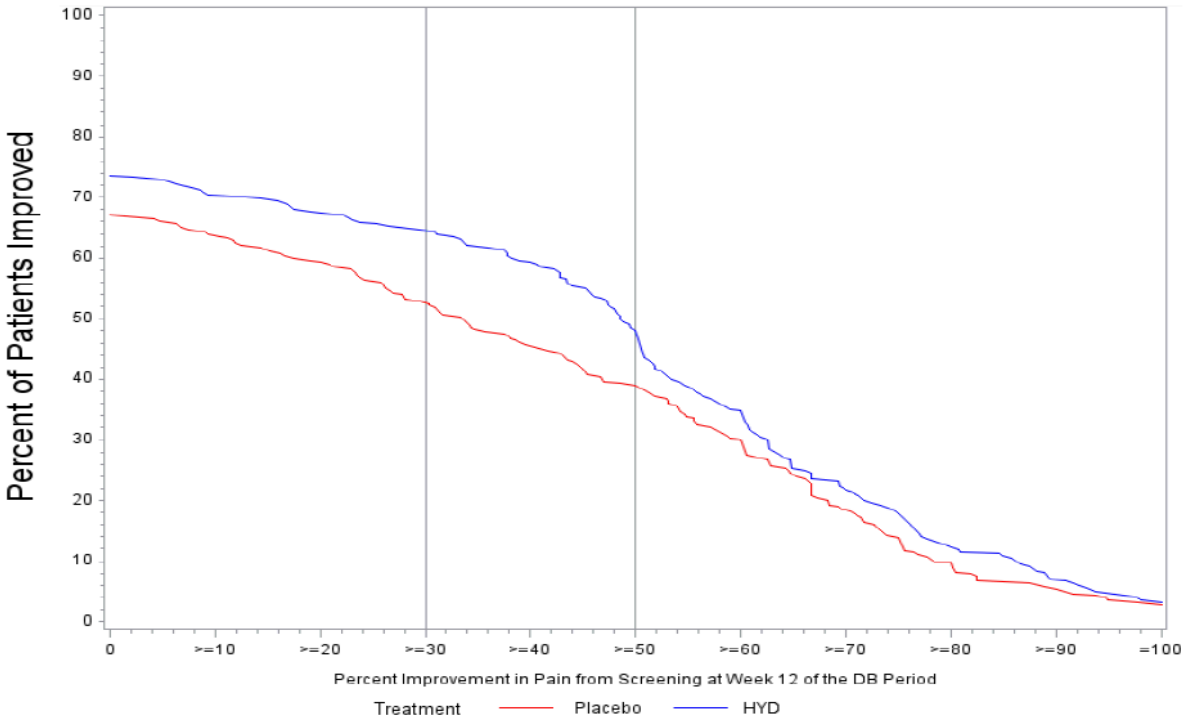
Study Period/Week **Mean Pain Intensity**	**Placebo[a]** **(N=292)**	**HYD** **(N=296)**
Baseline		
n	292	296
Mean (SD)	7.4 (1.19)	7.4 (1.13)
Prerandomization		
n	291	296
Mean (SD)	2.8 (1.15)	2.8 (1.16)
Double-blind Week 12		
n	199	218
Mean (SD)	3.7 (2.04)	3.3 (1.93)
Pattern 1: Completed Week 12**		
n (%)	210 (72)	229 (77)
LS Mean (SE)	4.17 (0.131)	3.47 (0.128)
Pattern 2: Discontinued Study Drug due to Adverse Event or ASHA Related Event**		
n (%)	11 (4)	18 (6)
LS Mean (SE)	7.40 (0.048)	7.40 (0.048)
Pattern 3: Discontinued Study Drug due to Other Reasons**		
n (%)	71 (24)	49 (17)
LS Mean (SE)	3.90 (0.114)	3.38 (0.112)
Repeated Measures Analysis/Least Squares Means (SE) at Double-blind Week 12 from PMM		
LS Mean (SE)	4.23 (0.126)	3.70 (0.128)
Treatment Comparison at Double-blind Week 12		
Difference in LS means from Placebo (Mean (SE))		-0.53 (0.180)
P value vs Placebo		0.0016
95% CI for difference from Placebo		(-0.882, -0.178)

Source: Clinical Study Report Table 14.2.1.1.1 and Table 14.2.1.1.2.

Dr. Zhou generated a continuous responder curve by treatment group, shown below. All non-completers were classified as non-responders. Her results confirmed the Applicant's results and showed that Hysingla-treated subjects had consistently higher responder rates than placebo-treated subjects. The two curves are significantly different when non-parametric tests were applied (Wilcoxon rank sums test: p-value = 0.023); Van der Warden test: p-value = 0.026).

Figure 1

Figure 3: Percent improvement in pain from screening baseline at week 12 of the DB period



Source: Dr. Zhou's review, p. 16

> Other secondary endpoints, including Patient Global Impression of Change (PGIC), Brief Pain Inventory (BPI), and rescue medication use generally supported the superiority of Hysingla ER over placebo, with the exception of the Medical Outcome Sleep Scale which showed no difference between the treatment groups. A slightly higher percentage of subjects treated with Hysingla ER did not use any rescue medication (22%) compared to placebo-treated subjects (17%), although the use of rescue in the Hysingla ER treated-group increased with increasing doses of study drug.

During the double-blind period, the amount of rescue use was based on the amount of study drug achieved following titration, 10 mg of immediate-release oxycodone for patients titrated to 20 and 40 mg of study drug, 15 mg of immediate-release oxycodone for patients titrated to 60 mg of study drug, 20 mg of immediate-release oxycodone for patients titrated to 80 mg of study drug, and 30 mg of immediate-release oxycodone for patients titrated to 100 mg of study drug,

As described by Dr. Fields:

> The mean daily number of oxycodone 5 mg tablets taken was higher in the placebo group compared to Hysingla ER. During Week 1 the mean daily number of tablets for the placebo group was 0.67 tablets for compared to 0.58 tablets for the Hysingla ER group. For Week 2, the mean use was 0.88 tablets vs. 0.61 tablets, and for Weeks 3-12, the mean use was 0.75 vs. 0.58 tablets. For Weeks 0-12 the mean daily number of tablets for the placebo group was 0.90 compared to 0.67 for the Hysingla ER group. The amount of

rescue taken was consistently higher for the placebo group compared to those taking Hysingla ER.

So the patients receiving Hysingla ER and less pain, fewer used rescue medication and those that did used less. All of these factors support a finding of efficacy for Hysingla ER.

Overall, it is well known that hydrocodone, used for decades in combination with a nonopioid, is an analgesic and that evidence of efficacy can be found in the efficacy data supporting approval of Vicoprofen. The single efficacy study conducted in support of this application demonstrates the efficacy of Hysingla, an extended-release formulation dosed once daily, in patients with chronic low back pain and is suitable for the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

8. Safety

The following indented sections represent excerpts from Dr. Fields' comprehensive summary of the safety findings for this application.

> The safety database for this application was made up of subjects from 11 Phase 1 studies and two Phase 3 studies of Hysingla, and consisted of 2,476 subjects who were exposed to at least one dose ranging from 20 to 160 mg.

The Phase 3 studies were relied on as principle sources of safety data and included HYD3002, the 12-week efficacy and safety study in patients with chronic low back pain, and HYD3003, an open-label, multicenter study to assess the long-term safety of Hysingla ER in patients with chronic nonmalignant, nonneuropathic pain which followed subjects for up to 76 weeks.

> In many of the Phase 1 studies, subjects received naltrexone block to prevent serious opioid-related adverse reactions, so that safety findings in those studies do not reflect the true safety profile of Hysingla ER.

> In the pooled Phase 3 studies, a total of 1827 subjects were exposed to at least one dose of Hysingla ER ranging from 20 to 120 mg. A total of 364 subjects were exposed for at least 12 months, and a total of 374 were exposed to at least one dose of 120 mg. Twelve percent of subjects who took 120 mg were exposed for at least 12 months. Overall, the mean age of subjects receiving Hysingla ER in pooled chronic pain studies was 50 years. There were more female subjects than male subjects (58% versus 42%). The racial makeup of the study population was predominantly White [77%] followed by Blacks [18%] and Asians [4%]; all other races were represented at ≤1%. The mean BMI was 31.4 kg/m^2; and 52% of subjects were in the ≥ 30 kg/m^2 category. There were more opioid-experienced subjects than opioid-naïve subjects (56% versus 44%).

> <u>Deaths</u>

There were a total of seven deaths that occurred during the Phase 3 trials, six in the Hysingla ER group and one in the placebo group. There were no deaths in the Phase 1 studies. Refer to Dr. Spaulding's review for detailed narratives of the deaths. In summary, the causes of death in the Hysingla-treated subjects included an overdose (multiple drugs including Hysingla, citalopram, and cyclobenzaprine), brain aneurysm, myocardial infarction, thrombotic thrombocytopenic purpura and metabolic acidosis, respiratory failure (in a patient with underlying COPD), and hypoxia (in a patient with underlying COPD). There was insufficient data provided to determine whether the overdose was intentional or accidental. Both patients with respiratory failure had complex and serious medical histories. Contribution of Hysingla ER to the overdose, and two deaths due to respiratory failure/hypoxia cannot be ruled out.

Nonfatal Serious Adverse Events

A total of 120 nonfatal serious adverse events (SAEs) were reported in 84 (5%) of exposed Hysingla-treated subjects, one of which was in a Phase 1 study, and 119 in the Phase 3 studies. The SAE that occurred during the Phase 1 study was in Study HYD1008, a PK study in patients with renal impairment. The event was reported as sepsis syndrome in a 48 year old black male subject with severe renal impairment. The investigator determined that the event was unlikely related to study drug, and I concur.

The most common nonfatal SAEs in Hysingla-treated subjects in the pooled Phase 3 studies were chest pain (6 [< 1%] subjects), drug abuse (5 [< 1%] subjects), and osteoarthritis (4 [< 1%] subjects). SAEs related to GI disorders (abdominal pain, GI hemorrhage, impaired gastric emptying, esophageal obstruction, rectal fissure, vomiting) were experienced by one subject each. Nonfatal SAEs considered possibly related to the study drug occurred in 10 subjects (total of 12 events) and included asthma, esophageal obstruction, impaired gastric emptying, lethargy, sedation, drug abuse, and overdose, each occurring in < 1% of subjects. Drug abuse-related AEs will be discussed later in this section.

There was one SAE of QT prolongation that is of note given the positive TQT study conducted by the Applicant. There were also two reports of esophageal obstruction associated with Hysingla, one in a patient with a preexisting esophageal stricture (endoscopy showed a glue-like mass lodged in the esophagus after three doses of Hysingla), and one in a patient with no apparent structural abnormality of the GI tract.

Adverse Events Leading to Discontinuation

The overall incidence of treatment emergent adverse events (TEAEs) in Hysingla-treated subjects leading to discontinuation of study drug in the pooled Phase 3 studies was 17%. The gastrointestinal and nervous system disorders (7% and 6%) were the most commonly reported system organ classes. The incidence of discontinuation due to adverse events in the double-blind study HYD3002 was 10% during the open-label run in phase, and during the double-blind phase was 4% in Hysingla-treated subjects versus 3% in placebo-treated subjects. Again the most common adverse events were GI and CNS related, including nausea, vomiting, dizziness, and headache, as would be expected for an opioid analgesic.

Common Adverse Events

Common adverse events reported in at least 2% of Hysingla-treated subjects compared to placebo-treated subjects for Study HYD3002 are described in the Applicant's table below for the run-in period as well as the double-blind period. The following is paraphrased from Dr. Spaulding's review:

> Overall, the incidence of TEAEs reported during the double-blind period was 41%. A higher percentage of Hysingla-treated subjects compared to placebo subjects experienced any TEAE (46% versus 35% respectively). The Gastrointestinal Disorders and Infections and Infestations system organ classes (SOCs) had the highest frequency of TEAEs reported for Hysingla ER subjects (18% each) followed by the Nervous System Disorders SOC at 10%. The most commonly reported preferred terms for Hysingla-treated subjects during the double-blind period were nausea (8%), vomiting (6%), constipation (3%), dizziness (3%), insomnia (3%), upper respiratory infection (2%) and influenza (2%).

The TEAEs that occurred during Hysingla ER exposure at a rate of at least 2% in the pooled Phase 3 chronic pain studies were similar in nature to those in Study HYD3002. The most common TEAES were nausea (21%), constipation (16%), vomiting (10%), dizziness (10%), headache (8%), and somnolence (8%). There were no new or unexpected common TEAEs reported. Review of the common TEAEs in the Phase 1 studies in subjects who were not naltrexone blocked did not reveal any new or unexpected events.

Overall, the common TEAEs reported for Hysingla ER during its development are those typically associated with opioid analgesics.

Laboratory, Vital Sign, and ECG Findings

Dr. Spaulding reviewed the laboratory findings and determined there were no clinically important findings for hematology and chemistry assessments in the study population.

Vital sign changes were also reviewed and noted to be not clinically meaningful. A small number of subjects experienced small changes in blood pressure, none of which required treatment.

Data from the 120-day safety update did not reveal any novel findings and did not change conclusion from Drs. Spaulding or Fields. This includes review of the additional ECG data identified by the Applicant from Studies HYD3002 and HYD3002.

Adverse Events of Special Interest

Gastrointestinal Obstruction/Choking/Sticking

Drs. Fields and Spaulding reviewed the adverse events of choking or gastrointestinal obstruction that appear related to the properties of the product, that it becomes tacky when wet and expands. A total of 11 (<1%) of subjects in the Hysingla ER clinical development program experienced this type of event. An SMQ based on prespecified terms related to choking and GI obstruction of the pooled chronic pain studies revealed eight reports, two dysphagia, two esophageal obstructions,

two vomiting, one choking, and one intestinal obstruction. Seven of the eight events appear to have been related to study drug. The case of intestinal obstruction was apparently not related, as this patient had a complication of his ostomy stoma. One of the esophageal obstructions occurred in a subject without any known GI structural abnormality, and one occurred in a subject with an esophageal stricture. There were also two reports of dysphagia and one "pill stuck in throat" in the Phase 1 studies. As a result, there will be labeling to describe the risk and alert prescribers to consider the risk of GI obstruction and choking when prescribing Hysingla ER.

Possible Abuse-Related Adverse Events And Aberrant Drug Behavior
To assess the risk of abuse-related behavior during pooled chronic pain studies (N=1827), the Applicant was to conduct an analysis of the relevant events utilizing an SMQ to search the database. Aberrant drug behavior was reported in nine subjects (<1%): five with drug abuse , one drug screen positive, one substance abuse, one intentional drug misuse, and one overdose. Three subjects obtained hydrocodone/acetaminophen immediate-release tablets from sources other than the investigators, one subject took extra rescue medication on one day due to increased pain (aberrant drug behavior according to the protocol, however, not abuse), one subject had a positive urine drug screen for THC, another admitted to using THC, and one subject had a nonfatal polydrug overdose involving benzodiazepine, zolpidem, cyclobenzaprine, gabapentin, and Hysingla ER. It was not clear if this was intentional. One subject took a single extra dose of Hysingla, and another took Hysingla ER twice daily for several days and said she had been instructed to do so with no reported adverse events.

Use of 10% or more in excess of the maximum prescribed study drug dose or 10% or more of study drug unaccounted for were investigated under the term, diversion. In Study HYD3002, a total of 158 subjects were investigated for possible diversion, and 39 cases were confirmed. In Six subjects reported that their study drug was stolen or used by someone other than themselves. Of the 24 reports of diversion in open-label study HYD3003, 10 subjects reported study drug stolen. The remaining patients were found primarily to have taken extra tablets of Hysingla ER or rescue oxycodone immediate-release.

The SMQ analysis showed a rate of aberrant drug use of less than 1% of Hysingla-exposed subjects, including the two subjects who took extra doses, and the one polydrug overdose. The incidence of diversion in the pooled chronic pain studies was approximately 3%. Aberrant drug behaviors and diversion are usually present in clinical trials of opioids. Study subjects know the intent of the study is to evaluate an opioid, and this may attract some participants with an intent for abuse. The number and types of behaviors reported during this development program do not appear unusual.

Audiological Adverse Events
Anecdotal reports of hearing loss associated with hydrocodone use led to the request for an evaluation of hearing during the clinical trials with Hysingla ER. CDRH, Division of Ophthalmic, and Ear, Nose, and Throat Devices, Ear, Nose, and Throat Branch (ENTB) was consulted during to provide advice to the Applicant regarding audiological assessments during design of the study and during the NDA review to assess the Applicant's findings. Cherish Giusto, Au.D. provided a review of the data to the Division on June 26, 2014, with secondary concurrence from Srinivas Nankumar, Ph.D., Chief, ENTB.

As stated in the CDRH review:

> There have been reports in the literature of hearing loss associated with the use of hydrocodone, usually with a hydrocodone/acetaminophen combination. These reports describe a sensorineural hearing loss that is typically sudden or rapidly progressive in nature, and often severe in degree. Currently, there is no clear consensus on the extent of hydrocodone's risk for ototoxic effects on hearing and vestibular function. Factors that contribute to the unclear nature of hydrocodone-associated hearing loss include: drug dosage, drug use period, patient risk factors (e.g., existing hearing loss, history of noise exposure) that may make them more susceptible to ototoxic effects, and the use of hydrocodone in conjunction with other agents (e.g., acetaminophen, NSAIDS,
>
> aspirin). Since progressive hearing loss has been associated with the chonic use of hydrocodone/acetaminophen combination products and the potential exposure to hydrocodone from this HYD product is higher than the labeled doses from combination products, it was important to monitor for any potential cochleo-vestibular ototoxicity from the use of HYD during the Phase 3 clinical trials for this product.

Audiology evaluations in the Phase 3 studies included assessment of air-conduction pure-tone audiometry, bone-conduction pure-tone audiometry, speech reception threshold, immittance audiometry (tympanometry), Dizziness Handicap Inventory (DHI), and Tinnitus Handicap Inventory (THI). While the Applicant concluded that there is not an increased risk for hearing impairment or vestibular disorders with Hysingla ER. The Office of Scientific Investigations determined that the audiology data from one study site (Taber) was not reliable. The Sponsor was aware of these issues and did not include audiological data from that site in the analyses.

The CDRH review concluded that the audiology report revealed no significant signal of acute decrements in hearing or vestibular function during the conditions of the study, but the evaluation was only able to identify a common finding based on the number of patients studies. The most frequently occurring event in the safety population was tinnitus in 2% of patients. As noted by Dr. Fields, because the audiology evaluation was not conducted in an outcome study, there is limited value to any additional analyses. The following are response is from the CDRH consult:

> **Question for CDRH (ENTB):** Do you concur with sponsor's conclusion that there is not an increased risk for hearing impairment or vestibular disorders with HYD?
>
> **Answer:** In general, we agree that the audiology data provides a reasonable assurance that there is not a significantly increased risk for hearing impairment or vestibular disorders with the use of HYD in the doses and time periods investigated during these Phase 3 trials from a clinical audiology perspective. However, we defer to the CDER review team regarding the significance of the treatment-emergent adverse event rates related to hearing and vestibular disorders, particularly the rate of tinnitus which occurred in 2% of the pooled chronic pain studies population (see Section 6.1 of the audiology report).

QT Prolongation

To complement the thorough QT study, the Applicant assessed the incidence of QT prolongation or cardiac repolarization events in the pooled chronic pain studies. A total of seven in Hysingla-treated subjects were reported to have QT prolongation or syncope, all during the open-label

HYD3003 study. Four of these seven reports were for syncope and three subjects had ECG findings of prolonged QT, following exposure to Hysingla ER doses of 40 mg in one subject and 80 mg in two. Two of the cases prolonged QT resolved when drug was discontinued, and one while still taking study drug. The two cases of syncope were not associated with QT prolongation on ECGs.

Given the finding of mild QT prolongation in the thorough QT study, it is possible the QT prolongations in the clinical trial were associated with Hysingla ER. The label will include appropriate language regarding the results of the QT study.

A thorough QT study was conducted using steady dosing of Hysingla ER from 20 mg to 160 mg ER over a period of 15 days. Dr. Nallani reviewed the study and found that, while there was no apparent exposure-response relationship for change in QTcI based on hydrocodone concentration, there were positive trends in exposure-response relationships for change in QTcI based on HYD metabolite norhydrocodone or hydromorphone concentration review.

The Interdisciplinary Review Team for QT studies (QT-IRT) reviewed the protocol prior to the conduct of the study, and the study report was submitted on May 28, 2014. The QT-IRT reviewed the study report and provided advice to the Division regarding labeling. The following is a summary of their findings taken verbatim from their review.

> This randomized study administrated of multiple doses (once daily for 3 days) of HYD titrated from 20 to 160 mg. A central tendency analysis of the individual corrected QT (QTcI) interval data at steady-state demonstrated that the maximum mean (90% upper confidence bound) difference in QTcI from placebo after baseline-correction was 9.9 (12.7) ms, 6.9 (10.2) ms, and 5.6 (8.5) ms at HYD 160 mg, 120 mg and 80 mg respectively. The largest 90% upper confidence bound for the mean differences at HYD 160 mg and 120 mg was above 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7, indicating that assay sensitivity was established.
>
> In this randomized, double-blind, placebo-and positive-controlled, multiple-dose escalation, parallel-design study, 208 subjects received HYD 80 mg, HYD 120 mg, HYD 160 mg, placebo and moxifloxacin 400 mg.

Table 5

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for HYD (80mg, 120 mg and 160 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
HYD 80 mg (Day 9)	24	5.6	(2.7, 8.5)
HYD 120 mg (Day 12)	24	6.9	(3.6, 10.2)
HYD 160 mg (Day 15)	10	9.9	(7.1, 12.7)
Moxifloxacin 400 mg (Day 9)*	3	11.6	(8.8, 14.5)
Moxifloxacin 400 mg (Day 12)*	3	9.7	(6.2, 13.2)
Moxifloxacin 400 mg (Day 15)*	4	8.7	(5.5, 11.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points are 7.7 ms, 4.9 ms, and 4.3 ms on Days 9, 12 and 15; respectively.

The HYD dose (160 mg) produces mean steady state exposure 2-fold that of the therapeutic dose (80 mg) for both parent drug and major metabolites. There was no evident exposure-response relationship for change in QTcI based on hydrocodone concentration. However, it seems there are positive trends in exposure-response relationships for change in QTcI based on HYD metabolite norhydrocodone or hydromorphone concentration.

As noted by Dr. Fields:

Overall, the QT-IRT determined that while there was some QT effect, it was mild, not apparently dose related, and not associated with any clinically significant adverse events. The team suggested the following language for the label Sections 5 and 12.6. Labeling discussions are ongoing at this time. Please see the approved label for the exact wording. Of note, other approved hydrocodone products do not have this language in their labels, consequently consideration must be given to requiring TQT studies for these products or incorporating similar language into their labels.

5.x QT INTERVAL PROLONGATION

QT prolongation has been observed with [TRADENAME]. [TRADENAME] should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias electrolyte abnormalities or who are taking medications that are known to prolong the QT interval, consider periodic monitoring with electrocardiograms and electrolytes. In patients who develop QTc prolongation, consider dose reduction *[see Clinical Pharmacology (12.6)]*.

12.6 CARDIAC ELECTROPHYSIOLOGY

QTc interval prolongation was studied in a double-blind, placebo- and positive controlled 3-treatment parallel-group, dose-escalating study in 185 healthy subjects. A central tendency analysis of the QTcI data at steady-state demonstrated that the maximum mean (95% upper confidence bound) difference in QTcI from placebo after baseline-correction was 10 (13) ms, 7 (10) ms, and 6 (9) ms at [TRADENAME] 160 mg, 120 mg and 80 mg respectively.

Abuse Deterrence

The Applicant conducted a series of in vitro physical and chemical manipulation laboratory assessments of Hysingla ER tablets in order to assess possible abuse-deterrent properties.

1. Physical manipulation methods were evaluated to attempt to reduce Hysingla ER to a powder using commonly employed household tools (two spoons, mortar and pestle, pill crusher, hammer, food grater, foot file, nutmeg shaver, razor blade, spice grinder, and coffee grinder). It was very difficult to cut or grind the Hysingla ER tablet. The coffee grinder was most successful, but as noted by Dr. Shen, resulted in destruction of the grinder.

2. Extraction studies evaluated the effects of water, coca cola, saline, 40% ethanol, methanol, 100% ethanol, 0.1N HCl aqueous solution (pH 1), and commercially available buffers of pH 3, 8, and 10, on intact and milled Hysingla ER tablets and IR hydrocodone/APAP. Ground Hysingla ER in the setting of high temperature released a large amount of hydrocodone.

3. Thermal stressing of Hysingla ER tablets to assess the impact of intentional heat pretreatment, using a laboratory oven and common household microwave did not substantially change the release of hydrocodone from Hysingla ER.

4. When exposed to an aqueous environment, Hysingla ER gradually forms a viscous hydrogel (gelatinous mass) that resists passage through a hypodermic needle.

5. Syringeability studies using heated and room temperature water and a variety of extraction time on intact, sliced, and milled Hysingla ER tablets and assessing syringeability with a number needle gauge sizes resulted in no more than 38% when milled and 45% when milled after heating.. When exposed to an aqueous environment, Hysingla ER gradually forms a viscous hydrogel (gelatinous mass) that resists passage through a hypodermic needle. Syringeability studies also indicate that a single IR hydrocodone/acetaminophen tablet, in part due to low potency (10 mg hydrocodone) most likely cannot be used to produce a suitable intravenous injection

6. Simulated smoking was attempted but showed that neither Hysingla ER nor Vicodin were not susceptible to vaporizing.

7. In vitro dissolution in simulated gastric fluid was studied to evaluate the effects on the dissolution rate of halved, quartered, sliced, and milled Hysingla ER compared to IR hydrocodone/APAP. Release of hydrocodone was inversely proportional to particle size.

8. As noted in the CMC section, free base isolation is extremely difficult to achieve

9. A bench-top study was conducted comparing Hysingla ER to OxyContin in order to assess the difficulty of physical manipulation.

Two clinical human abuse potential studies were conducted in support of this NDA. Study HYD1013 evaluated the pharmacokinetics and abuse potential in opioid non-dependent abusers by the oral route for intact, chewed, and milled Hysingla, compared to hydrocodone oral solution. The mean Cmax was highest following the hydrocodone oral solution, followed by milled, chewed, and intact Hysingla ER. The median Tmax followed the same trend. The mean drug liking scores, using a bipolar VAS scale, paralleled the pharmacokinetic data, with the highest scores for the oral solution followed by milled Hysingla ER. Chewing did not result in a greater drug liking score than intact Hysingla ER. The results are presented in the following two figures from Dr. Nallani's review.

Figure 2: Mean Hydrocodone Plasma Concentrations Versus Time (Oral Administration) in Study HYD1013.

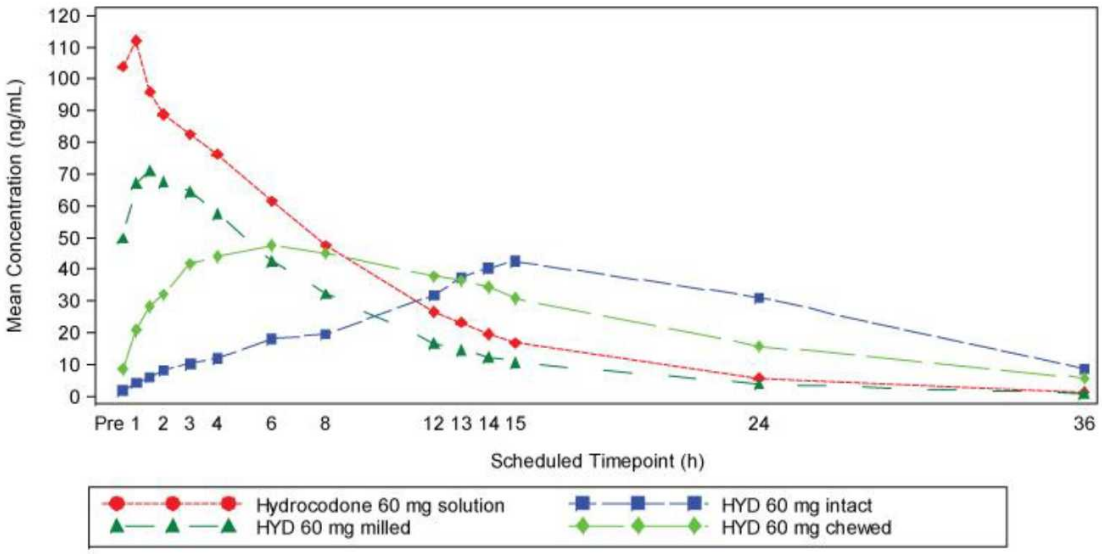
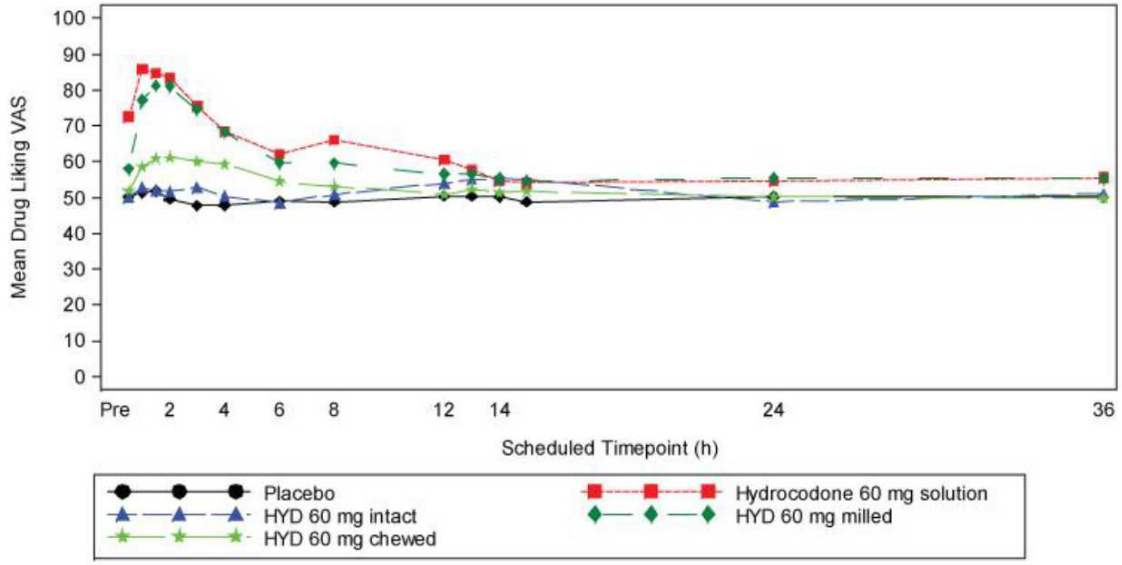


Figure 3: Mean Scores Over Time for Drug Liking VAS (Oral Administration, Chewed, Milled and Intact) in Study HYD1013.



Study HYD1014 evaluated the abuse potential and pharmacokinetics of crushed (fine and coarse) Hysingla ER in the intranasal route of administration in non-dependent opioid abusers with a history of intranasal abuse. Mean Cmax values and drug liking scores of hydrocodone were lower following Hysingla ER fine and coarse powder administered IN than following hydrocodone IR powder. Less of the Hysingla ER was insufflated than the hydrocodone IR powder that may have contributed to the lower exposure and drug liking score. Median Tmax was also later following both ground preparations compared to IR powder. The AUCs for the ground Hysingla ER were both lower than the IR powder. The following two figures from Dr. Nallani's review show the results.

Figure 4: Mean Hydrocodone Plasma Concentrations Versus Time following Intranasal Administration of Hysingla ER fine powder (Squares), coarse powder (Triangles) compared to hydrocodone powder (Circles) in Study HYD1014

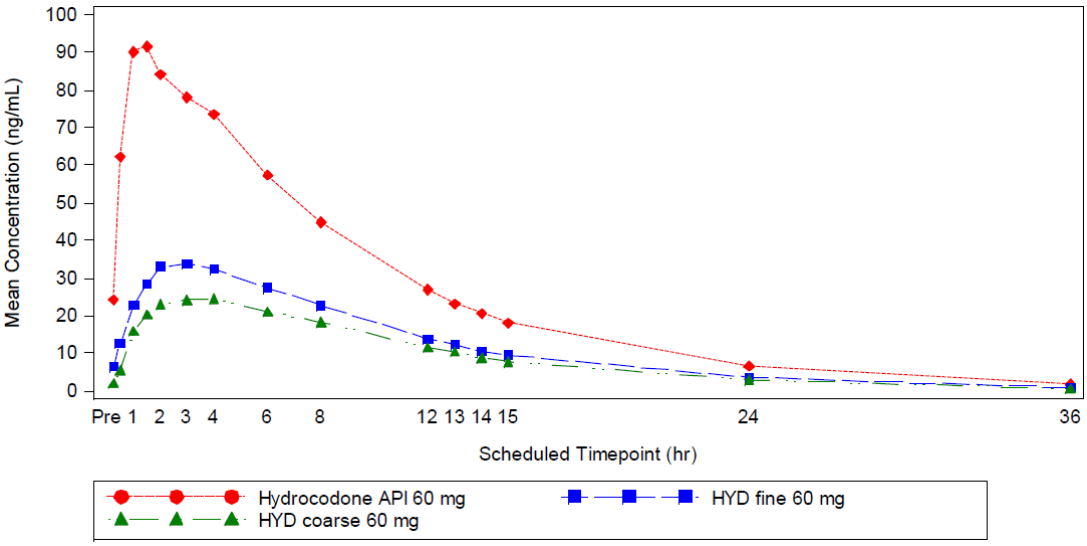
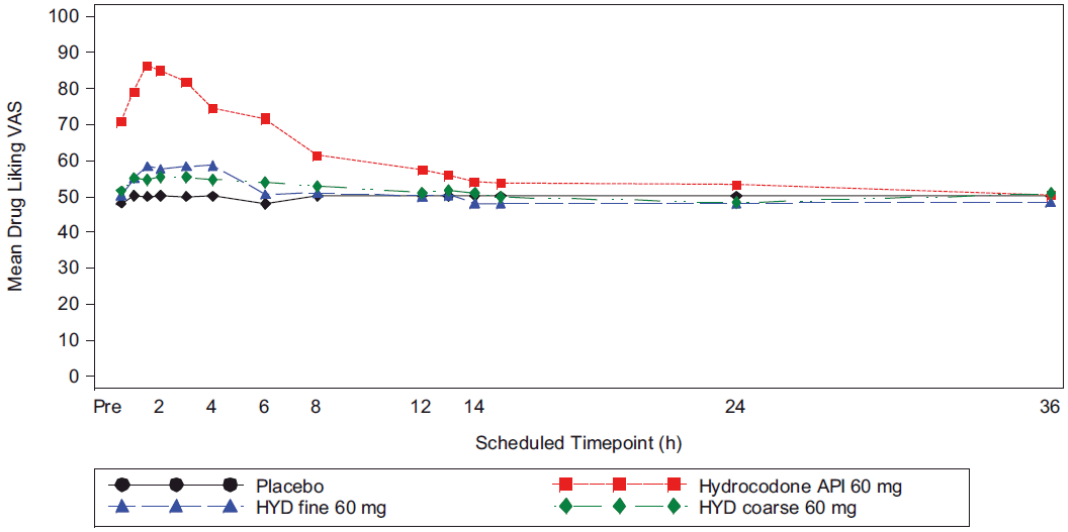


Figure 5: Mean Scores Over Time for Drug Liking VAS following Intranasal Administration of Fine Hysingla ER (Triangle) and Coarse Particle Size Hysingla ER (Diamond) compared to hydrocodone powder (Squares) and placebo (Circles) in Study HYD1014.



CSS initially concluded that the studies supported that Hysingla ER can be expected to have an abuse-deterrent effect for the intranasal and intravenous routes of abuse. This is based on the reduced drug liking scores following intranasal administration of coarsely and finely ground Hysingla ER relative to intact Hysingla ER and immediate-release hydrocodone, and by the difficulty in attempting to prepare a solution suitable for injection. Given time and determination, enough hydrocodone can be extracted from Hysingla ER for the purpose of intravenous abuse, but the product offers substantial deterrence based on the physical properties based on the properties of the formulation.

The initial finding by CSS regarding an oral abuse claim was that, although Hysingla ER tablets are resistant to chewing and grinding, they could be milled into particles small enough to allow compromise of the extended-release properties when the particles were placed in water and swallowed. CSS recommended against labeling for an oral abuse claim. On October 20, 2014 the Applicant submitted additional discussion in support of inclusion of labeling for abuse-deterrence by the oral route of abuse, noting in particular, that in order to reduce Hysingla ER to particles small enough to compromise it's ER properties, laboratory-grade milling machines were necessary. This, combined with the Applicant's findings that it is very difficult to chew or grind Hysingla ER by other means, supports labeling of the oral abuse potential study findings for chewing. CSS has concurred with this conclusion.

In summary, the in vitro and human abuse potential studies support labeling for abuse-deterrence by the intravenous, intranasal, and oral routes of abuse.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. Advisory committee meetings have been convened in the past for extended-release opioid products with potential abuse-deterrent properties. The Agency has had experience reviewing and labeling these types of products, and a draft guidance issued in 2013, *Abuse Deterrent Opioids, Evaluation and Labeling,* is now available to sponsors. Consequently the Agency determined that we have had sufficient experience labeling these products and an advisory committee meeting was not necessary.

10. Pediatrics

The pediatric study plan was discussed and agreed upon with the Pediatric Research Committee on July 9, 2014. The requirements under PREA are relevant because this product is a new dosing regimen for hydrocodone. As noted in Dr. Fields' review:

> The Applicant submitted a pediatric study plan requesting a waiver for studies in pediatric patients from birth to less than 7 years of age because studies of chronic pain in this age group would be impossible or highly impracticable due to the small population of patients in this age group. They also requested a waiver of studies in patients ages 7 to less than 12 years because they have failed to develop an age appropriate pediatric formulation with abuse-deterrent and extended-release characteristics. The PeRC agreed with both waiver requests, and stated that the Applicant must submit a summary of their attempts to develop an age appropriate formulation to be posted on the FDA website.
>
> The Applicant requested and the PeRC agreed to a deferral for pediatric patients ages 12 to less than 17 years because adult studies have been completed and the product is ready for approval. For opioid analgesics intended to treat chronic pain, efficacy from adult studies can be extrapolated to this age group. The required study or studies, therefore, must include pharmacokinetic and safety data to support the dosing and safety of the product. The following study and goal dates have been proposed by the Applicant and are acceptable.
>
> > 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 pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
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> > | Final Protocol Submission: | July 31, 2015 |
> > | Study Completion: | January 31, 2019 |
> > | Final Report Submission: | July 31, 2019 |

Recommendations from the maternal health staff were incorporated into labeling.

11. Other Relevant Regulatory Issues

Clinical Site Inspections

Substantial problems were found at two of the initial four clinical sites inspected by the Office of Scientific Investigations (OSI). (b) (5)). The Taber site (#0108A) was found to have at least five fraudulent records in which one subject's audiology test result was used for other subjects. These deficiencies do not appear to affect the efficacy analyses, and are only pertinent to the hearing assessments. There did not appear to be any underreporting of adverse events. The Applicant was aware of problems at this site, and did not include audiologic data obtained there in the analyses. However, OSI stated that the serious deviations/findings impact the validity and reliability of the submitted data and that they could not guarantee the accuracy of the remaining 14 audiometry reports. Not only were the audiometry data from this site excluded, the primary efficacy endpoint was reanalyzed by Dr. Zhou without data from this site.

The Harris site (#2059A) site (b) (5) exhibited an overall lack of oversight and control over the studies, which was apparent in data collected and maintained by the site. Four subjects were randomized in study HYD3002 and 156 in HYD3003. As stated in the OSI review, there were numerous examples of inadequate records with coordinators' and investigators' notes being in conflict. There were also multiple instances of failing to follow the protocol and maintain adequate records.

The OSI reviewer stated the audit indicates serious deviations/findings that would impact the validity and reliability of the submitted data. Dr. Zhou reanalyzed the primary efficacy endpoint without data from this site, and the results were similar to those obtained when this site's data were included.

An additional four sites were inspected to ensure that there were not more sites with data that could not be relied upon. The OSI review found that data from these four sites appear acceptable, and no serious deviations/findings were noted that would impact the validity or reliability of the submitted efficacy and safety data. Overall, of the eight study sites inspected, the data from six sites was determined to be acceptable for review based on the OSI inspections. It does not appear that there was a systemic problem of data reliability and, therefore, the data from the study sites other than the two (b) (5) are acceptable for support of this NDA.

Risk Evaluation and Mitigation Strategy (REMS)

As a member of the extended-release and long-acting opioid (ERLA) class of opioid analgesics, a REMS is required for this product and it will be part of the ERLA Opioid REMS. Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, FDA has determined that a REMS is necessary for Hysingla ER to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Three-Year Exclusivity
There is currently Hatch-Waxman three-year exclusivity in place for the first extended-release hydrocodone, Zohydro ER, approved on October 15, 2013. Zohydro ER was the first hydrocodone product indicated for chronic pain and the indication was supported by an adequate and well-controlled study On October 31, 2014, we were informed that an agreement was reached between the Applicant (Purdue) and the application holder for Zohydro ER, Zogenix, granting Purdue a permanent, irrevocable, non-transferable and exclusive waiver of the three-year Hatch-Waxman regulatory exclusivity period with respect to NDA 202880 for Zohydro ER capsules in support of pending NDA 206627. Therefore, the agency did not need to reach a decision regarding the implications, if any, of Zohydro ER's exclusivity for the approval of Hysingla.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) conducted a review of the proprietary name, HYSINGLA, and found it acceptable from both a promotional and safety perspective.

Labeling comments from the Maternal Health Team of the Pediatric and Maternal Health Staff, QT-IRT, Office of Prescription Drug Promotion and the Division of Medical Policy Programs Patient Labeling Team have been incorporated.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –Approval
- Risk Benefit Assessment

Overall the data provided by the Applicant support a finding that the benefits of Hysingla ER outweigh the risks for the proposed indication.

There is adequate evidence of efficacy for Hysingla ER based on the Agency's prior findings of efficacy for Vicoprofen and the adequate and well-controlled 12-week study conducted by the Applicant. The study provided support for this novel extended-release formulation with its proposed once daily dosing in a population with chronic low back pain and adequately supports the proposed indication.

There is evidence of safety for Hysingla ER based on the Agency's prior findings of safety for Vicoprofen, and the safety database from clinical trials conducted by the Applicant submitted in support of this application. The adverse event profile is consistent with mu agonist opioids. The audiology assessment, while limited in scope and further limited by the exclusion of data from two sites, was sufficient to exclude the presence of a high rate of ototoxicity. As a member of the class of drugs known as extended-release and long-acting opioid analgesics, the risks associated with

Hysingla ER will be further mitigated by participating in the ERLA Opioid REMS and the Applicant will participate in the postmarketing requirements that will evaluate the risks of abuse, misuse, addiction, overdose, death and hyperalgesia.

There are data that support that Hysingla ER can be expected to deter abuse by the oral, nasal, and intravenous routes of administration due to the physicochemical properties imparted on the formulation by excipients, particularly polyethylene oxide. However, as with all opioid analgesics, abuse of Hysingla ER is possible by simply taking too much orally. The highly motivated and sophisticated individual could defeat the extended-release characteristics and obtain drug for abuse by any route.

While the data support that Hysingla ER will be safe and effective, it is important to understand what that means. Opioid analgesics must be prescribed and used in the setting of adequate information about the limits of efficacy and the extent of possible adverse events, including addiction, overdose, and death. If a prescriber chooses to treat a patient with an opioid analgesic, it is incumbent on that prescriber to be knowledgeable about how to properly select patients, including screening to understand their risk for substance abuse, and to educate the patient about all of the topics listed in section 17 of the package insert. The patient information sheet that is part of the ERLA Opioid REMS is an important resource for the prescriber to use in assisting the patient's understanding about how to use the product safely, and a place to provide patient specific information. Furthermore, it is incumbent on the patient to use the product responsibly by following the prescribers instructions for how to use the opioid, and as importantly, how to store it and to dispose of it safely if there is left over product that is no longer needed. Patients with chronic pain can be safely and successfully managed with opioid analgesics but this requires that they are closely followed by their prescriber over time for any signs that they are experiencing a problem with managing their opioid use or managing their pain.

Hysingla ER and all other opioids have serious risks, even when used as directed. The dose prescribed by a prescriber takes into account many factors that patients and others may not fully understand. Therefore, taking more than prescribed can result in an overdose and death. Use by individuals for whom it was not prescribed can result in overdose and death, even if those individuals appear to have a similar problem as the patient. Attempting to manipulate the drug for any purpose – greater therapeutic effect or abuse – can result in overdose and death. Improper storage and improper disposal can result in ingestion by children and other household contacts and can result in overdose and death. As a mu agonist opioid, pharmacologic effects include physical tolerance. The drug substance hydrocodone is listed under schedule II of the Controlled Substances Act, because it has a known risk for abuse and its use can result in addiction. This information should be part of a conversation between patient and prescriber, not to scare patients, but to adequately inform them and engage them as active participants in the decision making process and in share the responsibility for safe use.

Hysingla ER will be marketed in 20, 30, 40, 60, 80, 100, and 120 mg strengths. To improve the safety of Hysingla ER upon initial introduction to the market, the Applicant was asked to delay introduction of the higher strengths; the 80 mg, 100 mg and 120 mg tablets, but, the Applicant declined the request. Delaying introduction of the highest strengths would have provided additional time for prescribers to learn how to use Hysingla ER safely. However, as the data

support the finding that, the benefits of Hysingla ER outweighs the risks, and because there are clear instructions for initiating treatment with Hysingla ER in the package insert, there was no clear scientific or medical rationale, and therefore, regulatory basis in this instance to support not approving all of the strengths of Hysingla ER. The request was made out of an abundance of caution, in part because of the tremendous amount of confusion, misunderstanding, and misinformation that followed approval of Zohydro ER that may also be occur following the approval of Hysingla ER. Zohydro ER was the first extended-release hydrocodone product indicated for chronic pain and approved in 10 mg, 20 mg, 30 mg, 40 mg and 50 mg strengths for twice daily dosing.

It is extremely important that prescribers understand that Hysingla ER is not the same as Zohydro ER, and is intended for once daily dosing. Incorrect statements about Zohydro ER included that the strengths were higher than any other opioid. Based on available information about relative oral potency[4], hydrocodone is approximately similar in potency to oxycodone, 1.5 to 2-fold as potent as morphine, about one third as potent as oxymorphone, and one third to one quarter as potent as hydromorphone. This information is presented in Table 6. The highest existing strengths of extended-release oxycodone on the market is 80 mg, of extended-release morphine is 200 mg, of extended-release oxymorphone is 40 mg, and of extended-release hydromorphone is 32 mg. So not only was the 50 mg dose of Zohydro ER not higher than products already on the market at the time of its approval, it was somewhat lower than for other opioids, based on these relative potency values. In this light, it is can be seen that the strengths of Hysingla ER are also in line with the currently marketed products.

Table 6 Comparison of Doses for ER Opioids

Opioid	Approximately comparable oral doses	Doses comparable to 120 mg hydrocodone	Maximum marketed ER product strength	Dosing Interval
Morphine	60 mg	180 mg (240 mg)*	200 mg	Q8, BID, QD
Hydrocodone **Hysingla ER** **Zohydro ER**	45 mg (30 mg)*		 120 mg 50 mg	 QD BID
Oxycodone	45 mg (30 mg)*	120 mg	80 mg	BID
Oxymorphone	10 mg	25 mg (40 mg)*	40 mg	BID
Hydromorphone	12 mg	32 mg (48 mg)*	32 mg	QD

*Estimates of relative oral potency differ. Relative to morphine, oxycodone and hydromorphone may be 1.5- to 2-fold stronger. Figures in parentheses represent the values for the 2-fold estimate.

Relative to approved hydrocodone products, currently available combination products with hydrocodone have as much as 10 mg per dosage unit, but unlike Zohydro ER which is dosed every 12 hours and Hysingla ER intended for once daily dosing, hydrocodone combination products are labeled for dosing as often as every 4 hours resulting in a substantially larger number of pills being dispensed.

[4] Relative oral potency estimates are not necessarily suitable for use as a conversion factor for patients switching from one opioid to another due to inter-individual variability. Conversion tables in product labeling is intended to serve this purpose.

- Recommendation for Postmarketing Risk Management Activities

Hysingla ER is part of the Extended-Release and Long-Acting Opioid REMS.

- Recommendation for other Postmarketing Study Commitments

As noted, a request for deferral of pediatric studies was found acceptable. The following study is required:

2808-1 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 pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Final Protocol Submission: July 31, 2015
Study Completion: January 31, 2019
Final Report Submission: July 31, 2019

The following five PMRs reflect requirements for the entire class of ERLA opioids.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of misuse, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which Hysingla ER is a member. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

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: (b) (4) /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: (b) (4) /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: (b) (4) /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:	(b) (4) /2014
Study Completion:	08/2015
Final Report Submission:	11/2015

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioids, of which Hysingla ER is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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 trial:

Final Protocol Submission:	(b) (4) 2014
Trial Completion:	08/2016
Final Report Submission:	02/2017

FDA has determined that, in addition to participation in the PMR studies required of all ER/LA opioid analgesic application holders listed above, you are required to conduct the following individual post-marketing studies of Hysingla ER extended-release tablets.

2808-1 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 pain severe enough

to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

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

Final Protocol Submission: July 31, 2015
Study Completion: January 31, 2019
Final Report Submission: July 31, 2019

2808-2 Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of Hysingla ER (Hydrocodone bitartrate) extended-release tablets actually result in a significant and meaningful decrease in misuse and abuse, and their consequences addiction, overdose, and death in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Hysingla ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013)[1], and proposed study populations and drug comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

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

Final Protocol Submission: 10/2015
Study Completion: 10/2019
Final Report Submission: 04/2020

2808-3 (b) (4)

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2015

2808-4 Conduct an embryo-fetal development study in the rat model to assess the potential impact of PEO on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the MTDD of Hysingla ER.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 02/2016
Study Completion: 08/2016
Final Report Submission: 02/2017

2808-5 Conduct an embryo-fetal development study in the study in the rabbit model to assess the potential impact of PEO on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the MTDD of Hysingla ER.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2016
Study Completion: 12/2016
Final Report Submission: 06/2017

2808-6 Conduct a pre- and post-natal development study in the rat model to assess the potential impact of PEO on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the MTDD of Hysingla ER.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2016
Study Completion: 02/2017
Final Report Submission: 08/2017

- Recommended Comments to Applicant

None

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

/s/

SHARON H HERTZ
11/20/2014