IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSSACHUSETTS

ZOGENIX, INC., 12400 High Bluff Drive, Suite 650 San Diego, CA 92130, Plaintiff, v. DEVAL PATRICK, in his official capacity as GOVERNOR OF THE COMMONWEALTH OF MASSACHUSETTS, Massachusetts State House, Office of the Governor, Room 105, Boston, MA 02133, and CHERYL BARTLETT, RN, in her official capacity as DEPARTMENT OF PUBLIC HEALTH COMMISSIONER, Massachusetts Department of Public Health 250 Washington Street, Boston, MA 02108. Defendants.	Civil Action No. _____ **DEMAND FOR JURY TRIAL**

VERIFIED COMPLAINT

Plaintiff Zogenix, Inc. ("Zogenix"), by its undersigned counsel, hereby brings this Verified Complaint against Defendants Deval Patrick, solely in his official capacity as Governor of the Commonwealth of Massachusetts ("Governor Patrick"), and Cheryl Bartlett, RN, solely in her official capacity as Commissioner of the Department of Public Health ("Commissioner Bartlett"), and states and alleges the following:

1. This is an action seeking temporary, preliminary and permanent injunctive relief, a declaratory judgment, and other appropriate relief to set aside as unconstitutional the recent actions of the Governor and Commissioner to ban the prescribing, ordering, dispensing, and administration of a pain medication deemed safe and effective by the federal Food and Drug Administration ("FDA") and specifically approved by FDA as safe and effective for marketing and sale in the United States.

2. Zogenix's product, Zohydro™ ER (Hydrocodone Bitartrate Extended-Release Capsules), was approved by FDA on October 25, 2013 for the management of severe pain in patients requiring continuous around-the-clock opioid therapy.

3. The active ingredient in Zohydro™ ER, hydrocodone, has been available in FDA-approved products since 1943 and is the same active ingredient found in a number of immediate-release hydrocodone combination analgesic products currently on the market. Products containing hydrocodone in combination with acetaminophen are some of the most commonly prescribed opioid analgesics currently available in Massachusetts and elsewhere for the treatment of chronic pain.

4. Zohydro™ ER is the first single-entity hydrocodone product available on the market and is the only hydrocodone product subject to schedule II controls under the Controlled Substances Act and the Massachusetts Controlled Substances Act – the most restrictive schedule available for an FDA-approved product.

5. Notwithstanding that FDA already has determined Zohydro™ ER to be safe and effective – and approved it for marketing and sale in the United States – Governor Patrick recently issued an "emergency declaration" empowering Commissioner Bartlett to issue an order prohibiting the prescribing, ordering, dispensing, or administration of hydrocodone-only

extended release drug products, a category that only includes Zohydro™ ER. Ex. A. The single substance ban will be lifted only when Commissioner Bartlett "has determined that adequate measures are in place to safeguard against the potential for diversion, overdose, and abuse…." *Id.* at 2.

6. When FDA approved Zohydro™ ER, it considered but rejected the idea of requiring the drug to utilize abuse-deterrent technology. Thus, in effectuating the present ban, the Commonwealth is attempting to override the reasoned decision by FDA not to require abuse-deterrent technology for Zohydro™ ER and taking upon itself the responsibility for regulating the safety of drugs already approved by FDA as safe and effective.

PARTIES

7. Plaintiff Zogenix, Inc. is a Delaware corporation with its principal place of business at 12400 High Bluff Drive, Suite 650, San Diego, California, 92130. Zogenix holds an approved New Drug Application, No. 202880, for Zohydro™ ER.

8. Defendant Deval Patrick is the Governor of the Commonwealth of Massachusetts. Governor Patrick maintains an office at the Massachusetts State House, Office of the Governor, Room 105, Boston, Massachusetts, 02133.

9. Defendant Cheryl Bartlett is the Commissioner of the Massachusetts Department of Public Health. Upon information and belief, Commissioner Bartlett maintains an office at the Massachusetts Department of Public Health, 250 Washington Street, Boston, Massachusetts, 02108.

JURISDICTION AND VENUE

10. Jurisdiction in this Court is grounded upon and proper under 28 U.S.C. § 1331 in that this is a civil action arising under the laws of the United States; and 28 U.S.C. §§ 2201-2202

in that there exists between Zogenix and the Defendants an actual, justiciable controversy as to which Zogenix requires a declaration of its rights by this Court as well as temporary, preliminary and permanent injunctive relief to prohibit the Defendants from violating federal laws and regulations and abridging its rights protected under the U.S. Constitution.

11. Venue is proper in this Court under 28 U.S.C. § 1391(b) because this is a civil action in which the Defendants maintain their offices and conduct business in this judicial district. Moreover, a substantial part of the events giving rise to the claims herein occurred within this judicial district.

12. Zogenix has standing to bring the present lawsuit because Defendants' actions have caused Zogenix actual injury, which is redressable through the specific relief requested herein. As a pharmaceutical company manufacturing and selling pain medication through interstate commerce pursuant to its approval by the FDA, Zogenix's operations also fall within the zone of interests to be protected by the Contract and dormant Commerce Clauses of the U.S. Constitution, as well as general federal preemption principles.

13. This case is ripe for adjudication. As further discussed below, the enforcement of the emergency declaration and order will result in an immediate and concrete invasion of Zogenix's legally protected interests under federal law.

NATURE OF THE CASE

1. Statutory Process for FDA Approval of Drugs:

14. Congress has vested FDA with responsibility for reviewing and approving all new prescription drugs sold in the United States. To that end, the Food, Drug, and Cosmetic Act ("FDCA") requires all new prescription drugs to obtain FDA approval under a new drug application ("NDA") before they can enter the marketplace. 21 U.S.C. § 355(a), (b).

15. Prior to receiving FDA approval, brand name or "pioneer" drug manufacturers must demonstrate the safety and effectiveness of their products. See 21 U.S.C. § 355(b). Drug manufacturers can accomplish this in several different ways: (i) they can submit full reports of safety and effectiveness, id. § 355(b)(1); (ii) they can submit full reports of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant, id. § 355(b)(2); or (iii) they can submit information establishing that the proposed product is identical in specified characteristics to a previously approved product, id. § 355(j).

16. An NDA applicant is required to submit extensive clinical evidence that the drug product is safe and effective; a list of the components of the drug; a statement of the drug's composition; a description of the manufacturing, processing, and packaging of the drug; samples of the drug as necessary; patent information on any patent that it claims will protect the drug product or its uses; and proposed labeling for the drug. 21 U.S.C. § 355(b)(1). To establish safety and effectiveness, an NDA must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A).

17. Upon receipt of an NDA, FDA is charged with performing a thorough analysis of the drug's safety and effectiveness—a process that requires the agency to carefully balance the benefits and risks to patients. 21 U.S.C. §§ 355(c), (d). FDA will approve an NDA only when all necessary data are submitted or referenced to establish the product's safety and effectiveness. *Id*. And FDA will refuse to approve an NDA if it finds that the application and the data presented to support the application do not establish the safety and effectiveness of the product. 21 U.S.C. § 355(d); 21 C.F.R. § 314.125.

18. All drugs have some ability to cause adverse effects. Thus, FDA's safety assessment of a drug is determined by:

> whether its benefits outweigh its risks. This benefit-risk assessment is the basis of FDA's regulatory decisions in the pre-market and post-market review process. It takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in [an NDA], as well as many other factors affecting the benefit-risk assessment, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks. This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, PDUFA V Plan (FY 2013-2017), Draft of February 2013 at 1, *available at* http://patientnetwork.fda.gov/sites/default/files/fda_benefit-risk_draft_plan_final_for_posting.pdf.

19. At the time of initial approval of an NDA, FDA also may require a risk evaluation and mitigation strategy ("REMS") for the drug if it is determined to be necessary to ensure that the benefits of a drug outweigh the drug's risks. 21 U.S.C. § 355-1. A REMS for an NDA product must include a timetable for submission of assessments of the REMS. 21 U.S.C. § 355-1(d). In addition, FDA may require that a REMS include any or all of the other REMS elements set out in the FDCA if specific criteria are met. 21 U.S.C. § 355-1(e), (f). Such additional elements may include elements to assure safe use ("ETASU"). FDA may require a REMS with ETASU if the drug has been shown to be effective but is associated with a serious adverse drug experience and can only be approved if such elements are required as part of a strategy to mitigate a specific serious risk listed in the labeling of the drug. 21 U.S.C. § 355-1(f)(1). The FDCA specifically provides that the serious risks that can be considered in requiring a REMS include adverse events occurring from an overdose of the drug, whether accidental or intentional, and adverse events occurring from abuse of the drug. 21 U.S.C. 355-1(b).

20. ETASU can include a requirement that healthcare providers who prescribe the drug have particular training or experience; pharmacies, practitioners, or health care settings that dispense the drug are specially certified; the drug be dispensed to patients only in certain healthcare settings; the drug be dispensed to patients with evidence or other documentation of safe use conditions; each patient using the drug be subject to certain monitoring; and each patient using the drug be enrolled in a registry. 21 U.S.C. § 355-1(f). Before imposing the ETASU, FDA must ensure that the ETASU are commensurate with the specific risks listed in the drug's labeling and not unduly burdensome on patient access to the drug, taking into consideration patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing healthcare. In addition, such ETASU must conform with elements to assure safe use for other drugs with similar, serious risks and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs so as to minimize the burden on the healthcare delivery system. 21 U.S.C. § 355-1(f)(2).

2. Zohydro™ ER

21. Zogenix submitted an NDA for its drug Zohydro™ ER on May 1, 2012 under Section 505(b)(2) of the FDCA. 21 U.S.C. § 355(b)(2); Ex. B at 4. After eighteen months of careful scrutiny, FDA approved Zohydro™ ER on October 25, 2013 for the management of pain severe enough to require daily, around-the clock, long-term opioid treatment for which alternative treatment options are inadequate. Ex. C at 1.

22. Unlike all other hydrocodone products on the market used for chronic pain, Zohydro™ ER does not contain acetaminophen, thereby avoiding the potential for acetaminophen toxicity in patients for whom Zohydro™ ER is indicated. The use of products containing acetaminophen in high doses over long periods of time has the potential to cause liver

injury, acute liver failure, or even death. Acetaminophen overdose is a leading cause of acute liver failure in the United States, with 63 percent of unintentional acetaminophen overdoses attributed to the use of opioid-acetaminophen combination products. *See* Ex. D at 1. The availability of an acetaminophen-free formulation of extended release hydrocodone is an important therapeutic option for certain chronic pain patients.

23. Thus, Zohydro™ ER provides an important treatment option for patients on immediate release hydrocodone who need an extended-release product; for patients who are at risk for hepatic injury from acetaminophen; and for patients on other ER opioids in which another option for opioid rotation is of value.

24. During the approval process for Zohydro™ ER, FDA considered requiring abuse-deterrent technologies for the drug but ultimately concluded that the overall risk-benefit balance of Zohydro™ ER was sufficient to support approval of the NDA without an abuse-deterrent formulation. FDA outlined its reasoning in its Summary Approval. Ex. B. Among other factors, FDA emphasized the medical benefits of an acetaminophen-free hydrocodone to treat chronic pain patients, noting that a patient being treated with a combination hydrocodone product would be able to switch to Zohydro™ ER and reduce the number of doses per day and maintain a consistent blood level, "which is widely believed to be provide better long-term pain control and to reduce the 'rush' associated with high blood levels that appear to be sought after by opioid abusers." *Id.* at 33. In addition, for patients who have responded well to hydrocodone products but now need a higher dose due to tolerance or increased pain arising from to their underlying condition, Zohydro™ ER would permit prescribers to titrate those patients to an appropriate dose of hydrocodone without the development of toxicities associated with the hydrocodone combination products. *Id.* FDA also stated that the technology used to produce abuse-deterrent

opioid formulations "is still in the nascent stages." *Id.* Further, FDA has concluded that it is not "in the interest of public health at this time to require all opioid products or all [extended release/long-acting] opioid products" to feature the abuse deterrent formulation. *See* Ex. E at 3. In addition to abuse-deterrent formulations' known ineffectiveness at affecting abuse by swallowing whole pills, FDA noted that "the availability of opioid formulations that are not abuseable, that are not potentially addictive, and that do not have the potential to cause respiratory depression and death in overdose is not likely in the near future." Ex. B. at 33.[1]

25. FDA instead determined that there were effective measures in place to protect patients while still making Zohydro™ ER available for patients in need: The labeling of the product includes prominent warnings about abuse, a boxed warning about the known serious risks of addiction, abuse, and misuse, and statements urging prescribers to assess each patient's risk before prescribing the drug and to monitor patients regularly for the development of addiction, abuse, and misuse. And Zohydro™ ER – unlike all other hydrocodone products – is included in the Extended Release/Long-Acting Opioid Analgesics REMS designed to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse. FDA concluded that these measures combined were sufficient to support approval of the product. Ex. B at 31.

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[1] The Drug Enforcement Administration (DEA), in consultation with the Department of Health and Human Services (HHS), recently proposed to reschedule all hydrocodone combination products from Schedule III to Schedule II because they share the same potential for abuse as a single-agent hydrocodone formulation, such as Zohydro™ ER. Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II, 79 Fed. Reg. 11037 (Feb. 27, 2014). Federal regulators thus have determined that drug products that combine hydrocodone with other active pharmaceutical ingredients neither mitigate nor diminish their potential for abuse. Accordingly, it appears that Defendants did not rely on any principled or evidence-based justification for distinguishing Zogenix's single-agent hydrocodone formulation from hydrocodone combination products, in terms of the potential for abuse.

3. Zogenix's Contracts

26. Zogenix maintains contracts with wholesalers who supply, and retailers who operate, Massachusetts pharmacies. In fact, pursuant to these contracts, several pharmacies already have stocked Zohydro™ ER.

27. Zogenix also contracts with Inflexxion, a Massachusetts company that developed cutting-edge abuse tracking methods in conjunction with the federal National Institutes of Health ("NIH").

4. Governor Patrick's Declaration of a Public Health Emergency

28. Without warning to or discussion with Zogenix regarding the safety and effectiveness of Zohydro™ ER, on March 27, 2014, Governor Patrick issued a press release (the "Press Release") announcing that the Governor had declared a public health emergency in Massachusetts and that the Governor had directed the Department of Public Health ("DPH") to take several action steps aimed at combatting opioid overdoses. *See* Ex. F. The Press Release announced that the declared public health emergency provided "emergency powers" to Commissioner Bartlett to, among other actions: "[i]mmediately prohibit the prescribing and dispensing of any hydrocodone-only formulation (commonly known as Zohydro) until determined that adequate measures are in place to safeguard against the potential for diversion, overdose, and misuse." *Id.* at 1-2.

29. That same day, the Governor issued a one-page Declaration of Emergency under M.G.L. chapter 17, section 2A, citing general concerns about opioid addiction and concluding that "an emergency exists which is detrimental to the public health" in Massachusetts. Ex. G at 2.

30. Also on March 27, 2014, the Commissioner and Public Health Council ("PHC") approved an emergency order (the "Order") providing: "No registered individual practitioner shall prescribe or order, and no one shall dispense or administer any hydrocodone bitartrate product in hydrocodone-only extended-release formulation until the Commissioner has determined that adequate measures are in place to safeguard against the potential for diversion, overdose and abuse." Ex. A. There is exactly one "hydrocodone bitartrate product in hydrocodone-only extended-release formulation": Zohydro™ ER.

31. The Commissioner and DPH explained the Order in a March 27, 2014 memorandum as follows: "This order will protect against overdose and abuse of hydrocodone-only extended-release formulation [sic], and provides the means for the Commissioner to lift the prohibition when there are adequate safety measures, such as an abuse-deterrent formulation, which will then allow for the prescribing of hydrocodone-only products to patients with severe pain without running as great a risk that the medication will be diverted or abuse [sic]." Ex. G.

32. This memorandum came as a surprise to Zogenix; it was never consulted before the memorandum issued. And the memorandum doubtless came as a surprise to FDA. As previously noted, during the course of the approval process for Zohydro™ ER, FDA expressly considered whether abuse-deterrent technology should be required for the drug, and it concluded that the benefits of the formulation outweighed any attendant risks. Ex. B at 30-33. Thus, in banning Zohydro™ ER pending its implementation of abuse-deterrent technology, and in determining that the drug is not safe in its current formulation, the Commonwealth placed itself squarely in opposition to the FDA's expert determination and in conflict with federal law. But it did so without any indication that it developed or considered the same factual record surrounding Zohydro™ ER that was presented to the FDA in connection with the agency's determination.

Prohibiting the sale of Zohydro™ ER in Massachusetts also is inconsistent with the Commonwealth's obligations under the drug rebate Medicaid statute. 42 U.S.C. § 1396r-8.

33. Defendants' ban will have an impact on patients beyond the borders of Massachusetts. On March 31, 2014, the director of the Prescription Monitoring and Drug Control division of the DPH issued a Circular Letter to all providers who were Massachusetts Controlled Substance Registrants that informed the providers of the emergency declaration and order and supplied sample "Q&As" that might arise from the Defendants' actions. Ex. A at 2. One question asked whether a Massachusetts provider could still prescribe hydrocodone-only extended release drugs, i.e., Zohydro, to residents of other states. *Id.* The response stated, "No. The order states that no provider registered in Massachusetts shall prescribe any hydrocodone bitartrate product in hydrocodone-only extended-release formulation in Massachusetts." *Id.*

5. <u>The Need for Prompt Judicial Intervention:</u>

34. Defendants' actions will cause real and irreparable harm for patients in Massachusetts with chronic pain. Zohydro™ ER addresses a specific set of patient needs. It fills a noticeable and important gap for chronic pain patients - an acetaminophen-free, extended-release product suitable for round-the-clock pain treatment. While there are other opioid products on the market, some patients are unable to achieve adequate pain relief from, or unable to tolerate, other active ingredients in FDA-approved combination opioid products. This therapy also provides an additional tool for the common practice of opioid rotation in patients with chronic pain. Zohydro™ ER provides an important option for patients while also being the most comprehensively regulated hydrocodone product on the market.

35. Without access to Zohydro™ ER, hydrocodone patients in Massachusetts will either have to remain on immediate release therapy, with a 4-6 hour dosing interval, or be

converted to a different drug substance if they require around the clock care or face risks from the ubiquitous presence of acetaminophen in the immediate-release combination products.

36. Responsive to Massachusetts' concerns related to opioid misuse, and as discussed above, fully 63 percent of unintentional acetaminophen overdoses can be attributed to the use of opioid combination pain medicines. Ex. D at 1. Each year, about 50,000 to 60,000 patients are admitted to emergency rooms for acetaminophen poisoning, and on average more than 500 die each year of acetaminophen related liver toxicity. *Id.* at 5. Depriving Massachusetts patients of access to Zohydro™ ER will not alleviate the hydrocodone safety problems in the state and will compromise public knowledge of the unique contribution that the product has made to preventing acetaminophen poisoning.

37. In addition, Defendants' conduct, unless enjoined, will cause immediate and irreversible harm to the reputation and goodwill of Zohydro™ ER and Zogenix and will irreparably disrupt the launch of this product. The Commonwealth's actions are likely to cause physicians, pharmacists, and patients – both in Massachusetts and across the country - wrongly to believe that Zohydro™ ER is not safe and effective.

38. The longer that physicians associate Zohydro™ ER with unacceptable risks of opioid abuse, the more the reputation of the drug itself and Zogenix at large will be compromised.

39. Health care providers may also have to turn to competing hydrocone-based products, regardless of health risks to patients who will benefit from the unique formulation of Zohydro™ ER. This conversion would further lower Zogenix's standing in the market and reduce its overall market share.

40. Zogenix also stands to suffer substantial lost sales in Massachusetts as a result of the ban. It has projected millions of dollars in sales for Zohydro™ ER in Massachusetts in the coming years.

41. Zogenix has invested over $75 million on the research and development of Zohydro™ ER since 2007. Zohydro™ ER is one of Zogenix's only two FDA-approved and marketed products. Wall Street analyst and company projections had expected Zohydro™ ER to become Zogenix's leading product in terms of revenue by 2015 and the overwhelming majority of Zogenix' product revenue in 2016 and beyond. But after Governor Patrick's announcement, the average stock price for Zogenix dropped 31 percent, from $3.72 (Mar. 3 – 26, 2014) to $2.58 (Apr. 4, 2014), resulting in lost market capitalization in the hundreds of millions of dollars.

CLAIMS FOR RELIEF

Count I
(United States Constitution: Preemption)

42. Zogenix realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 41 of the Complaint as though set forth fully herein.

43. The Supremacy Clause of the United States Constitution provides that federal laws made under the authority of the United States shall be the "supreme law of the land," the laws of any state to the contrary notwithstanding. U.S. CONST. art. VI, § 2.

44. The Supremacy Clause mandates that federal law preempts any state regulation that poses an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.

45. Under the Food, Drug, and Cosmetic Act ("FDCA"), Congress has delegated to the U.S. Food and Drug Administration ("FDA") the authority to protect and promote the public

health by approving for public use "safe and effective" drugs. The FDA has approved Zohydro™ ER as a safe and effective drug.

46. The ban broadly prohibits the prescription, ordering, dispensation, or administration of any hydrocodone bitartrate product in hydrocodone-only, extended-release formulation, until the Department of Public Health Commissioner has determined that "adequate measures" are in place to safeguard against overdose or abuse.

47. Zohydro™ ER is the only drug on the market in Massachusetts meeting the definition of a hydrocodone bitartrate product in hydrocodone-only, extended-release formulation.

48. Taken as a whole, the ban represents an impermissible effort by Massachusetts to establish its own drug approval policy and directly regulate the availability of drugs within the state. It conflicts with the FDA's mandate under the FDCA, disregards federal policies, undermines the FDA's comprehensive regulatory scheme for nationally-effective drug approvals, and otherwise impedes the accomplishment and execution of the full purposes and objectives of federal law.

49. The ban also specifically undermines the FDA's assessment that Zohydro™ ER is a safe and effective product that may be distributed in all fifty states. In so doing, it impedes the FDA's Congressional mandate to approve a range of safe treatments to promote the public health.

50. Plaintiff has no adequate remedy at law for the violation of the Supremacy Clause.

51. The ban will cause substantial, imminent, and irreparable injury to Plaintiff unless the ban is vacated and Defendants are enjoined from enforcing the ban.

Count II
(United States Constitution: Contract Clause)

52. Zogenix realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 51 of the Complaint, as though set forth fully herein.

53. The Contract Clause of the United States Constitution provides that no state shall pass any law "impairing the obligation of contracts." U.S. CONST. art. I, § 10, cl. 1.

54. The ban broadly bans any prescription, ordering, dispensation, or administration of Zohydro™ ER in Massachusetts.

55. Zogenix has valid contracts with wholesalers who supply Zohydro™ ER to Massachusetts pharmacies. These wholesalers already have stocked products at retail locations within the state. Because their subject matter has become illegal under the Massachusetts ban, these contracts between Zogenix and its wholesalers are now substantially impaired. The ban also will impair Zogenix's ability to receive payment under its contract terms.

56. Zogenix also has valid contracts with Inflexxion, a company retained to track abuse patterns for Zohydro™ ER within Massachusetts. The ban irretrievably frustrates the purpose of the agreement and impairs Zogenix's ability to receive the services for which it bargained.

57. For the reasons set forth herein, the ban does not reflect a significant and legitimate public purpose. The state has not appropriately explained the contours of a public emergency necessitating the drastic step it has taken. Furthermore, it applies only to ban Zohydro™ ER while ignoring both the unique advantages of Zohydro™ ER to specific patients and the dangers of other hydrocodone products and opioid products.

58. For the reasons set forth herein, the ban is not based upon reasonable conditions and is not of a character appropriate to the state's stated public purpose. The ban is *ultra vires* and could never be adequately tailored, to the extent that Massachusetts lacked authority to ban Zohydro™ ER in the first place. Moreover, it is too grossly under- and over-inclusive to reflect any level of tailoring, on its own terms.

59. Plaintiff has no adequate remedy at law for the violation of the Contracts Clause.

60. The ban will cause substantial, imminent, and irreparable injury to Plaintiff unless the ban is vacated and Defendants are enjoined from enforcing the ban.

Count III
(United States Constitution: Commerce Clause)

61. Zogenix realleges, reasserts, and incorporates by reference herein each of the allegations contained in paragraphs 1 through 60 of the Complaint, as though set forth fully herein.

62. The Commerce Clause of the U.S. Constitution prevents a state from taking any action which may fairly be deemed to have the effect of impeding the free flow of trade between the states.

63. Prescription drug regulation is an arena that is inherently national in nature in that the FDA has long set uniform standards for drug regulation across all states.

64. The ban imposes significant burdens on interstate commerce because it interferes with the FDA's national and uniform system of regulation. If Massachusetts (and other states) are allowed to make determinations as to what drug formulations are appropriately safe, the result will be a patchwork of state-specific regulation governing how prescription drugs are designed and formulated that would effectively eviscerate the mission of the FDA and create 50

different (and potentially conflicting) sets of rules for deciding what constitutes safe and effective pharmaceuticals.

65. The ban also imposes significant burdens on interstate commerce because it harms patients living in Massachusetts, as well as patients residing outside of Massachusetts who see health care providers in the state. Because health care providers are prohibited from prescribing or dispending Zohydro™ ER to any patients (regardless of their state of residence), patients across several states will not be able to access Zohydro™ ER, thus impacting commerce beyond the borders of the state.

66. The burden imposed on interstate commerce by the ban is clearly excessive in relation to the putative local benefits touted by Defendants. The total prohibition on prescribing and dispensing Zohydro™ ER is the most excessive form of action that can be taken. By contrast, the putative local benefits of limiting opioid abuse are both hypothetical and minimal, given the FDA's consideration of the issue and decision to approve the drug.

67. Zogenix has no adequate remedy at law for the violation of the Commerce Clause.

68. The ban will cause substantial, imminent, and irreparable injury to Zogenix unless the ban is vacated and Defendants are enjoined from enforcing the ban.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully prays for the following relief:

A. A declaration pursuant to 28 U.S.C. § 2201 that the Governor's and Commissioner's conduct in effectuating a ban on the prescription, ordering, dispensing, and administration of Zohydro™ ER violates the United States Constitution;

B. Temporary, preliminary and permanent injunctive relief and/or a final order enjoining the Defendants from implementing or enforcing the Declaration of Emergency, the

Commissioner's Order or any other action banning the prescription, ordering, dispensing, and administration of Zohydro™ ER. In the alternative, temporary, preliminary and permanent injunctive relief and/or a final order vacating the Governor's Declaration of Emergency, the Commissioner's Order, and any other conduct undertaken by or at the direction of Defendants relating to the Commonwealth's effort ban Zohydro™ ER;

C. An order awarding plaintiff's costs, expenses and attorneys fees; and/or

D. Such other and further relief as the Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff respectfully demands a trial by jury of any and all issues triable of right before a jury.

Dated: April 7, 2014

Respectfully Submitted,

ZOGENIX, INC.,

By Its Attorneys

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VERIFICATION OF COMPLAINT

I, the undersigned, having read the allegations of the foregoing Verified Complaint, hereby certify based upon my personal knowledge and under penalty of perjury that the factual allegations asserted in the Verified Complaint are true and correct, and that matters asserted upon information and belief are believed to be true and correct.

Executed this 7th day of April, 2014.

Stephen J. Farr. Ph.D.
President, Zogenix, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

1. **Title of case (name of first party on each side only)** Zogenix, Inc. v. Deval Patrick, in his official capacity as Governor of the Commonwealth of Massachusetts and Cheryl Barnett, RN, in her official capacity as Dept. of Public Health Commissioner

2. **Category in which the case belongs based upon the numbered nature of suit code listed on the civil cover sheet. (See local rule 40.1(a)(1)).**

☐ **I.** **410, 441, 470, 535, 830*, 891, 893, 895, R.23, REGARDLESS OF NATURE OF SUIT.**

☐ **II.** **110, 130, 140, 160, 190, 196, 230, 240, 290,320,362, 370, 371, 380, 430, 440, 442, 443, 445, 446, 448, 710, 720, 740, 790, 820*, 840*, 850, 870, 871.**

☑ **III.** **120, 150, 151, 152, 153, 195, 210, 220, 245, 310, 315, 330, 340, 345, 350, 355, 360, 365, 367, 368, 375, 385, 400, 422, 423, 450, 460, 462, 463, 465, 480, 490, 510, 530, 540, 550, 555, 625, 690, 751, 791, 861-865, 890, 896, 899, 950.**

***Also complete AO 120 or AO 121. for patent, trademark or copyright cases.**

3. **Title and number, if any, of related cases. (See local rule 40.1(g)). If more than one prior related case has been filed in this district please indicate the title and number of the first filed case in this court.**

4. **Has a prior action between the same parties and based on the same claim ever been filed in this court?**

YES ☐ **NO** ☑

5. **Does the complaint in this case question the constitutionality of an act of congress affecting the public interest? (See 28 USC §2403)**

YES ☐ **NO** ☑

If so, is the U.S.A. or an officer, agent or employee of the U.S. a party?

YES ☐ **NO** ☐

6. **Is this case required to be heard and determined by a district court of three judges pursuant to title 28 USC §2284?**

YES ☐ **NO** ☑

7. **Do <u>all</u> of the parties in this action, excluding governmental agencies of the united states and the Commonwealth of Massachusetts ("governmental agencies"), residing in Massachusetts reside in the same division? - (See Local Rule 40.1(d)).**

(state officials sued in their official capacities) **YES** ☑ **NO** ☐

A. **If yes, in which division do <u>all</u> of the non-governmental parties reside?**

Eastern Division ☑ **Central Division** ☐ **Western Division** ☐

B. **If no, in which division do the majority of the plaintiffs or the only parties, excluding governmental agencies, residing in Massachusetts reside?**

Eastern Division ☐ **Central Division** ☐ **Western Division** ☐

8. **If filing a Notice of Removal - are there any motions pending in the state court requiring the attention of this Court? (If yes, submit a separate sheet identifying the motions)**

YES ☐ **NO** ☐

(PLEASE TYPE OR PRINT)

ATTORNEY'S NAME Kenneth J. Parsigian (BBO # 550770)

ADDRESS Latham & Watkins LLP, John Hancock Tower, 20th Floor, 200 Clarendon St., Boston, MA 02116

TELEPHONE NO. (617) 948-6000

JS 44 (Rev. 12/12)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

Zogenix, Inc.

(b) County of Residence of First Listed Plaintiff San Diego County
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Kenneth J. Parsigian (BBO # 550770) and Steven J. Pacini (BBO # 676132), Latham & Watkins LLP, John Hancock Tower, 20th Floor, 200 Clarendon St., Boston, MA 02116, (617) 948-6000

DEFENDANTS

Patrick Deval, in his official capacity as Governor of Masachusetts
Cheryl Barnett, in her official capacity as Dept. of Pub. Health Comm'r

County of Residence of First Listed Defendant Suffolk County
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

CIVIL RIGHTS
- ❒ 440 Other Civil Rights
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ❒ 463 Alien Detainee
- ❒ 510 Motions to Vacate Sentence
- ❒ 530 General
- ❒ 535 Death Penalty

Other:
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ❒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 375 False Claims Act
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
28 U.S.C. §§ 2201-2202

Brief description of cause:
State action preempted under the Supremacy Clause and violating the Contract and dormant Commerce Clauses

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☒ Yes ❒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE
04/07/2014

SIGNATURE OF ATTORNEY OF RECORD
/s/ Kenneth J. Parsigian

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below**; NOTE: federal question actions take precedence over diversity cases.**)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerk(s) in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the six boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

EXHIBIT G

DEVAL L. PATRICK
GOVERNOR

JOHN W. POLANOWICZ
SECRETARY

CHERYL BARTLETT, RN
COMMISSIONER

The Commonwealth of Massachusetts

Executive Office of Health and Human Services
Department of Public Health
Bureau of Health Care Safety and Quality
99 Chauncy Street, 11th Floor, Boston, MA 02111
617-753-8000

TO: Commissioner Cheryl Bartlett and Members of the Public Health Council

FROM: Deborah Allwes, Director of Prescription Monitoring and Drug Control
Jamie Pianka, Director of Office of Emergency Services
Hilary Jacobs, Director of Bureau of Substance Abuse Services

DATE: March 27, 2014

RE: Request for Approval of the Public Health Council for the Commissioner to Take Action to Address the Public Health Emergency of Opiate Overdose and Abuse; and

Proposed Emergency Amendments to 105 CMR 700.000 and 105 CMR 171.000 Related to the Use of Naloxone and Other Opioid Antagonists by First Responders

---

Introduction

The Governor of the Commonwealth has determined that an emergency exists which is detrimental to the public health with respect to the number of opiate-related overdoses and amount of opiate addiction in the Commonwealth.

The staff of the Department of Public Health are concerned that the Commonwealth is experiencing a large number of unintentional opioid-related overdose deaths. According to the Massachusetts State Police, at least 140 people died from suspected heroin overdoses in Massachusetts between November 2013 and February 2014. The rate of unintentional opioid-related overdose deaths has reached levels previously unseen in Massachusetts. In addition, powerful opiate medications with potential for abuse and overdose are being diverted for non-medical use.

For the first time, there is an FDA-approved medication which consists entirely of hydrocodone, in much higher levels than any currently available hydrocodone combination product. This

hydrocodone-only extended release product is not in an abuse-deterrent formulation.[1] Since the FDA-approved medication does not include abuse-deterrents in its formulation, there is a high likelihood of misuse, diversion and abuse of the medication, further adding to the opiate abuse epidemic and increasing the likelihood of additional opiate-related overdoses.

To respond to this public health emergency, the Governor has issued a Declaration of Emergency Detrimental to the Public Health. This Declaration is made pursuant to M.G.L. c. 17, §2A, which states that:

> Upon declaration by the governor that an emergency exists which is detrimental to the public health, the commissioner may, with the approval of the governor and the public health council, during such period of emergency, take such action and incur such liabilities as he may deem necessary to assure the maintenance of public health and the prevention of disease.
>
> The commissioner, with the approval of the public health council, may establish procedures to be followed during such emergency to insure the continuation of essential public health services and the enforcement of the same.
>
> Upon declaration by the governor that such emergency has terminated, all powers granted to and exercised by the commissioner under this section shall terminate.

Actions to Address the Public Health Emergency

The Commissioner proposes to the Public Health Council the following actions to address the public health emergency:

1. Prohibit the prescribing and dispensing of any hydrocodone bitartrate product in hydrocodone-only extended-release formulation

In response to the Governor's Declaration, and in the event the Public Health Council approves, the following Order shall be issued by Commissioner Bartlett:

> No registered individual practitioner shall prescribe or order, and no one shall dispense or administer any hydrocodone bitartrate product in hydrocodone-only extended-release formulation until the Commissioner has determined that adequate measures are in place to safeguard against the potential for diversion, overdose and abuse.

This order will protect against overdose and abuse of hydrocodone-only extended-release formulation, and provides the means for the Commissioner to lift the prohibition when there are adequate safety measures, such as an abuse-deterrent formulation, which will then allow for the prescribing of hydrocodone-only products to patients with severe pain without running as great a risk that the medication will be diverted or abuse.

[1] "Abuse-deterrent formulation" means an FDA-approved formulation of a controlled substance that targets known or expected routes of abuse for that formulation.

2. Order expanded access to naloxone for individuals in a position to assist a person experiencing an opiate-related overdose

To expand the use of naloxone or other opioid antagonist, and in the event the Public Health Council approves, the following Order shall be issued by Commissioner Bartlett:

> Naloxone or other opioid antagonists approved by the Department may be dispensed to a person at risk of experiencing an opiate-related overdose or any person in a position to assist a person at risk of experiencing an opiate-related overdose by a licensed pharmacist. The pharmacist must dispense the naloxone or other opioid antagonist in accordance with written, standardized procedures or protocols developed by an actively practicing physician registered with the Commissioner to distribute or dispense a controlled substance in the course of professional practice pursuant to section 7. Such procedures or protocols must be filed at the pharmacist's place of practice and with the board of registration in pharmacy before implementation.

This order is similar to the statute which was enacted to permit pharmacists to dispense emergency contraception to consumers without a prescription. That statute, M.G.L. c. 94C, § 19A, was enacted to ensure that women could access emergency contraception before the FDA took action to make emergency contraception an over the counter medication. This order would provide a similar level of availability for naloxone.

This order would allow a person who is at risk of opiate-overdose, or a person whose family member or friend is at risk, to purchase naloxone and have it available in order to possibly save the life of a person who is experiencing an opiate-related overdose. Naloxone has no effect on a person who is not experiencing an opiate-related overdose, and can be made available in a kit with a nasal atomizer, making it relatively easy to administer.

3. Expand access to naloxone for first responders

To respond to the Governor's direction that the Commissioner, with the Public Health Council's approval, expand access to naloxone or other opioid antagonists for first responders, the Drug Control Program (DCP) and the Bureau of Health Care Safety and Quality are requesting the Public Health Council adopt, on an emergency basis, amendments to regulations at 105 CMR 700.000 and 105 CMR 171.000. These amendments permit first responders to carry and administer naloxone or other opioid antagonist approved by the Department.

Specifically, staff proposes the following regulatory amendments:

1. Amendments to 105 CMR 700.000: Implementation of M.G.L. c. 94C
2. Amendments to 105 CMR 171.000: Massachusetts First Responder Training

The proposed amendments are authorized by M.G.L. c. 94C, § 7(g) and M.G.L. c. 111, § 201 and supported by Chapter 192 of the Acts of 2012, codified at M.G.L. c. 94C, §§ 19 and 34A.

Chapter 192 of the Acts of 2012 amended M.G.L. c. 94C, §§ 19 and 34A to expand the Good Samaritan laws as they pertain to naloxone. M.G.L. c. 94C, § 19 states that "(d) naloxone or other opioid antagonist may lawfully be prescribed and dispensed to a person at risk of experiencing an opiate-related overdose or a family member, friend or other person in a position to assist a person at risk of experiencing an opiate-related overdose." M.G.L. c. 94C, § 34A permits a "person acting in good faith [to] receive a naloxone prescription, possess naloxone and administer naloxone to an individual appearing to experience an opiate-related overdose." However, unless municipalities register with the Department, they cannot purchase naloxone for use by their first responders. The proposed amendments add naloxone to the medications that may be administered by first responders and other authorized employees of a municipality duly registered with the Department. These amendments will help municipalities respond to the opiate overdose problem in their communities.

The proposed amendments are consistent with the statutory intent of Chapter 192 of the Acts of 2012, and are necessary in order to respond to this public health emergency. The amendments will:

- permit first responders to administer naloxone or other opioid antagonists approved by the Department, in accordance with the Massachusetts First Responder Training regulations;
- add naloxone or other opioid antagonists to the medications that first responders can carry and administer when municipalities are duly registered with the Department; and
- institute procedures to ensure that the naloxone or other opioid antagonist is packaged and dispensed properly.

These proposed amendments will provide municipalities with an effective and safe means to respond to opioid overdoses in their community, and will respond to the request of the Commissioner, made in response to the Governor's declaration of a public health emergency.

Public Health Council Approval

It is respectfully requested that the Public Health Council vote to approve the Orders set forth above, vote to adopt the amendments to 105 CMR 171.000 and 105 CMR 700.000 on an emergency basis, and to further approve that the Commissioner may, during the period of emergency, take such other actions, incur such liabilities, and establish such procedures which are consistent with, and of necessity are required by, the provisions of the Governor's Declaration.

EXHIBIT F

DEVAL PATRICK
GOVERNOR

Media Contact

Heather Nichols
Bonnie McGilpin
Juli Hanscom
617-725-4025

Alec Loftus (HHS)
617-573-1612

For Immediate Release - March 27, 2014

GOVERNOR PATRICK DECLARES PUBLIC HEALTH EMERGENCY, ANNOUNCES ACTIONS TO ADDRESS OPIOID ADDICTION EPIDEMIC

Dedicates $20 million to enhance substance abuse treatment programs; Convenes emergency session of Public Health Council to immediately act on emergency measures

Governor Patrick makes an announcement relative to opiate addiction and recovery at the Department of Public Health. (Photo: Eric Haynes/Governors Office)

BOSTON – Thursday, March 27, 2014 – Governor Deval Patrick today declared a public health emergency in Massachusetts in response to the growing opioid addiction epidemic. The Governor directed the Department of Public Health (DPH) to take several action steps that will combat overdoses, stop the epidemic from getting worse, help those already addicted to recover and map a long-term solution to ending widespread opiate abuse in the Commonwealth.

The use of oxycodone and other narcotic painkillers, often as a route to heroin addiction, has been on the rise for the last few years in Massachusetts. At least 140 people have died from suspected heroin overdoses in communities across the Commonwealth in the last several months, levels previously unseen. From 2000 to 2012, the number of unintentional opiate overdoses increased by 90 percent.

"We have an epidemic of opiate abuse in Massachusetts, so we will treat it like the public health crisis it is," said Governor Patrick. "I have directed DPH to take certain immediate actions and to give me further actionable recommendations within 60 days, to address this challenge and better protect the health of people suffering from addiction and the families and loved ones who suffer with them."

The Governor's Public Health Emergency declaration provides emergency powers to DPH Commissioner Cheryl Bartlett, RN. At the Governor's direction, Commissioner Bartlett will work with the Public Health Council to take the following actions:

1. Universally permit first responders to carry and administer Naloxone (Narcan), a safe and effective opioid antagonist that, when timely administered, can reverse an overdose and save a life. Naloxone will also be made widely available through standing order prescription in pharmacies in order to provide greater access to family and friends who fear a loved one might overdose.

2. Immediately prohibit the prescribing and dispensing of any hydrocodone-only formulation (commonly known as

Zohydro) until determined that adequate measures are in place to safeguard against the potential for diversion, overdose and misuse. The introduction of this new painkiller into the market poses a significant risk to individuals already addicted to opiates and to the public at large.

3. DPH is mandating the use of prescription monitoring by physicians and pharmacies to better safeguard against abuse or misuse. This was previously a voluntary program.

4. Re-task the Commonwealth's Interagency Council on Substance Abuse and Prevention with added members from public health, provider organizations, law enforcement, municipalities and families impacted by the opiate epidemic, to make recommendations in 60 days on further actions that can be taken, including, but not limited to: how to better coordinate services, ensure a full range of treatment regardless of insurance, and how to divert non-violent criminal defendants struggling with addiction into treatment programs.

The Administration will also dedicate an additional $20 million to increase treatment and recovery services to the general public, to the Department of Corrections and to Sheriffs' Departments.

In conjunction with this public health emergency declaration, Commissioner Bartlett today issued a public health advisory to help education and raise awareness about the treatment options currently available to combat and prevent the spread of opioid addiction.

"These actions will help slow the rise of this dangerous addiction;" said Commissioner Bartlett. "Together, these steps will raise awareness in our communities, help save loved ones who tragically fall down from their disease and build important bridges to long-term recovery."

The Governor also announced today that he will partner with other governors and federal stakeholders to develop a regional action plan to bring an end to the opioid epidemic. Earlier this week, the Governor sent letters to Senator Manchin, Congressman Lynch and Secretary Sebelius in support of efforts at the federal level to ban Zohydro Extended Release (ER).

Supportive Statements:

"This epidemic reaches far beyond the addict," said Senate President Therese Murray. "The costs of drug addiction are high, both to families and the economy, and it poses an extreme threat to the safety of our communities. Recognizing the rising levels of drug abuse in the Commonwealth, we have been trying to address the need for treatment beds and services for the past ten years to get ahead of this crisis. The Senate's Special Committee on Drug Abuse and Treatment Options has been working to find how we can address this difficult and life-threatening problem and I want to thank the Governor and the Department of Public Health for their dedication to finding a solution. In addition to these steps, it is critical that we put in place an education program in elementary schools, similar to the anti-smoking program, so all students are aware of the dangers and effects of addiction by the time they get to middle school. The age of those who are using and overdosing keeps getting younger and by the time they reach high school it is already too late. It is our responsibility to get ahead of addiction and provide residents with the resources to lead drug-free, independent lives."

"In my role as Chair of the Special Senate Committee on Drug Abuse and Treatment Options, I have met with and heard from countless people with a heart wrenching story to tell," said Senator Jen Flanagan. "I am thankful that the Governor is putting much needed resources into this epidemic. As the Senate Committee continues to travel throughout the Commonwealth to hear from those on the front line, as well as affected families; we are eager to work with the Governor's office and others to enhance the availability treatment options in Massachusetts."

"The steps taken today reinforce that we must renew our focus on prevention – preventing people from starting down the path to addiction by appropriately limiting the prescribing of opiates, preventing deaths through the use of Narcan, and preventing people from being denied treatment because of a lack of programs and lack of insurance coverage," said Senator John Keenan "We have a number of bills making their way through the legislative process that will further enhance these efforts, and together we'll continue our fight to end this epidemic."

"We truly are in a state of emergency when it comes to opiate addiction, and the Commonwealth has had to do a lot with limited resources," said Representative Liz Malia. "Expanding services will fill some of the existing gaps in the system and allow those in need to access treatment in real time – when they need it and in the most appropriate setting."

"Those of us who have spent our careers working in the addiction treatment field have never experienced anything that approaches the current opiate abuse epidemic," said Chuck Faris, CEO of Spectrum Health Systems. "The pain inflicted on families, the increase in crime and the loss of lives is unprecedented. We applaud the Governor for his leadership on this public health challenge. We look forward to his decisive action that will save lives and protect the public."

"On March 26, I was invited to sit with other parents and family members to share experiences of our loved ones' addictions with Governor Patrick and his Administration. I left there with guarded optimism," said Paul Doherty. "His response today is beyond anything I had anticipated or I could have hoped for. I applaud Governor Patrick's quick response to this crisis. Having Governor Patrick recognize the urgency of this epidemic will bring attention and necessary resources to help those who are directly affected by the disease of addiction as well as those who have dedicated their lives to helping those who suffer from this disease."

"I know I speak for each and every one of the over 5,000 members of Learn To Cope, families who struggle every day in finding resources, treatment and hope for our loved ones and all of the families who have lost loved ones to overdose, when I say today we have hope that Governor Patrick, who has heard our concerns and, manning all of the resources at the state's disposal, we are moving forward with solutions to the horrendous epidemic of opiate addiction that is ravaging our

Commonwealth and the nation," said Mary D'Eramo, of Learn to Cope.

###

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EXHIBIT E

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MAR 20 2014

The Honorable Lamar Alexander
United States Senate
Washington, D.C. 20510-4206

Dear Senator Alexander:

Thank you for your letter of February 12, 2014, cosigned by Senator Mitch McConnell and Senator Tom Coburn, regarding the approval of Zohydro ER. The Food and Drug Administration (FDA or the Agency) shares your concerns about the abuse and misuse of opioids, including Zohydro ER.

Over the last several years, FDA actively addressed many complex issues associated with the regulation and safe and appropriate use of opioid products, and in particular the class of products to which Zohydro ER belongs, i.e., extended release/long-acting (ER/LA) opioids. In doing so, we are mindful of the need to balance the use of pain medicines by patients who need them to manage their pain, with the need to address the abuse and misuse of prescription opioid medications, which have resulted in many reports of injuries and deaths across the United States. FDA encourages, seeks to incentivize, and, in appropriate cases, requires efforts to address the abuse and misuse of prescription opioid medications.

We have restated your questions below in bold, followed by our responses.

1. **What conditions are in place around the production and distribution of this drug, and how were those conditions evaluated to ensure their effectiveness for preventing misuse, abuse, and diversion?**

   On September 10, 2013, FDA invoked its authority under section 505(o) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to require safety labeling changes and post-market studies for all ER/LA prescription opioid analgesics. Zohydro ER is the first drug approved with the new labeling, and the manufacturer of Zohydro will be required to conduct post-market study requirements applicable to ER/LA opioids. The approved labeling includes prominent warnings about abuse, including a boxed warning about the known serious risks of addiction, abuse, and misuse. The labeling also urges prescribers to "assess each patient's risk" before prescribing the drug and to "monitor all patients regularly for the development of [addiction, abuse, and misuse]."

   In addition, Zohydro is a Schedule II controlled substance, and as such, it can only be dispensed through a physician's written prescription, for which no refills are

allowed. There are also stringent recordkeeping, reporting, and physical security requirements for Schedule II controlled substances.

Moreover, Zohydro ER is subject to the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (ER/LA Opioid Analgesic REMS), which is intended to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse. The ER/LA Opioid Analgesic REMS requires the distribution of a Medication Guide with each prescription filled, as well as a requirement that training be made available to all those who prescribe ER/LA opioids.

There is no way to completely prevent misuse or abuse of prescription opioid analgesics, even those that have been formulated to have abuse-deterrent features, as such formulations make abuse by certain routes of administration more difficult, but not impossible. While FDA works with companies to facilitate development of novel analgesics that are intrinsically more difficult to abuse or misuse, the greatest tool available to limit these risks is prescriber and patient education. The ER/LA Opioid Analgesic REMS has been designed to provide education to prescribers. Mandatory education about opioids for all DEA registrants would further expand these educational efforts.

2. How does FDA balance patient needs with regard to access to safe and effective pain medication with the potential for abuse, misuse, and diversion?

FDA, together with other Federal agencies, is working to address the large and growing problem of opioid misuse and abuse while seeking to ensure that patients in pain have appropriate access to opioid analgesics. Chronic pain remains a major problem in the United States, and in addition to hearing from those whose lives have been impacted by opioid abuse, at each public meeting, we hear from patients who suffer due to chronic pain and who are desperate for additional options for managing their pain. As cited in the 2011 Institute of Medicine (IOM) report, "Relieving Pain in America," at least 116 million U.S. adults suffer from chronic pain conditions.[1] Also noted in this IOM report (p. 113), "[c]urrently available treatments have limited effectiveness for most people with severe chronic pain." To improve the appropriate use of opioids, FDA has worked to improve the labeling of ER/LA opioid medications to reflect our best understanding of the risks and benefits of these products, including the serious risks associated with addiction, abuse, and misuse. Among other changes, the proposed new labeling for these products clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Also, as noted in response to Question 1, all ER/LA opioid analgesics are subject to the ER/LA Opioid Analgesics REMS, which is intended to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse.

[1] *http://books.nap.edu/openbook.php?record_id=13172&page=R1*

3. You have previously confirmed that the FDA has the legal authority under the Federal Food, Drug and Cosmetic Act to require drugs, including generic versions, to have an abuse-deterrent formulation. How does the FDA plan to use this authority in regards to approving both brand and generic opiates? Please provide examples of the circumstances in which FDA would use this authority.

We strongly encourage the development of opioids that can be expected to significantly reduce abuse, and we have recently implemented a policy that provides substantial incentives for sponsors of such products. For example, such products may be eligible for one or more of FDA's expedited review and approval programs, including fast-track designation and priority-review timelines, if the applicable statutory and regulatory criteria are met.

However, we do not believe it is feasible or in the interest of public health at this time to require all opioid products or all ER/LA opioid products to be abuse-deterrent. Rather, we intend to take a case-by-case approach to regulatory decisions concerning the safety and effectiveness of opioid products, in light of the data available to us with respect to each action.

Under FDA's current approach, abuse potential is one aspect of a product's safety that FDA considers, together with all other appropriate factors, in determining whether a product's benefits outweigh its risks. For example, in 2013, FDA announced regulatory decisions related to OxyContin and Opana ER. The sponsors of both products reformulated them with the intention of deterring manipulation for purposes of abuse or misuse. In the case of OxyContin, FDA determined that the original product posed an increased potential for abuse by certain routes of administration compared to the reformulated product. Based on the totality of the data and information available to the Agency, FDA concluded that the benefits of original OxyContin, which lacked abuse-deterrent properties, no longer outweighed its risks, and that original OxyContin was withdrawn from sale for safety or effectiveness reasons. As a result of that decision, FDA will not accept or approve applications for generic versions of the original formulation of OxyContin.

In contrast, for Opana ER, FDA determined that there was insufficient evidence that the original formulation poses an increased risk of abuse compared to reformulated Opana ER. Based on the totality of the data and information available to the Agency, FDA determined that the original formulation's benefits continue to outweigh its risks. FDA therefore concluded that original Opana ER was not withdrawn from sale for safety or effectiveness reasons, and generic versions of the original formulation of Opana ER remain approved.

Consistent with this product-specific approach, FDA approved Zohydro ER after concluding that its benefits outweigh its risks, notwithstanding that the product does not have abuse-deterrent properties.

4. **How does FDA plan to monitor the abuse, misuse, and diversion of pure hydrocodone products, including overdose rates, and evaluate and update the conditions put in place to prevent such abuse, misuse, and diversion if necessary? Please include any plans to work with law enforcement and stakeholders on implementing the most effective strategies to prevent abuse, misuse and diversion, such as the standards for and requirement of abuse deterrent formulations.**

   FDA has created an epidemiology team dedicated specifically to evaluating issues relating to prescription drug abuse. This team has access to data that can monitor drug utilization patterns, which are close to real time in nature.

   There is very limited ability to monitor abuse via spontaneous reports and the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES); however, as the Drug Abuse Warning Network (DAWN) discontinued collecting data after 2011, we really have no substantive manner in which to monitor events relating to drug abuse presenting to emergency departments. We are actively working with the National Center for Health Statistics to determine the feasibility of collecting DAWN-like information from other hospital surveys, and to determine the feasibility of getting drug-specific information from death certificates in which drug involvement was apparent. It is unclear at this point whether either of these efforts will produce useful data. We are also working with Brandeis University to determine whether national data on patterns of drug abuse can be obtained from the state-level Prescription Drug Monitoring Programs (PDMPs). In the meantime, we are relying on sponsors, via their post-marketing study requirements to provide epidemiologic data, noting that it is not real time in nature.

   With regard to the question concerning implementing strategies to prevent abuse and misuse, as mentioned above, FDA has implemented a number of strategies, including the September 2013 ER/LA opioid analgesic safety labeling changes and the institution of post-marketing requirements.

Thank you, again, for contacting FDA concerning this important matter. Please let us know if you have further questions. The same letter has been sent to your cosigners.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

EXHIBIT D

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REVIEW ARTICLE

Removal of Opioid/Acetaminophen Combination Prescription Pain Medications: Assessing the Evidence for Hepatotoxicity and Consequences of Removal of These Medications

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Abstract

Opioid/acetaminophen combination products are widely prescribed for the management of moderate to moderately severe pain. Acetaminophen, when improperly used, can lead to liver damage and even acute liver failure. In June 2009, an FDA advisory committee recommended elimination of prescription acetaminophen combination products because of the risk of hepatotoxicity associated with use of these medications. The FDA advisory committee reviewed numerous observational studies and adverse event reporting data. The aims of this article are to: 1) provide a summary and epidemiologic critique of the studies and evidence the FDA advisory committee reviewed; 2) examine the potential consequences, such as poorly managed pain or a shift to treatment with other medications with greater potential toxicity and/or restricted availability, if the FDA follows the advisory committee vote; and 3) outline alternate strategies the FDA should consider for reducing hepatotoxicity associated with opioid/acetaminophen combination products.

Key Words. Safety; Hydrocodone; Oxycodone; Pain Management; Opioids

Introduction

On June 29–30, 2009, the Food and Drug Administration (FDA) convened an advisory committee to discuss the safety of acetaminophen-containing over-the-counter (OTC) and prescription medications. Following presentation and review of information on acetaminophen hepatotoxicity, the advisory committee voted 20–17 to recommend elimination of prescription acetaminophen combination products [1]. This was one of 10 votes held during the course of the 2-day meeting. Ironically, the committee voted 24–13 against eliminating nonprescription acetaminophen combination products.

Data presented to the committee suggested that acetaminophen was the leading cause of acute liver failure (ALF) in the United States, with 63% of unintentional overdoses associated with opioid/acetaminophen use. The proportion of ALF cases associated with acetaminophen increased from 28% in 1998 to 51% in 2003. While these studies may give valid counts of events and highlight that improper use of acetaminophen-containing medications can lead to severe and life-threatening liver damage, the number of acetaminophen users, a denominator necessary to calculate risk and thereby provide an appropriate response by the FDA, is conspicuously absent as well as difficult to define. As all of these studies were retrospective and observational and had inherent design limitations, the evidence from them must be carefully evaluated.

This is especially important, as the impact of removal of these medications from the market would be far-reaching and have a substantial effect on the practice of pain management. Pain is the most common reason that persons seek medical attention. Twenty-six percent of people 20 years old and older who participated in the 1999–2002 National Health and Nutrition Examination Survey reported a problem with pain lasting more than 24 hours in the month prior to being interviewed [2]. There is compelling evidence that unrelieved pain has significant adverse physiological and psychological effects [3–5]. Pain has significant economic consequences as well, costing $61.2 billion per year in lost productive time and resulting in over 50 million lost workdays annually [6,7].

Opioid/acetaminophen combination products are very commonly prescribed for the management of pain. In fact, hydrocodone/acetaminophen combination products are the most prescribed drugs in the United States, accounting for more than 89 million prescriptions dispensed in 2003 [8]. The elimination of opioid/acetaminophen combination products would come at a significant sacrifice to those whose pain is well controlled with these drugs. Patients may experience loss of pain control with decreased quality of life. They may be treated with less effective therapies or with medications with potentially more serious adverse effects. Patients' timely access to treatment could be compromised due to a reduction in the availability of conveniently prescribed, effective pain medications. Changes could require more frequent and/or more numerous provider visits, resulting in an increase in health care utilization and costs.

The primary objective of this work was to review the strengths and weaknesses of the data and primary studies considered by the FDA advisory committee that voted to recommend removal of opioid/acetaminophen combination products from the market. A second objective was to consider whether the evidence presented warrants the removal of these medications especially in light of their benefits and the unintended consequences/potential risks associated with their removal from the market.

Evidence for Acetaminophen-Associated Hepatotoxicity from the Use of Acetaminophen-Containing Prescription Pain Medications

The evidence for acetaminophen-associated hepatotoxicity presented to the FDA advisory committee came from numerous sources and published studies that assessed acetaminophen-associated adverse events (ALF and acetaminophen-associated deaths), the incidence of acetaminophen overdose, and health care utilization associated with acetaminophen-associated hepatotoxicity. No efficacy and safety data were required at the time most of the opioid/acetaminophen combination products were approved by the FDA [9]. The lack of randomized, controlled safety studies leaves only results from observational studies to estimate the risks associated with opioid/acetaminophen combination products. A thorough review of each of these sources indicates that while acetaminophen containing medications may be implicated in some events, *the absolute risk and rate associated with these medications and the incremental contribution from these medications cannot be estimated from current data*.

Epidemiologic Studies Assessing Acetaminophen-Associated Hepatotoxicity

Evidence presented to the advisory committee included a study by Larson et al. [10], which assessed risk factors for ALF and outcomes among patients with acetaminophen-associated ALF at tertiary care facilities in the United States. Patients with ALF who presented to participating centers of the Acute Liver Failure Study Group from 1998 through 2003 were identified. Broad diagnostic criteria were used to define acetaminophen-associated ALF: probable use of a toxic dose of acetaminophen within the week prior to admission, detection of any amount of acetaminophen in the patient's serum, or an elevated serum alanine aminotransferase level with a report of acetaminophen ingestion. Acetaminophen use was classified as either intentional or unintentional ingestion. Unintentional ingestion and overdose may occur when acetaminophen is taken inconsistently with its prescribed use. This may occur if a person takes more doses of a medication with acetaminophen than is indicated, or this may occur when a person takes multiple medications containing acetaminophen and the total amount of acetaminophen from the various medications exceeds a safe amount.

During the 6-year period, 662 ALF cases were identified and 275 (42%) were identified with acetaminophen-related hepatotoxicity; among these acetaminophen-associated cases, 131 (48%) were unintentional overdose. The proportion of ALF cases attributed to acetaminophen rose from 28% in 1998 to 51% in 2003 and the absolute number of ALF cases increased from 85 to 128. Forty-four percent of the acetaminophen-associated ALF subjects reported ingestion of opioid/acetaminophen combination products.

There are several facts that should be noted while reviewing the evidence from this study. First, it is based solely on the number of ALF cases identified over a 6-year period. No estimate of total medication users in the catchment area of the Acute Liver Failure Study Group sites was provided. This makes the quantification of risk impossible. Without a denominator-based risk estimate, the magnitude of impact on public health cannot be assessed. Moreover, while the number of ALF cases and the percent of acetaminophen-associated ALF cases rose over time, it is very likely that the number of users of OTC acetaminophen and opioid/acetaminophen combination products also increased. For example, between 2001 and 2005, prescriptions for acetaminophen combination medications increased 38.1% [11]. It is possible that the incidence or risk of ALF associated with these products remained stable or even decreased over time. *Without denominator-based information, it is impossible to determine in which direction risk is changing*.

Second, the overall rise in acetaminophen-associated ALF cases over time could be explained by various external factors separate and distinct from an increase in use of acetaminophen containing medications. Changes in patient demographics, such as an increase in the age of the population, could have effects. Patients over 40 years of age who overdose on acetaminophen have a higher risk of ALF, liver transplant, and death [12]. The proportion of ALF cases related to acetaminophen may also increase over time if the proportion of ALF cases due to other causes decreases. For example, the proportion of ALF cases due to hepatitis B, the most common cause of ALF in the 1980s, is likely to have decreased due to vaccination campaigns in the 1990s.

An important limitation of this study is the lack of information on the medical history of these patients. It is possible that some who took opioid/acetaminophen combination products also had pre-disposing medical conditions (e.g., neoplasms, IV drug use, arthritis, heart failure, blood transfusions). Other drug use may have pre-disposed some of these patients to ALF resulting in acetaminophen being incorrectly identified as the cause. Toxicology screens were available for 77 subjects and positive for 58 subjects: 10 tested positive for marijuana, 11 for cocaine, 5 for amphetamines, and the remaining were positive for substances which were probably prescribed medications. Cocaine is known to have toxic effects on human hepatocytes [13]. Without identifying and adjusting for these confounding factors, one may not attribute the elevated number of ALF cases in this group entirely or directly to the use of acetaminophen. The fact that about one-quarter of the opioid/acetaminophen users were elderly and had multiple co-morbidities could have led to overestimation of the number of acetaminophen-associated cases. In addition to these limitations cited previously, an ALF case could be classified as acetaminophen-associated if the person recalled ingesting a toxic dose in the prior week; recall bias could misclassify the person's true acetaminophen exposure, particularly if someone's mental status was altered due to ALF. Similarly, a case was labeled acetaminophen-associated if *any* serum level of the drug was detected. This means that even therapeutic use of the drug could have been incorrectly included in the case definition.

The investigators reported that 19 persons (7%) reported taking 4 g of acetaminophen per day, which is the maximum recommended daily dose. These persons were older and more likely to use or abuse alcohol than were those who took greater than this amount. Thus, the apparent risk associated with therapeutic doses of acetaminophen is confounded by alcohol or other unmeasured factors. This gives pause to arguments that the current recommended maximum daily dose, when used properly, results in hepatotoxicity.

Using the data from this study the authors estimated that at least 250 cases of acetaminophen-associated ALF present to transplant centers in the United States each year. However, the authors also noted that national survey data indicate that 36% of Americans take an acetaminophen-containing product at least once per month, indicating that the incidence of acetaminophen-associated ALF is probably low given the widespread use of these medications. While 250 cases of acetaminophen-related ALF may occur each year in the United States, more than 112 million people use acetaminophen each month, which translates to a yearly risk of less than two per 10 million. The yearly odds of being struck by lightning, considered a rare event, are one in 700,000 [14].

Realizing that most studies on ALF were conducted in tertiary care facilities and that these patient populations may differ from the general population, Bower et al. [15] conducted a population-based surveillance study of ALF. Each week an intensive care unit medical staff member at participating hospitals in the metropolitan Atlanta area determined whether there were patients who met the ALF case definition. Patients or family members provided information on medication usage. ALF etiology was determined by patient or family member reports and laboratory findings. Diagnosis of acetaminophen toxicity required a toxic serum acetaminophen level based on an acetaminophen toxicity nomogram or a history of ingesting an acetaminophen level in excess of the therapeutic dose. Non-acetaminophen-related hepatotoxicity was based on reported exposure to a suspected drug and exclusion of other causes, including viral infections, autoimmune hepatitis, alcohol use/abuse, and ischemia.

Ninety-four patients were classified as ALF cases; acetaminophen-associated ALF was the most common etiology. Acetaminophen toxicity was identified in 46% of adult ALF cases; 45% were due to intentional overdose and 55% to unintentional overdose. Among the adult ALF cases where acetaminophen was implicated, alcohol was believed to be a contributing factor in six cases (27%). Acetaminophen was the second leading etiology for pediatric ALF cases and was implicated in 25% of cases. Using the number of ALF cases and the estimated catchment population for the participating hospitals, the investigators estimated there are approximately 1,600 cases of ALF per year in the United States.

There are significant limitations to population-based surveillance studies as stated earlier. In addition, the surveillance area contained only 94 ALF cases; the small sample size renders the extrapolation to the entire United States population unreliable. A total of 1,600 ALF cases per year in the United States translates to about 5 per million people. If as the authors conclude, 46% of these cases are related to acetaminophen, the ALF acetaminophen-related risk is 2.3 per million.

As with any study where participants are asked to report past exposures, recall bias may have affected reports of past drug exposures. The diagnoses of exclusion for assigned acetaminophen- associated ALF were based on a limited set of etiologies. The authors did not consider alcohol or biliary pathologies as rule-out diagnoses. This may lead to an over-estimation of acetaminophen-associated hepatotoxicity.

Analyses of Adverse Event Reporting and Acetaminophen-Related Hepatotoxicity

Analyses of adverse event reporting systems, namely the FDA Adverse Events Reporting System (AERS) and Toxic Exposure Surveillance System (TESS), have also been conducted to examine acetaminophen-related hepatotoxicity. AERS is a database of adverse event reports voluntarily sent from consumers and health care providers; when manufacturers learn of an adverse event associated with their product from a consumer or health care provider, they are required to report the event to AERS [16].

TESS is a surveillance database that includes exposures reported to select poison control centers throughout the country [17].

Analyses of AERS data showed that the crude count of all adverse events related to either OTC acetaminophen or opioid/acetaminophen combination products was 2,458 in 2005. This included both serious and non-serious events. That figure is higher than that for ibuprofen, ketoprofen, naproxen, and aspirin. The AERS data from 2002–2006 show that acetaminophen was the number one drug associated with hepatotoxicity. In an analysis of AERS data using the Multi-Item Gamma Poisson Shrinker algorithm, which generates scores that indicate the relative reporting rate of an adverse event for one drug relative to other drugs and events in the database, there were high association scores between acetaminophen and hepatic events [18].

Using AERS data to determine the association between an adverse event and a drug is problematic for numerous reasons [19]. First, it is impossible to use AERS alone to quantify a risk or rate because the total number of users is unknown. The data only reflect adverse event reporting rates, which are subject to numerous biases. Media coverage of a particular drug may increase reporting for that drug. Webber effects, where reporting rates peak during the early years of a product's introduction, can affect relative reporting rates of drugs. In addition, as reporting adverse events is voluntary, there may be differential reporting of pharmaceutical products and underreporting in general. Reports are generally not investigated; in the United States, they do not have to be medically confirmed, and the quality of the reports is widely variable. In addition, the crude counts presented are not adjusted for patient characteristics. As stated previously, concomitant medication and/or alcohol use and underlying disease may vary across users of analgesics and therefore confound the observed association. The analysis did not stratify the adverse events by degree of severity. Non-serious events may not be clinically meaningful, and it is unknown how many of these cases are non-serious. Obviously, analyses of AERS data should not be considered hypothesis-confirming.

A subsequent investigation of deaths reported among acetaminophen users detected by AERS data revealed inadequacies that can threaten the validity of measures obtained from this system. In a follow-up study, 100 cases were randomly chosen in 2005. Four were found to be duplicates. Of the remaining 96, 24 were excluded from subsequent analyses because further review of the reports revealed no mention of an acetaminophen containing medication; death was mostly likely due to a co-morbid condition or a co-suspect drug or substance. Review of the remaining 72 deaths indicated that an opioid/acetaminophen combination pain medication was associated with 43 deaths (59%). Of the 72 deaths, 4 (6%) were associated with unintentional overdose; 11 (15%) were associated with intentional misuse; 9 (13%) with unknown intent, and the remaining 67% with suicide.

The vast majority (82%) of the deaths associated with opioid/acetaminophen combination products were due to misuse (including suicide); overdose of unknown intent was indicated in an additional 13% of deaths. These deaths therefore do not implicate opioid/acetaminophen combination products when properly used. Many medications, including OTC ones such as aspirin, can be deadly when intentionally overdosed. These factors make it impossible to draw conclusions from the use of this database.

In another analysis of AERS data [19], 282 adult cases with liver injury possibly associated with acetaminophen exposure were identified. One hundred and twenty-two patients reported exposure to an opioid/acetaminophen combination medication. Among 70 patients who reported exposure to more than one acetaminophen containing medication, 50 (71%) reported taking an opioid/acetaminophen combination medication. This study suffers from the same limitations as those stated for the previously described AERS study: there is no denominator to enable estimation of a risk and there is no reference group with which to compare this risk. In addition, nearly half of the persons in this study were unable to specify the acetaminophen-containing medication they ingested, casting into doubt actual exposure to significant amounts of acetaminophen.

Analysis of the TESS database examined reported poison exposure cases and deaths among opioid/acetaminophen combination prescription medication users [18]. Cases of poison exposure were included when acetaminophen was mentioned as the primary exposure. Of the 41,999 cases in 2005, 1,470 (3%) resulted in a major effect, defined as life-threatening or one that resulted in a disability or disfigurement.

As is the case with the AERS data, there is no known denominator for these counts so it is not possible to present risks or rates based on these numbers. The information is limited because there are no data on a reference group. Without a comparison group, the incremental risk for a given outcome due to an exposure cannot be determined. However, the data come from poison control centers serving nearly 296 million people. Therefore, the estimated annual risk of a major adverse effect from a prescription acetaminophen combination medication is less than five per million.

Nourjah et al. [20] used five national databases to estimate acetaminophen-associated overdoses and AERS data to identify reasons for the overdoses. Data sources included: the National Hospital Ambulatory Care Survey (NHAMCS), an annual survey of ambulatory services and hospital emergency departments characterizing cause of injury; the National Electronic Injury Surveillance System (NEISS), an annual survey that collects information on consumer product-related injuries treated at emergency departments at 66 hospitals; the National Hospital Discharge Survey (NHDS), conducted annually by the Centers for Disease Control and Prevention to describe inpatients

discharged from non-federal hospitals in the United States; the National Multiple Cause of Death File; and lastly, the TESS.

According to NHAMCS data there were 56,000 emergency department visits annually for acetaminophen overdoses during 1993–1999; 56% cases involved intentional overdose. Data from NHDS indicated there was an average of 26,256 hospitalizations annually due to acetaminophen overdose during 1990–1999; 74% involved intentional overdose. There were 1,375 deaths between 1996 and 1998 where acetaminophen was either the primary or a contributing cause of death; in 73% of these deaths, suicide or intentional overdose was mentioned. The number of acetaminophen overdoses estimated from TESS data in 2001 was 112,809.

AERS data were searched to identify cases of hepatic injury in the United States, where an acetaminophen-containing medication was the suspected cause. Among the 478 cases of serious hepatotoxicity reported in AERS data, 198 (41%) were related to unintentional overdoses. Of the 103 cases that contained dosing information, 70% indicated the patient had exceeded the maximum recommended daily dose of 4 g. Of the 170 cases of unintentional overdose who had used acetaminophen for therapeutic reasons, and among the 89 patients for whom dose information was available, 44 (49%) reported alcohol use and 29 (33%) reported a history of liver disease. The mean total daily dose for these subgroups was 6.1 g and 6.3 g, respectively.

The estimates obtained in this study suffer from the same limitations stated for previously cited studies. The estimates for annual emergency department visits and hospitalizations from NHAMCS and NHDS are extrapolations of reported data. As the investigators emphasized, the case definition and identification of cases may have varied and it was not possible to confirm diagnoses of cases by a review of medical records. Estimates from TESS data in particular may be high, as these data are based on calls to poison control centers and are not confirmed by healthcare providers.

Estimates from AERS data are limited by various factors stated earlier, such as that the data reflect adverse reporting rates which are subject to numerous biases. Of note, among those who used acetaminophen for a therapeutic indication and reported dose information, nearly half reported alcohol use and nearly one third reported prior liver disease. These data again highlight that confounders such as alcohol use and concomitant disease may be responsible for many of the reported acetaminophen-related cases of ALF and deaths.

Summary of the Evidence

A review of the limited studies on opioid/acetaminophen combination products and hepatotoxicity reveals that there is no reliable information from which we can draw conclusions about the absolute or relative risk of these medications. The epidemiologic studies that have been cited and the analyses of AERS and TESS data were not denominator-based and, therefore, cannot be used to provide a valid estimate of risk.

Furthermore, as ALF is a rare event, the epidemiologic studies involved relatively small numbers of observations. This fact, coupled with how data were collected, did not allow investigators to adjust for potential confounders like concomitant medical conditions, age, and other medications that may have affected the observed association between ALF and acetaminophen exposure. In addition, the small number of observations does not allow investigators to explore how variations within opioid/acetaminophen combination exposure categories relate to the outcome. Currently, opioid/acetaminophen combination products vary in the dose of opioid and acetaminophen, which ranges from 300 mg to 750 mg acetaminophen per tablet with many doses in between (e.g., 325, 400, 500, 650, and 660 mg).

In order to know the incremental risk of ALF associated with use of opioid/acetaminophen combination products, an epidemiologic study needs to be conducted where there is a reference group. If a reference group of individuals not using opioid/acetaminophen combination products were included, and adjustment were made for identified confounders, the incremental risk of ALF due to opioid/acetaminophen medications could be evaluated. Hepatotoxicity among opioid/acetaminophen users and patients using other analgesics such as opioid/NSAID combination or opioids alone could be compared.

Consequences of Following Advisory Committee's Recommendation

Eliminating opioid/acetaminophen combination products will have a very significant impact on pain management. In one analysis of claims data for hydrocodone or short-acting oxycodone pain medications, one in six claimants received an opioid/acetaminophen combination medication at some time over an 8-year period [21]. The actual consequences on patient care of removing the most commonly prescribed pain medications for patients with moderate to moderately-severe pain are unknown. There are multiple potential adverse consequences that should be considered. Removing opioid/acetaminophen combination products from the market will have widespread effects on pain management, healthcare utilization, and the ability to meet the needs of patients in pain. These unintended consequences must be balanced against the risk of hepatotoxicity from opioid/acetaminophen combination products.

At the advisory committee meeting, Dr. Jane Filie presented an overview on pain management [22]. Currently, there are more than 50 million people in the United States who are disabled due to pain, and this number is expected to increase as the population ages. The undertreatment of pain continues to be a significant public health problem. For some patients, management of pain

begins with non-opioid analgesics for mild to moderate pain; an opioid/non-opioid combination medication might be used if pain intensity increases; more severe pain would require treatment with a pure opioid agonist. The removal of opioid/acetaminophen combination products could therefore jeopardize an important step in pain management for patients suffering from moderate to moderately-severe pain. Given the deleterious impact of pain of this intensity on patients' ability to work, sleep, and engage in normal activities of daily living, the unintended consequences of removing these products from the market need to be carefully evaluated.

Potential for Increased Adverse Events Due to Increase in NSAID Use

If opioid/acetaminophen combination prescription pain medications are removed from the market, patients who are well-managed with these medications will need to be treated with alternate therapies. The remaining opioid combination analgesics that are Schedule III would include opioid/NSAID combination prescription pain medications. For patients who are unable to tolerate NSAIDs this is particularly concerning, as acetaminophen products are an important alternative. A shift in treatment to opioid/NSAID combination prescription pain medications may also induce more frequent and devastating adverse events given the substantial evidence for complications resulting from NSAID use in general and the known adverse events that occur. It should be noted that these events commonly occur within the therapeutic range and in those who are felt to be able to tolerate NSAIDs or aspirin. Adverse events include gastrointestinal ulcers, bleeding, perforation [23] and acute renal failure [24].

Numerous studies have shown that hospitalizations and deaths due to NSAIDs used alone impose a large burden on the healthcare system. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) Post-Marketing Surveillance Program prospectively followed more than 11,000 arthritis patients identified through eight institutions in the United States and Canada. In a subset of patients, the annual rate of hospitalization for a gastrointestinal event was 1.5% for rheumatoid arthritis patients taking NSAIDs and 0.7% for osteoarthritis patients taking NSAIDs. After applying these rates to the estimated number of arthritis patients using NSAIDs and deaths resulting from gastrointestinal events requiring hospitalization, the authors estimated there were 30,000 NSAID-associated gastrointestinal hospitalizations per year resulting in 4,400 deaths among rheumatoid arthritis patients, and an estimated 56,000 NSAID-associated gastrointestinal hospitalizations per year resulting in 8,800 deaths among osteoarthritis patients [25]. The extrapolation of the risk of hospitalization and death in the cohort to the estimated number of arthritis patients using NSAIDs is a limitation, as the later number is not well defined. However, in comparison, there were an estimated 56,000 emergency department visits, 26,000 hospitalizations and possibly over 450 deaths in the US each year [20] related to acetaminophen use across all diseases. Using NSAIDs instead of acetaminophen would increase not decrease morbidity and mortality. One study estimated that if 10% of acetaminophen users shifted to NSAIDs there would be 35 less acetaminophen poisoning associated deaths but an additional 166 deaths from gastrointestinal bleeds and 144 from acute renal failure [26].

Impact of Switch to Treatment with Single Entity Opioids

While oxycodone/acetaminophen combination drugs are in Schedule II, the other opioid/acetaminophen combination products are in Schedule III (hydrocodone and codeine), Schedule IV (propoxyphene) or not scheduled (tramadol). Prescription orders for Schedule III and IV drugs can be called in, and a maximum of five refills is allowed within 6 months from the date of issue. In contrast, a physician must write a prescription for Schedule II drugs except in emergencies, and no refills are allowed. Therefore, if patients are prescribed opioids in Schedule II, rather than the Schedule III or IV or unscheduled opioid/acetaminophen combination drugs, prescribers may be more burdened. A decrease in Schedule III medications may make it difficult for providers to issue prescriptions and thus impact access to medication. Patients may be burdened as well because insurance providers may only pay for a 30-day supply of the medication. This would result in more frequent clinic visits. Given the cost of an outpatient visit from the Centers for Medicare and Medicaid Services, this could result in more than $700 per patient per year just to prescribe this type of medication.

While there is concern that patients taking opioid/acetaminophen combination pain medications could develop addiction and tolerance, and thus escalate their intake and put themselves at risk of acetaminophen toxicity, there is also concern that there may be an increase in harmful use of single entity opioids if patients are switched to these drugs. There are limited published data to assess harmful use of opioid/acetaminophen in the treatment of chronic pain [9]. In one study, patients with chronic non-cancer pain taking NSAIDs, tramadol or hydrocodone were interviewed up to nine times over a 12-month period and assessed for abuse/dependence. For NSAIDs, tramadol and hydrocodone, the percent of patients who had a positive abuse score at least once during follow-up was 2.5%, 2.7%, and 4.9%, respectively; the percent of patients who had a positive abuse score more than once, indicating persistence of abuse, was 0.5%, 0.7%, and 1.2%, respectively [27]. However, while abuse scores may be higher among patients taking hydrocodone it must be remembered that NSAIDs and tramadol, which has weak opioid activity, may provide inadequate analgesia for more severe pain and be insufficient for pain relief.

Several studies have estimated prevalence or incidence of harmful use of single entity opioids [28–31]. The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System combines data on cases of drug abuse from four signal detection systems with data from other sources on the number of unique recipients of

a dispensed drug in a given geographic area to approximate national rates of abuse for various opioid analgesics [31]. This study is limited by the fact that the rate estimates are based on combining data from various sources and that not all people who are dispensed a drug (in the denominator of the rate calculation) would be detected by the surveillance system (and thus counted in the numerator of the rate calculation), and that some persons who abuse a drug and are detected by the surveillance system (and thus counted in the numerator) may not be prescribed the drug (and therefore not counted in the denominator). Nonetheless, the rates of prescription opioid abuse of hydrocodone medications (always combinations with acetaminophen or aspirin or ibuprofen) were among the lowest compared with those for eight other prescription opioids. The other eight prescription opioids included tramadol, and opioids which are sometimes or always administered as single entity products (the seven included short-acting oxycodone, extended release oxycodone, fentanyl, morphine, methadone, hydromorphone, and buprenorphine). The abuse rate of the hydrocodone products group was lower compared to the rates of each of these seven other opioids. The hydrocodone products group was comprised of opioid combination product users only; the other seven opioids included either single opioid product users or both single and opioid combination product users. This suggests that opioid combination medications may have a lower abuse potential than single entity opioids. In analyses of all four signal detection systems, hydrocodone had the lowest or second lowest rate of abuse after tramadol.

Rather than having single entity opioids as the only treatment option, limiting and not removing acetaminophen from opioid/acetaminophen products has been suggested as one approach to reduce hepatotoxicity associated with these medications. As no efficacy data were submitted during the approval process for nearly all opioid/acetaminophen combination products there are little data on the efficacy of opioid/acetaminophen combination products vs opioids alone. However, there is biologic plausibility that the combination of medications is advantageous. The combination may present additive and synergistic analgesic effects while decreasing adverse events, as individual components can be administered at lower doses [9]. Therefore, reducing rather than eliminating acetaminophen from these products may be advantageous. Currently, opioid/acetaminophen combination products contain amounts of acetaminophen ranging from 300 mg up to 750 mg. Results from some studies show that the number needed to treat for at least 50% pain relief for treatment with 15 mg oxycodone vs 5 mg oxycodone/325 mg acetaminophen vs 10 mg oxycodone/650 mg acetaminophen was similar which suggests that the dose of oxycodone may be lowered if acetaminophen is given [32]. Moderate acetaminophen doses in combination with oxycodone may be as effective or more effective than high doses of acetaminophen. Hepatotoxicity risk that may be associated with opioid/acetaminophen combination products could potentially be reduced by eliminating products that contain higher amounts of acetaminophen while retaining products with moderate acetaminophen doses. Limiting the variability of the acetaminophen dose could also reduce hepatotoxicity. Variability in the acetaminophen dose of prescription pain medications may contribute to confusion for both providers and patients about the actual amount of acetaminophen in a product, and thus lead to unintentional overdose.

Increased Pill Burden for Patients

Removing opioid/acetaminophen combination products from the market and requiring patients to take separate opioid and acetaminophen medications will mandate that providers educate their patients on new dosing schedules. Taking multiple pills may increase misuse, decrease patient adherence to medical management plans, and present an undue burden on patients experiencing pain who may already have a high pill burden. Decreased adherence may lead to worsening pain control and a subsequent negative impact on quality of life and productivity

Limited Alternatives Available to Patients

Hydrocodone/acetaminophen is the most commonly prescribed medication [8]; there is no single entity hydrocodone product on the market. If opioid/acetaminophen combination prescription pain medications were eliminated, patients using hydrocodone/acetaminophen may need to take one of the single entity opioids. Tramadol is one commonly prescribed single entity opioid, but it is classified as a weak opioid [33] and therefore may be insufficient to meet the needs of all patients in pain. An analysis of prescriptions in 2007 for hydrocodone and oxycodone products showed that the total number of prescriptions for oxycodone products was approximately 40 million, considerably less than the nearly 120 million prescriptions dispensed for hydrocodone products [22]. It is questionable whether manufacturers would be able to respond to the needs of patients given the low production of alternate medications relative to current hydrocodone utilization. It could take a substantial amount of time for production of the medications to be adjusted to meet the needs of the market if other medications were not available. This could result in patients lacking adequate treatment until production ability catches up with patient needs.

Alternate Interventions

In lieu of removing opioid/acetaminophen combination prescription pain medications, there are several measures the FDA could recommend to increase the safe use of acetaminophen and lower risk of hepatotoxicity without jeopardizing patient access to appropriate pain treatments. Eliminating patient access to this large segment of pain medications will affect pain control for a large number of the more than 100 million Americans who suffer acute or chronic pain each year. Previous working groups have described various initiatives that the FDA could embrace to address this issue. In 2008, a working group voted against elimination of opioid/acetaminophen combination products, citing the potential risks mentioned earlier that

may be associated with removal of these medications [34]. As stated in the report from that meeting, the potential for improper acetaminophen use to cause hepatotoxicity should not be a reason to discourage its proper use. Among the recommended interventions the working groups did support were enhancing education, improving labeling, and limiting dose strength. In addition, limiting the variability of the dose of acetaminophen in opioid/acetaminophen combination products could minimize patient/clinician confusion, and reduce the risk of inadvertent overdose.

Many consumers are unaware that overuse of acetaminophen can result in hepatotoxicity, and are also unaware of the numerous OTC and prescription medications that contain acetaminophen, so a logical intervention would be for the FDA to increase its efforts to educate both consumers and healthcare providers. To reach healthcare providers, free on-line continuing education initiatives could be provided and reinforced through content in peer-reviewed journals and professional society websites/publications. Articles on acetaminophen-associated hepatotoxicity could be published in the FDA *Consumer* and the consumer webpage. The FDA could also support studies on consumer awareness of acetaminophen and liver toxicity [34].

Enhanced product labeling could also reduce the risk of acetaminophen-associated hepatotoxicity. The ingredient acetaminophen could be bolded to alert the consumer, and prominent "shelf-talkers" could be affixed to the OTC sections of the pharmacy. A parallel approach would be to develop a universal symbol to designate the presence of acetaminophen in a product. Just like the universal poison symbol warns of the presence of a dangerous toxic substance, a new symbol on the packages of acetaminophen-containing medications could accomplish the same effect. A warning about severe liver injury associated with overuse could appear on the packaging along with warnings about taking any alcohol with the product. A boxed warning could indicate that overuse of these drugs, as a class, cause hepatotoxicity.

The acetaminophen dose in opioid/acetaminophen combination products could be narrowed or made more uniform; this could have the dual effect of reducing the risk of hepatotoxicity caused by unintentional overdose, and would also simplify the clinician's task of educating patients about maximal dosages. Currently, combination medications may contain as much as 750 mg or as little as 300 mg of acetaminophen per dose. Medications on the market could include only those containing 500 mg acetaminophen or less; there would still be an analgesic effect from the acetaminophen, but the likelihood of acetaminophen-associated hepatotoxicity would be less if they were used improperly.

Conclusions

If the FDA follows the advisory committee's recent vote to eliminate opioid/acetaminophen combination products from the market there will be many repercussions and it is unclear whether the objective of decreasing ALF will be met. While acetaminophen can cause hepatotoxicity when used improperly, the evidence that opioid/acetaminophen combination products present a substantial risk to the public is not compelling enough to warrant their removal from the market. No denominator-based studies utilizing appropriate statistical techniques such as adjusting for confounding factors exist to inform a decision about the true risk of opioid/acetaminophen combination products in contributing to serious hepatotoxicity. Furthermore the many patients who are well-managed with opioid/acetaminophen prescription pain medications would have to be shifted to medications with greater toxicity and/or limited availability. In light of these reasons, the FDA should act very cautiously before eliminating these products.

There are numerous approaches the FDA working in collaboration with pharmaceutical companies, professional organizations and advocacy groups could implement to address opioid/acetaminophen combination products and hepatotoxicity. Enhancing patient education so consumers are aware of the acetaminophen content in all products that contain acetaminophen is one approach. Improved labeling on OTC and prescription packaging should prominently indicate the presence of acetaminophen in a product and the risk of hepatotoxicity when taken in excess. Medication guides and better practitioner training for communicating risk could also be implemented. Reducing the amount of acetaminophen and the variability in the amount in opioid/acetaminophen combination products is another potential intervention. These alternate approaches should be seriously considered instead of eliminating opioid/acetaminophen combination products which have been of great benefit to pain patients.

Disclosure Information

EM has no financial disclosure to declare. MSD and CK are employees of Analysis Group, Inc., which has received research funding from Endo Pharmaceuticals Inc., Chadds Ford, PA, for this work. JD has received honorarium from Analysis Group, Inc.

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EXHIBIT C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202880

NDA APPROVAL

Zogenix, Inc.
5858 Horton Street
Suite 455
Emeryville, CA 94608

Attention: Edward F. Smith III, PhD, MBA, RAC
Vice President, Regulatory Affairs and Product Quality/Safety

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) dated April 30, 2012, received May 1, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zohydro ER (hydrocodone bitartrate) extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg.

We acknowledge receipt of your amendments dated June 1, 8, and 14, July 5 and 27, August 6, 24, and 31, October 4, November 13, 14, 21, and 30 (2), and December 28, 2012, and January 11 (2), 18 and 25, February 27, May 30, July 30 and 31, and September 20 and 23, 2013.

This new drug application provides for the use of Zohydro ER (hydrocodone bitartrate) extended-release capsules for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert and the

Medication Guide. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed immediate-container labels that are identical to the enclosed immediate-container labels and the immediate-container labels submitted on February 27, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202880**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for ages birth to less than 7 years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients with chronic pain in this age group is extremely small.

We are deferring submission of your pediatric studies for ages 7 to less than 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

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

Final Protocol Submission:	September 30, 2014
Study Completion:	March 31, 2019
Final Report Submission:	September 30, 2019

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

Final Protocol Submission:	September 30, 2017
Study Completion:	September 30, 2021
Final Report Submission:	March 31, 2022

Submit the protocol(s) to your IND 065111, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

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

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

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

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

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events:

misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

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

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

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

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

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

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

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies and clinical trial to provide the best information possible.

Submit the protocols to your IND 065111, with a cross-reference letter to this NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Additionally under the authorities of Section 505(o)(3) of the FDCA, 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 serious risk of genotoxicity and carcinogenicity potentially associated with hydrocodone.

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

2066-3 Conduct an in vivo comet assay in liver to evaluate the potential genetic toxicology of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress
Study Completion: October 31, 2013
Final Report Submission: November 30, 2013

2066-4 Conduct a 2-year bioassay in the rat model to evaluate the carcinogenic potential of hydrocodone.

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

2066-5 Conduct a 2-year bioassay in the mouse model to evaluate the carcinogenic potential of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress
Study Completion: January 24, 2014
Final Report Submission: June 30, 2015

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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, we have determined that a REMS is necessary for Zohydro 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.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Zohydro ER poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zohydro ER. FDA has determined that Zohydro ER is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Zohydro ER. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Zohydro ER.

Pursuant to 505-1(f)(1), we have also determined that Zohydro ER can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse that are listed in the labeling. The elements to assure safe use will inform and train healthcare providers about the potential risks and the safe use of Zohydro ER.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval

of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on July 30, 2013, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

This REMS will use a single shared system for the elements to assure safe use and implementation system in the approved REMS. This single shared system, known as the extended-release/long-acting (ER/LA) opioid analgesics REMS, currently includes the products listed in Appendix 1. Other products may be added in the future if additional NDAs or ANDAs are approved.

Your REMS must be fully operational before you introduce Zohydro ER into interstate commerce.

Because Zohydro ER will be a member of the extended-release/long-acting (ER/LA) opioid analgesics REMS, the assessment plan will be the same assessment plan required for the other products covered by this single shared system. Because the 6-month and 12-month assessments have been submitted, the assessment reports for Zohydro will align with the third assessment of the ER/LA opioid analgesic REMS assessment plan. Therefore, your REMS assessment plan should include, but is not limited to, the REMS assessments that follow.

Scheduled REMS Assessments

1. The third ER/LA opioid analgesic REMS assessment, due July 9, 2014, which is two years from the approval date of the ER/LA opioid analgesic REMS, should include the following information:

    a. Prescriber Letter 3: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

    b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals, based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:

        i. Within two years from the time the first REMS-compliant training became available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained;
        ii. Within three years from the time the first REMS-compliant training became available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;

iii. Within four years from the time the first REMS- compliant training became available, 192,000 prescribers (based on 60% of active prescribers) are to have been trained.

c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS–compliant training for purposes of meeting the milestones in 3a., and must evaluate:

i. whether the content of the training covers all elements of the FDA "blueprint" approved as part of the REMS;
ii. whether the post-course knowledge assessment measures knowledge of all sections of the FDA "blueprint"; and
iii. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies.

d. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients.

e. Surveillance Results: Results of surveillance for misuse, abuse, overdose, addiction, and death. Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible.

f. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioids, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills;

g. Patient Access: An evaluation of changes in patients access to ER/LA Opioids.

h. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.

i. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

2. The fourth and subsequent REMS assessments, due July 9, 2015, and annually thereafter, should include the following information:

    a. Prescriber Letter 3: 1) number of prescriber letters electronically sent, received, undeliverable, and opened, and 2) number of prescriber letters mailed and undeliverable.

    b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training (see 1.b above).

    c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training (see 1.c above).

    d. Evaluation of Prescriber Understanding:
        i. The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.
        ii. The results of any long-term evaluation of prescribers of ER/LA opioids who have taken ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.

    e. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. (See 1.d above).

    f. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death (see 1.e above).

    g. Drug Utilization Patterns: An evaluation of drug utilization patterns (see 1.f above).

    h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.

    i. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.

    j. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Definitions: For purposes of these REMS assessments, the following definitions apply:

1. *REMS-compliant training*: Training will be considered "REMS-compliant training" if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA "blueprint", 3) it includes a post-course knowledge assessment of all of the sections of the "FDA blueprint", and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.

2. *FDA Blueprint*: A document entitled, "Blueprint for Prescriber Continuing Education Programs Extended-Release and Long-Acting Opioids," approved as part of this REMS, that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids.

Other REMS Assessment Requirements

Under section 505-1(g)(2)(C), FDA may require the submission of a REMS assessment if FDA determines that that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or minimize the burden on the health care delivery system of complying with the strategy.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 202880 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 202880 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 202880
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 202880
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

EXPIRY DATING PERIOD

A 24-month expiry dating period is granted for Zohydro ER, all dosage strengths in 100 count HPDE bottles, when stored at (b) (4) 25°C ((b) (4) 77°F) with excursions permitted from 15° to 30°C (59° to 86°F).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Appendix 1: List of applications having the ER/LA opioid analgesics REMS
Content of Labeling
Carton and Container Labeling
REMS

Appendix 1: List of applications having the ER/LA opioid analgesics REMS

NDA 021260	AVINZA (morphine sulfate) extended-release capsules
NDA 021306	BUTRANS (buprenorphine) Transdermal System for transdermal administration
NDA 006134	DOLOPHINE (methadone hydrochloride) tablets and its generic equivalents
ANDA 087997	Methadone Oral Solution and its generic equivalents
ANDA 087393	Methadone Oral Solution and its generic equivalents
ANDA 089897	Methadone Oral Concentrate
NDA 019813	DURAGESIC (Fentanyl Transdermal System) for transdermal administration and its generic equivalents
NDA 022321	EMBEDA (morphine sulfate and naltrexone hydrochloride) extended-release capsules
NDA 021217	EXALGO (hydromorphone HCl) extended-release tablets
NDA 020616	KADIAN (morphine sulfate) extended-release capsules and its generic equivalent
NDA 019516	MS CONTIN (morphine sulfate) controlled-release tablets and its generic equivalents
NDA 200533	NUCYNTA ER (tapentadol) extended-release oral tablets
NDA 201655	OPANA ER (oxymorphone hydrochloride) extended-release tablets
NDA 021610	OPANA ER (oxymorphone hydrochloride) extended-release tablets and its generic equivalents
NDA 020553	OXYCONTIN (oxycodone hydrochloride controlled-release) tablets
NDA 202880	ZOHYDRO ER (hydrocodone bitartrate) extended-release capsules

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

/s/

BOB A RAPPAPORT
10/25/2013

EXHIBIT B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202880Orig1s000

SUMMARY REVIEW

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

Summary Review for Regulatory Action

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

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Ellen Fields, M.D., M.P.H.
Clinical Review	Robert A. Levin, M.D.
Biostatistics Review	Katherine Meaker, M.S.; Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
ONDQA-CMC/Quality Review	Yong Hu, Ph.D.; Prasad Peri, Ph.D.
Biopharmaceutics Review	Minerva Hughes, Ph.D.; John Duan, Ph.D.
Clinical Pharmacology Review	David J. Lee, Ph.D.; Yun Xu, Ph.D.
OSI	Cynthia Kleppinger, M.D.; Janice K. Pohlman, M.D., M.P.H.; Susan Thompson, M.D.
Project Management	Dominic Chiapperino, Ph.D.; Parinda Jani
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS; Lubna Merchant, Pharm.D., M.S.; Carol Holquist, R.Ph.
OSE/DRISK	Danielle Smith, Pharm.D., M.S.; Reema Mehta, Pharm.D., M.P.H.; Claudia Manzo, Pharm.D.
OSE/OPE/DEPI-II	Alex Secora, M.P.H.; Cynthia Kornegay, Ph.D.; Judy Staffa, Ph.D., R.Ph.
OMP/OMPI/DMPP	Sharon Mills, BSN, RN; Barbara Fuller, RN, MSN; LaShawn Griffiths, MSHS-PH, BSN;
OMP/OPDP	L. Shenee' Toombs, Pharm.D.; Eunice Chung-Davies, Pharm.D.
Controlled Substances Staff	Lori Love, M.D.; James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Michael Klein, Ph.D.
CDRH	James Kane, Ph.D.

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

1. Introduction

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

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

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

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

2. Background

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

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

3. CMC

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

Drug Substance

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

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

Drug Product

As stated in Dr. Hu's review:

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

Other CMC information

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

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

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

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

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

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

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

4. Nonclinical Pharmacology/Toxicology

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

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

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

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

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

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

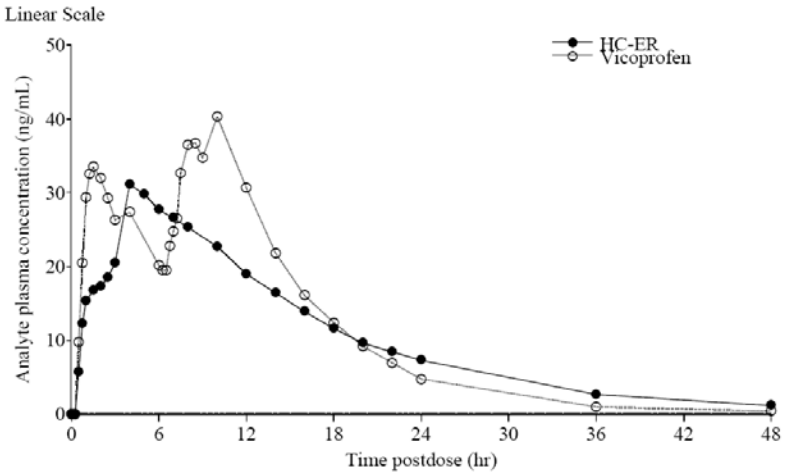
I concur with the review team that there are no outstanding nonclinical pharmacology or toxicology concerns that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

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

> Clinical Pharmacology
> The clinical pharmacology information in this NDA submission included six Phase 1 studies and two Phase 2 studies. Additionally, the Applicant conducted a population pharmacokinetic (PK) analysis using the information observed from conducted studies to support the hydrocodone dose linearity purpose. The following is a summary of Dr. Lee's review.
>
> *Relative Bioavailability (Study ZX002-1102)*
> This was a Phase 1, open-label, randomized, two-dose, two-period cross-over study with minimum 5-day washout between treatments. The study was conducted in 15 healthy subjects between 18 and 45 years of age who received a single dose of 30 mg Zohydro ER and two consecutive doses of 2-tablets of Vicoprofen 6 hours apart for a total of 4 tablets. Subjects were fasted appropriately for both treatment groups. All doses were administered with 240 mL of ambient temperature water.
>
> Mean hydrocodone Cmax values were 32 ± 7 and 46 ± 7 ng/mL for Zohydro ER and Vicoprofen treatments, respectively. Mean hydrocodone Cmax were not similar between the two treatments as indicated by the bioequivalence evaluation. Although Zohydro ER has both IR and ER characteristics, it is not surprising that it was not bioequivalent for Cmax when compared to a product with only IR characteristics.
>
> Mean hydrocodone AUC values were 513 ± 92 and 559 ± 122 ng.h/mL for Zohydro ER and Vicoprofen treatments, respectively. The bioequivalence analysis indicated that the AUC values from the two treatments were equivalent.
>
> The following figure taken from page 59 of Dr. Lee's review is a graphic representation of the relative BA results:

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

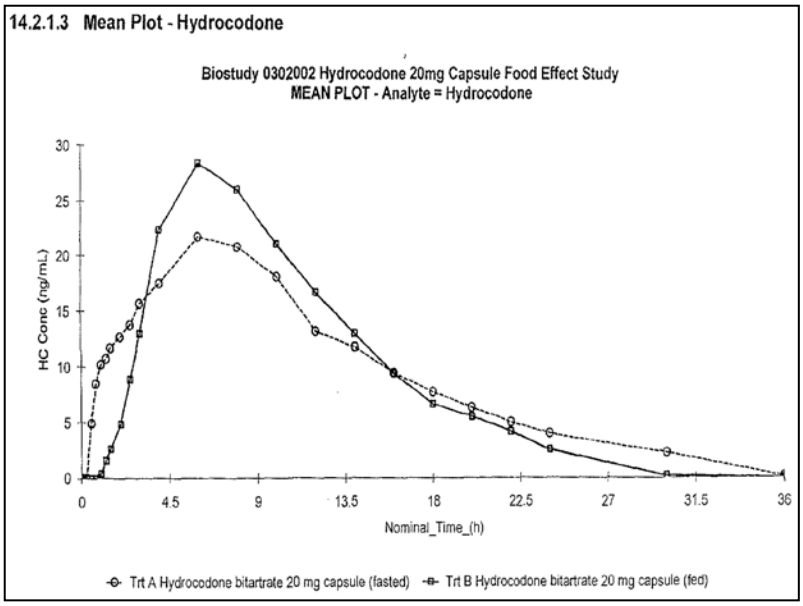


Source: Section 14, Figure 14.2.1-1a

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

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

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



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

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

Alcohol interaction

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION/RECOMMENDATION:

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

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

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

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

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

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

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

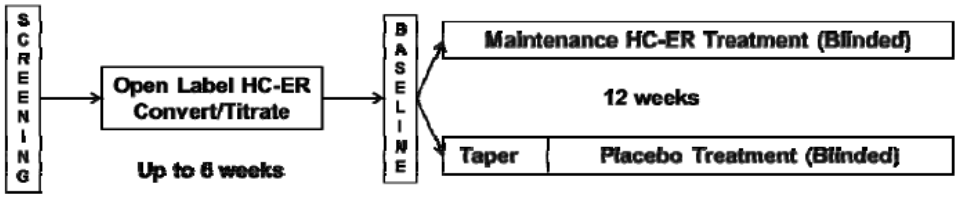
7. Clinical/Statistical-Efficacy

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

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

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

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



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

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

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

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

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

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

Study 801 Results

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

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

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

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

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

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

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

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

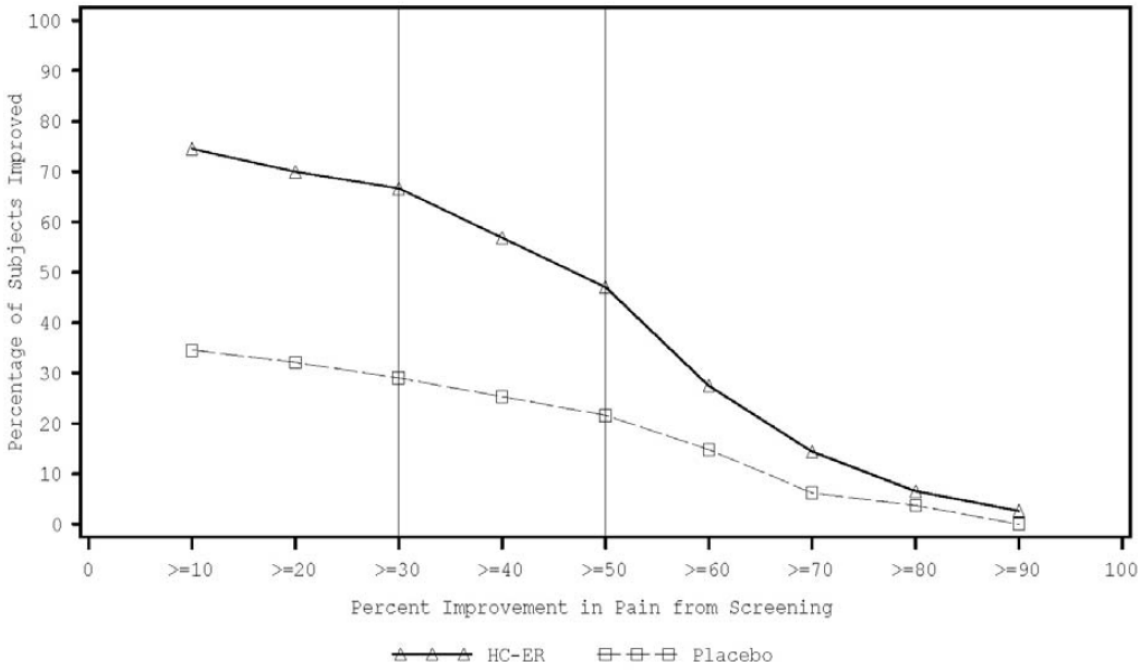
Change from Baseline	HC-ER (N=151)	Placebo (N=151)
Mean (SD)	0.48 (1.563)	0.96 (1.550)
Range	-3.0 – 5.3	-2.4 – 6.7
LS Mean	0.48	0.95
p-value[a]	*0.008*	

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

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

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

Percentage Improvement in Average Pain from Screening to Final Visit



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

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

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

8. Safety

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Special Safety Issue-audiology assessments

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

Misuse, Abuse, and Diversion

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

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

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

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

9. Advisory Committee Meeting

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

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

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

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

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

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

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

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

   Vote: Yes= 7 No = 6 Abstain = 1

   Discussion

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

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

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

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

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

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

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

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

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

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

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

I concur with Dr. Fields' conclusions.

10. Pediatrics

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

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

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

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

Pediatric Subjects Ages 12 to <17

- Protocol submitted for review 12 months from NDA approval
- Study start – 24 months from NDA approval
- Study stop – 66 months from NDA approval
- Final report submitted – 72 months from NDA approval

Pediatric Subjects Ages 7 to <12

- Protocol submitted for review – 48 months from NDA approval
- Study start – 60 months from NDA approval
- Study stop – 96 months from NDA approval
- Final report submitted – 102 months from NDA approval

11. Other Relevant Regulatory Issues

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

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

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

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

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

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

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

12. Labeling

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

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

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

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

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

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

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

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

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

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

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

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

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

- Postmarketing Risk Management Activities

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

- Postmarketing Study Requirements

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The following are postmarketing requirements for pediatric studies under PREA:

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

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

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

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

Non-Clinical PMRs

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

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

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

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

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

Final Protocol Submission: Protocol acceptable, study in progress

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

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

/s/

BOB A RAPPAPORT
10/25/2013

EXHIBIT A

DEVAL L. PATRICK
GOVERNOR

JOHN W. POLANOWICZ
SECRETARY

CHERYL BARTLETT, RN
COMMISSIONER

The Commonwealth of Massachusetts

Executive Office of Health and Human Services
Department of Public Health
Bureau of Health Care Safety and Quality
99 Chauncy Street, 11th Floor, Boston, MA 02111
617-753-8000

Circular Letter: DHCQ 14-3-610

TO: Massachusetts Controlled Substance Registrants

FROM: Deborah Allwes, BS, BSN, RN, MPH, Director of Prescription Monitoring and Drug Control

DATE: March 31, 2014

RE: Prohibition of prescribing and dispensing of any hydrocodone bitartrate product in hydrocodone-only extended-release formulation

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Introduction

The Governor of the Commonwealth has determined that an emergency exists which is detrimental to the public health with respect to the number of opiate-related overdoses and amount of opiate addiction in the Commonwealth.

The Department notes that the U.S. Food and Drug Administration (FDA) has recently approved a new medication which consists entirely of hydrocodone in higher levels than any currently available hydrocodone combination product. This hydrocodone-only extended release product is not in an abuse-deterrent formulation.[1] The Department is concerned about the high likelihood of misuse, diversion and abuse of the medication, further adding to the opiate abuse epidemic and increasing the likelihood of additional opiate-related overdoses.

In response to the Governor's Declaration, and with the approval of the Public Health Council on March 27, 2014, Cheryl Bartlett, the Commissioner of Public Health, issued the following emergency order:

> No registered individual practitioner shall prescribe or order, and no one shall dispense or administer any hydrocodone bitartrate product in hydrocodone-only extended-release formulation until the Commissioner has determined that adequate measures are in place to safeguard against the potential for diversion, overdose and abuse.

[1] "Abuse-deterrent formulation" means an FDA-approved formulation of a controlled substance that targets known or expected routes of abuse for that formulation.

This order will protect against overdose and abuse of hydrocodone-only extended-release formulation until such time as there are adequate safety measures in place. The Department will notify all registrants when this prohibition is lifted.

Question: What providers are covered under this order?
Answer: All registered individual providers and all practitioners with a Massachusetts Controlled Substance Registration (MCSR), as defined in 105 CMR 700.001 *et seq*.

Question: I am a provider in Massachusetts providing care to a patient who resides in another state. Can I write a prescription for hydrocodone-only extended release to be filled in another state?
Answer: No. The order states that no provider registered in Massachusetts shall prescribe any hydrocodone bitartrate product in hydrocodone-only extended-release formulation in Massachusetts.

Question: I am a physician in a hospital or extended care facility. Can I order hydrocodone-only extended release for an admitted patient under my care?
Answer: No. The order states that no registered individual practitioner shall prescribe or order, and no one shall dispense or administer any hydrocodone bitartrate product in hydrocodone-only extended-release formulation.

Question: Can a pharmacy in Massachusetts fill a prescription for hydrocodone-only extended release that is from a neighboring state?
Answer: No. Hydrocodone-only extended release products may not be dispensed in Massachusetts.

Question: May I continue to prescribe and dispense other opiate medications?
Answer: Yes. This emergency order only applies to the new hydrocodone-only extended release product. It does not affect your ability to prescribe and dispense other opiate medications.

If you have any questions about this letter, please contact:

Prescription Monitoring and Drug Control Program
Bureau of Health Care Safety and Quality
Massachusetts Department of Public Health
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