



Recent FDA Activities in Safe Use of Opioids

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February 4, 2014

NIH



Recent FDA Activities in Safe Use of Opioids

- ER-LA opioid relabeling and PMRs
- Zohydro approval
- Hydrocodone Combination
Product Upscheduling
- Abuse-deterrent Opioid Products



ER-LA Opioid Re-labeling and Post- marketing Study Requirement (PMR)

Background

- Need for prescribers to understand risks of extended release long-acting (ER-LA) opioids
- Need to clearly describe the patient who could benefit from these drugs
- Considerable public comment on how best to label ER-LA opioids
 - Citizen’s Petitions to change indications
 - Comments from Part 15 hearing held in 2012 on issue
- FDA concluded labeling revisions needed

Labeling Language

Old Language

- Xxx is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time

New Language

- Xxx is indicated 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

Additional Label Changes

- **Boxed Warning:** increased emphasis on risks, including abuse, overdose, death, and Neonatal Opioid Withdrawal Syndrome
- Urges prescribers to “assess each patient’s risk” for abuse before prescribing and to “monitor all patients regularly for the development of abuse”

Goals of Labeling Changes

- Move away from an indication based on a subjective severity scale
- Move towards individual assessment of the impact of the patient's pain, to determine both whether or not it is severe enough to warrant ER-LA opioids and whether alternatives would be inadequate
- Highlight risks of ER-LA opioids

Next Steps

- Companies have to submit responses to letters with labeling changes
- FDA working to change Medication Guide, Blueprint, Patient Medication Information to reflect new language

Post-Marketing Requirements

- FDA also concluded additional data were needed
- Studies and trials to be conducted by manufacturers of the ER-LA opioids to better assess:
 - the known risks of abuse, abuse, hyperalgesia, overdose and death when ER-LA opioids are used long-term
 - the relationship between opioid dose and duration and these risks
- Part of overall risk-benefit profile for ER-LA opioids

Studies of Long-term Efficacy and Safety of Opioids in CNCP

- FDA meeting regularly with industry working group to define study designs
- Studies are designated 2065-1 through 5

Studies of Long-term Efficacy and Safety of Opioids in CNCP

- 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:
 - 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.

Studies of Long-term Efficacy and Safety of Opioids in CNCP

- 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

Studies of Long-term Efficacy and Safety of Opioids in CNCP

- 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

Studies of Long-term Efficacy and Safety of Opioids in CNCP

- 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

Studies of Long-term Efficacy and Safety of Opioids in CNCP

- 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

Studies of Long-term Efficacy and Safety of Opioids in CNCP

- 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.**



Approval of Single-Entity Hydrocodone Product (Zohydro)

Zohydro Approval

- Zohydro meets statutory requirements for approval
 - Similar doses and anticipated uses as several other ER-LA opioids (e.g., oxymorphone, oxycodone, hydromorphone)
 - FDA will monitor use after marketing
- Part of larger FDA efforts to improve the use of opioids
 - No abuse-deterrent formulation available: sponsor working to develop it
 - Allows users of high doses of hydrocodone to avoid use of acetaminophen and liver toxicity
- Required to have the new augmented labeling to support safe use
 - Increased safety information
 - New indication
 - Sponsor is required to participate in PMR studies



Hydrocodone Upscheduling

Background

- Opioid misuse and abuse ongoing US issue
- Hydrocodone is marketed only as combination products for pain and for cough-suppression
 - Ongoing abuse and misuse
 - Over 8 billion tablets dispensed last year!
- What is the appropriate level of control ('Schedule') for these products?
- Scheduling: FDA conducts scientific analysis and makes recommendation (through OASH) to DEA

Hydrocodone Rescheduling Recommendation

- On December 11, 2013 FDA sent to HHS the recommendation to reschedule hydrocodone combination products from C-III to C-II. This recommendation was concurred with separately by NIDA.
- On December 17th, 2013 HHS (through the OASH, Dr. Koh) sent DEA the recommendation to reschedule hydrocodone combination products from C-III to C-II.
- Currently DEA is working on their analysis to determine whether or not to issue a Notice of Proposed Rulemaking (proposing upscheduling or whatever they conclude). We don't have any insight into that process or timeline for its completion.



Abuse-deterrent Opioids

Abuse-deterrent Opioids

- FDA continues to support and encourage development of abuse-deterrent opioids
- Guidance regarding requirements for generic opioid products remains under discussion
- Careful consideration of the impact of new abuse-deterrent formulations on already approved products is essential
 - How to determine comparative abuse-deterrence and safety
 - How to appropriately label
 - How to continue to provide incentives to development



Thank You

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