Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
October 21 -22 2010

Hilton Washington DC North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland

Summary Minutes

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the October 21-22 2010 Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of **the Food and Drug Administration were approved on __November 1, 2010.**

I certify that I attended the October 21-22 meeting of the Anesthetic and Life Support Drugs Advisory Committee Meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Kalyani Bhatt
Designated Federal Official, ALSDAC

_____/s/_____
Jeffrey R. Kirsch, M.D.
Chair

Quick Minutes
Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
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A verbatim transcript will be available in approximately four to six weeks, sent to the Division and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/ucm193298.htm
All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA and sponsors. The meeting was called to order by Jeffrey R. Kirsch, M.D. (Chair, ALSDAC); the conflict of interest statement was read into the record by Kalyani Bhatt (Designated Federal Official). There were approximately 100 persons in attendance. There were 12 speakers for the Open Public Hearing session.

Issue: The committees discussed considerations for the design of postmarketing studies for new drug application (NDA) 22-272 , OxyContin (oxycodone hydrochloride controlled-release) Tablets, Purdue Pharma, Inc. and NDA 22-321 Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsules, Alpharma Pharmaceuticals, LLC and King Pharmaceuticals Research & Development, Inc., approved for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The postmarketing studies are intended to be epidemiological or observational studies that will assess the known serious risks of these products and whether product-specific properties which are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences: addiction, overdose, and death

Attendance:

Anesthetic and Life Support Drugs Advisory Committee Members Present (Voting):
Randall Flick, M.D., M.P.H., Jeffrey R. Kirsch, M.D. (Chair), Osemwota A. Omoigui, M.D.
(Consumer Representative), Daniel Zelterman, Ph.D.

Drug Safety and Risk Management Advisory Committee Members Present (Voting):
Elaine H. Morrato, Dr. P.H., Lewis Nelson, M.D., Sidney Wolfe, M.D. (Consumer Representative)

Non-Voting Participant
Mark P. Fletcher, M.D., FAAAAI, (Acting Industry Representative, Anesthetic and Life Support Drugs Advisory Committee)

Special Government Employee Consultants Present (Temporary Voting Members):
Warren Bickel, Ph.D., M.D., Warren B. Bilker, Ph.D., Susan Krivacic (Patient Representative), John Mendelson, M.D., Edward Michna, M.D., Sharon Walsh, Ph.D.

Regular Government Employee Consultants Presenting (Voting):
Richard Denisco, M.D., Robert Kerns, Ph.D. Cynthia Morris-Kukoski, Pharm.D.

Speakers (Non-voting, Presenting Only)
Leonard Paulozzi, M.D., M.P.H., Albert Woodward, Ph.D., M.B.A.

Guest Speaker (Non-Voting, Presenting Only)
James Anthony, Ph.D.

Anesthetic and Life Support Drugs Advisory Committee Members Absent:
Sorin Brull, M.D., Edward Covington, M.D., Jayant K Deshpande, M.D., John M. Markman, M.D., Robert K. Stoelting, M.D., Knox Todd, M.D., M.P.H., Bartholomew Tortella, M.T.S., M.D., M.B.A., (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Absent:
Allen Vaida, Pharm.D. FASHP

FDA Participants Present (Non-Voting)
Bob Rappaport, M.D., Sharon Hertz, M.D., Larissa Lapteva, M.D., Ellen Fields, M.D., M.P.H., Judy Staff, Ph.D., R.P.H., Mary Willy, Ph.D.

Open Public Speakers:

Micke A. Brown, BSN, RN, Director of Communications/American Pain Foundation, Past President of/American Society for Pain Management Nursing
Andrea G. Barthwell, M.D. FASM, Founder and CEO-Two Dreams Outer Banks
Barbara St. Marie, PhDc. Adult and Gerontology Nurse Practitioner Supervisor, Pain and Palliative Center Care Management
Mina Kim, Pharm.D. Pain Management/Palliative Care Pharmacy Resident
Charlie Cichon Executive Director, The National Association of Drug Diversion Investigators (NADDI)
Barbara A. Hastie, Ph.D. Assistant Professor Community Dentistry & Behavioral Science University of Florida College of Dentistry
Robert Tillman, Ph.D., Director of Policy and Advocacy American Academy of Pain Management
Peggy B. Sapp, President & CEO Inofrme4d Families/The Florida Family Partnership
Michael Haggerty, SDI
Michelle Lipinski, Director, Northshore Recovery High School, Dena Bowers (student), Richard Dillon Eaton (student), Jason Kusiak (student)
Michael Toscani, Pharm.D.,
Joe Markmann, Director, Health care Policy/Wolters Kluwer Health Pharma Solutions Group

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

Hilton Washington DC North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland

AGENDA

October 21–22, 2010

Agenda: The committee will discuss considerations for the design of postmarketing studies for new drug application (NDA) 22-272 , OxyContin (oxycodone hydrochloride controlled-release) Tablets, Purdue Pharma, Inc. and NDA 22-321 Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsules, Alpharma Pharmaceuticals, LLC and King Pharmaceuticals Research & Development, Inc., approved for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The postmarketing studies are intended to be epidemiological or observational studies that will assess the known serious risks of these products and whether product-specific properties which are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences: addiction, overdose, and death.

Day 1- October 21, 2010

Call to Order Introduction of Committee	**Jeffrey R. Kirsch, M.D.** Chair, ALSDAC
Conflict of Interest Statement	**Kalyani Bhatt** Designated Federal Officer, ALSDAC
Opening Remarks Products **CDER/FDA**	**Bob Rappaport, M.D.** Director, Division of Anesthesia and Analgesia

Nature of the Problem of Prescription Opioid Misuse and Abuse

Overview of the Risk of Abuse and Regulatory Discussions to Date to Reduce Abuse of Opioid Analgesics	**Larissa Lapteva, M.D.** Deputy Director for Safety, Division of Anesthesia and Analgesia Products CDER/FDA
Premarketing Assessment of Abuse Deterrent Formulations	**James Tolliver, Ph.D.** Pharmacologist, Controlled Substance Staff Office of the Center Director CDER/FDA

Abuse of Marketed Opioid Analgesics and Their Contribution to the National Problem of Drug Abuse	**Len Paulozzi, M.D., M.P.H. (Speaker)** Division of Unintentional Injury Prevention National Center for Injury Prevention and Control Centers for Disease Control and Prevention
Clarifying Questions	

Data Resources and Metrics Used to Assess Prescription Opioid Misuse and Abuse

Designing Observational Studies on Drug Abuse **Speaker)**	**James C. (Jim) Anthony, Ph.D. (Guest** Professor, Department of Epidemiology College of Human Medicine Michigan State University
Substance Abuse and Mental Health Services Administration: Resources and Methods	**Albert Woodward, Ph.D., M.B.A. (Speaker)** DAWN Team Leader (acting) Center for Behavioral Health Statistics and Quality Substance Abuse and Mental Health Services Administration
Available Data Resources to Assist in Measuring Abuse Behaviors, Patterns, and Outcomes	**Catherine Dormitzer, Ph.D.** Epidemiologist, Division of Epidemiology Office of Surveillance and Epidemiology CDER/FDA
Clarifying Questions	

Study Designs to Assess Prescription Drug Abuse

Design Considerations in Epidemiological Studies of Abuse-Deterrent Opioids	**Cynthia Kornegay, Ph.D.** Epidemiologist, Division of Epidemiology Office of Surveillance and Epidemiology CDER/FDA
Statistical Considerations for Epidemiological Studies of Abuse-Deterrent Formulations	**Stephine Keeton, Ph.D.** Mathematical Statistician, Division of Biostatistics 7 Office of Biostatistics CDER/FDA
Clarifying Questions	

Industry Presentation

Purdue Pharma LP Introduction	**Craig Landau, M.D.** Purdue Chief Medical Officer, Vice President, Clinical, Medical and Regulatory Affairs
Overview and rationale of study program	**Paul Coplan, D.Sc.** Purdue Executive Director, Risk Management and Epidemiology
Overdose rates in OxyContin patients and non-patients at Kaiser Permanente	**Nancy Perrin, Ph.D.** Senior Investigator, Kaiser Permanent
Exposures reported to Poison Centers	**Rick Dart, MD, Ph.D.** Director, Rocky Mountain Poison and Drug Center Professor of Surgery and Pharmacy, University of Colorado Executive Director of the RADARS® System
OxyContin abuse among entrants to substance abuse treatment programs	**Theresa Cassidy, MPH** Director of Epidemiology, Inflexxion
Using surveys to assess the impact of a new formulation of OxyContin	**Howard Chilcoat, Sc.D.** Purdue Director, Epidemiology
Law enforcement events in the drug diversion program of RADARS® System	**Rick Dart, M.D., Ph.D.**
Doctor-shopping for OxyContin as measured by Prescription Monitoring Programs	**Paul Coplan, D.Sc.**
Internet discussion about reformulated OxyContin abuse	**Theresa Cassidy, MPH**
Changes in abuse patterns in a cohort of people abusing OxyContin in rural Kentucky	**Carl Leukefeld, DSW** Professor of Behavioral Science, University of Kentucky College of Medicine
Summary and conclusions	**Paul Coplan, D.Sc.**
Clarifying Questions	
Adjourn	

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AGENDA *(Continued)*

October 21-22, 2010

Agenda: The committee will discuss considerations for the design of postmarketing studies for new drug application (NDA) 22-272 , OxyContin (oxycodone hydrochloride controlled-release) Tablets, Purdue Pharma, Inc. and NDA 22-321 Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsules, Alpharma Pharmaceuticals, LLC and King Pharmaceuticals Research & Development, Inc., approved for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The postmarketing studies are intended to be epidemiological or observational studies that will assess the known serious risks of these products and whether product-specific properties which are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences: addiction, overdose, and death.

Day 2- October 22, 2010

Call to Order Introduction of Committee	**Jeffrey R. Kirsch, M.D.** Chair, ALSDAC
Conflict of Interest Statement	**Kalyani Bhatt** Designated Federal Officer, ALSDAC

Industry Presentation

King Pharmaceuticals, Inc.

Introduction and Background Affairs	**Linda Wase, M.D.** Executive Vice President, Medical King Pharmaceuticals, Inc
Challenges of Developing Abuse Deterrent Formulations	**Nathaniel Katz, M.D., M.S.** President, Analgesic Solutions, Inc. Natick, MA Adjunct Assistant Professor of Anesthesia, Tufts University School of Medicine

King's Proposed Epidemiology Approach to Assess Abuse Deterrence for EMBEDA®

David Brown, Ph.D., MPH
Senior Director, Epidemiology
King Pharmaceuticals, Inc.

Summary

Linda Wase, M.D.
Executive Vice President, Medical Affairs
King Pharmaceuticals, Inc

Clarifying Questions

Open Public Hearing

Questions to the Committee

Adjourn

FOOD AND DRUG ADMINISTRATION
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Questions for the Committee

1. Considering the measures and databases currently available, which are likely to be the most effective and efficient metrics and surveillance systems for use in evaluating the impact on abuse and misuse in the community of the introduction of abuse-deterrent opioid formulations?

   The committee consensus at this time is that there is not a specific independent metric or surveillance system in place which could be used to evaluate a new abuse deterrent opioid product. The advisory committee members suggested that the Agency should use their scientific judgment in assessing which are the best and most appropriate combination of the multiple metrics and surveillance systems currently in place.

   Additional comment by the committees was: in order to assess whether or not system proposals put forward by product sponsors accurately capture true community effects, as the Agency moves forward and as technology and market penetration improve in the electronic health record industry and it becomes more robust and common, these records should be used to develop more sophisticated sets of systems for monitoring patients.

   Please see transcript for additional discussion.

2. Are new surveillance systems needed in order to evaluate the effect of abuse-deterrent formulations on abuse and misuse? If so, describe what types of systems are needed.

   The committee consensus (also mentioned by the committee during the Question 1 discussion) was that the use of a combination of currently available publically and privately funded survey tools is adequate for surveillance to evaluate the effect of abuse-deterrent formulations on abuse and misuse. However, the committee urges the electronic health record industry to structure data entry for outcomes related to drug abuse and misuse in a fashion that will allow for automated retrieval of this information in a de-identified fashion. The committee thought that any surveillance system should include data on physicians prescribing practices as they are impacted by the perception of "tamper resistance or abuse resistance".

   Please see transcript for additional discussion.

3. Abuse of opioids encompasses several populations at risk including patients, household contacts and individuals unrelated to patients. Abuse of these products may also involve more than one route or method of administration. Discuss how to incorporate these different aspects of abuse and misuse into the evaluation of the effects of the abuse-deterrent formulations.

   The consensus of the committee was that the "Guidance to Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" could serve as regulatory precedence for a frame work on how to assess and develop a plan for evaluation. The concepts presented in this guidance are consistent with the sponsors' presentations and how they presented their proposals.

   Please see transcript for additional discussion.

4. It is unlikely that abuse-deterrent formulations will completely prevent abuse and misuse of opioids. There may be different degrees of change across the measures used to assess abuse and misuse. Can a minimal reduction in abuse and misuse necessary to support a finding of abuse deterrence be determined a priori for these measures?

   Overall, the committee agreed that even a minimual reduction in abuse and misuse of a product in the market would be beneficial.

   Please see transcript for additional discussion.

5. For some drugs, the abuse-deterrent formulations and the non-abuse-deterrent formulations of the same active drug substance will both be on the market at the same time.

a. In this situation, discuss whether non-abuse-deterrent formulations with the same active drug substance as the abuse-deterrent formulation represent appropriate comparators.

The committee's consensus was that it is appropriate to use the same drug substance that is on the market and to compare it to the new product that contains the same active ingredient. The committee indicated that this type of comparison would be appropriate both pre- and post-marketing.

Please see transcript for additional discussion.

b. Is there any situation in which it would be considered useful to compare the indicators of abuse and misuse from products with different drug substances?

Yes, the committee's consensus was that it is very relevant to compare other drugs that are the same in class as long as they have comparable abuse potential when they are in the community. However, the committee expressed that comparisons should not be made between single entity and multiple entity (combination) products as this would likely be problematic as the abuse potential for these two types of products is dissimilar

Please see transcript for additional discussion.

6. In some instances, the abuse-deterrent formulation will replace the non-abuse-deterrent formulations that were previously marketed.

a. In this situation, would it be appropriate to limit the evaluation of abuse deterrence to comparisons with the older products?

The committee consensus was that it is important to compare the abuse-deterrent formulations to the older formulations but since other products may also be on the market it is not appropriate to limit the evaluation to just the same product historically.

Please see transcript for additional discussion.

b. Would it be necessary or possible to take into account changing patterns in abuse of other drug substances over time?

Yes, overall, the committee felt it would be necessary to take into account changing patterns in abuse of other drug substances over time.

Please see transcript for additional discussion.

7. Discuss how a novel analgesic that is introduced to the market in an abuse-deterrent formulation could be evaluated for abuse-deterrent properties?

The committee felt that the sponsors should compare rates of diversion or misuse (normalized to market share) by the route that the specific product was designed to deter. In addition, many felt that it would be preferable that the comparison be to a product currently on the market

Please see transcript for additional discussion.

8. Discuss what constitutes an adequate duration of observation for postmarketing studies of abuse deterrence.

    a. How should market penetration be taken into consideration?

The committee felt that the market penetration of the product at issue would need to be assessed and this estimate of penetration would be used as a denominator for assessment of event frequency.

Please see transcript for additional discussion.

    b. Discuss how sustainability of the effects of an abuse-deterrent product can be assessed over time

The committee's consensus was that a three year minimum observation period was necessary to demonstrate sustainability of the effects of an abuse-deterrent product, for the purposes of labeling. The committee also suggested interim analysis of the data on an every six month basis.

Please see transcript for additional discussion.

9. The products included to help elucidate the discussion today represent two very different approaches to the development of abuse-deterrent formulations:

    a. physicochemical resistance to manipulation, and

b. incorporation of an opioid antagonist.

They also represent two different marketing paradigms:

c. one in which the original product is removed from the market, and

d. one in which the original formulation without abuse-deterrent properties will remain on the market at the same time as the product with the abuse- deterrent properties.

Discuss which aspects of Purdue's proposed studies and King's proposed studies would be potentially useful in the assessment of the abuse-deterrent effects of products, in general, that have been developed to be abuse-deterrent. Please take into consideration the proposed methodologies, outcome measures, study populations, duration of studies and comparators.

Overall, the majority of members of the committee agreed with the philosophy of the study that each company selected for their individual product. In addition to the measurements defined by each company, the committee members also wanted to be assured that suicide statistics would be captured in the mortality statistics and that each company would report on the impact of their product on prescribing practices of physicians.

Please see transcript for additional discussion.

10. Considering your conclusions and recommendations thus far, please discuss which studies, or elements of those studies, would most likely provide consistency in measurement. This is essential in that, as a regulatory body, the Agency must provide a clear and consistent goal for companies requesting a determination of whether or not their product produces a clinically relevant reduction in abuse in the community that would support the inclusion of a claim of abuse-deterrence in the product label.

The majority of the committee felt that they would like to see the agency require both sponsors to specify the exact form of abuse or misuse that their product was designed to deter and then demonstrate efficacy of their strategy in a human population.
The committee members advocated that the companies design outcomes using existing databases of monitoring on an every 6 month basis, for minimum study period of three years using a comparison to other similar products that are on the market.

Please see transcript for additional discussion.

The meeting adjourned at 3:40 PM