Anesthetic and Life Support Drugs Advisory Committee Meeting
September 9-10, 2003

The following is an internal report, which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov.dockets/ecomments. Slides shown at the meeting will be available at the same website.

These summary minutes for the September 9 and 10, 2003 meeting of the Anesthetic and Life Support Drugs Advisory Committee were approved on October 8, 2003.

I certify that I attended the September 9-10, 2003 meeting of the Anesthetic and Life Support Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Johanna Clifford, MS,RN,BSN Nathaniel Katz, M.D.

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

The Anesthetic and Life Support Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 9-10, 2003, at the Holiday Inn, located at 8120 Wisconsin Avenue, Bethesda, Maryland. The meeting was chaired by Nathaniel Katz, MD, M.P.H.

Anesthetic and Life Support Drugs Advisory Committee Members Present (voting):
Solomon Aronson, M.D., Madelyn Kahana, M.D., Steven Shafer, M.D., Mary Beth Bobek, Pharm.D., Vera Bril, M.D., Bhupinder Saini, M.D. and Carol Rose, M.D.

Anesthetic and Life Support Drugs Advisory Committee Consultants (voting):
Louis Baxter, M.D. (Drug Abuse Subcommittee), Domenic Ciraulo, M.D. (Drug Abuse Subcommittee), Stephanie Crawford, Ph.D., M.S. (Drug Safety and Risk Management), John Cush, M.D. (Arthritis Advisory Committee), Robert Dworkin, Ph.D., Jacqueline Gardner, Ph.D., M.P.H. (Drug Safety and Risk Management Advisory Committee), Jane Maxwell, Ph.D. (Drug Abuse Subcommittee), Steven Passik, Ph.D., Russell Portenoy, M.D., Gregory Skipper, M.D., Brian Strom, M.D., M.P.H. (Drug Safety and Risk Management Advisory Committee), David Wlody, M.D.

Acting Industry Representative (non-voting):
Charles McLeskey, M.D.

Guest Speakers:
Judy Ball, Ph.D., M.P.H., (SAMHSA), Joe Gfroerer (SAMHSA), Mary Jeanne Kreek, M.D., Arthur Lipman, Pharm.D., Deborah Trunzo (SAMHSA), Elizabeth Willis Ed.D. (DEA), Terrance Woodworth, M.S. (DEA)

FDA Guest Speakers :
Steven Galson, M.D., M.P.H., Celia Winchell, M.D., Silvia Calderon, Ph.D., Gianna Rigoni, Pharm.D., M.P.H.

FDA Participants:
Robert Meyer, M.D., Bob Rappaport, M.D., Deborah Leiderman, M.D., M.A., Victor Raczkowski, M.D., Anne Trontell. M.D., M.P.H. and Sharon Hertz, M.D.

Open Public Hearing Speakers:
September 9, 2003:
Congressman Harold Rogers, US House of Representatives
Congressman Frank Wolf, US House of Representatives
B. Eliot Cole, M.D., M.P.A. – American Academy of Pain Management
Jeffery Ebel – Clint Pharmaceuticals
Art Van Zee, M.D. – St Charles Clinic

Siobhan Reynolds – Pain Relief Network
Gregory Walter, M.D.
Mary Baluss – Pain Law Initiative, National Foundation for the Treatment of Pain
Bruce Canaday – American Pharmacists Association
Arthur Van Horn, M.D.
Jan Towers, Ph.D., NP-C – American Assoc. for Nurse Practitioners
David Joranson – University of Wisconsin
Daniel Carr, M.D. – Tufts New England Medical Center

September 10, 2003:
Tom Stinson, M.D.
Art Van Zee, M.D. – St. Charles Clinic

The Committee discussed risk management plans for modified-release opioid products. The members and the invited consultants were provided the background material from the FDA prior to the meeting.

The meeting was called to order at 8:05 a.m. by Nathaniel Katz, M.D., M.S. (Committee Chair). The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Johanna Clifford, M.S., R.N., B.S.N. The agenda proceeded as follows:

September 9, 2003:

Opening Remarks	Bob Rappaport, M.D., FDA
Risk Management of Opiate Analgesics	
FDA's Role in the Risk Management of Opiate Analgesics	Steven Galson, M.D., M.P.H, FDA
Risk Management and the Controlled Substances Act: The FDA Perspective	Deborah Leiderman, M.D., M.A., FDA
DEA's Role in Risk Management of Opiate Analgesics	Terrance Woodworth, M.S., DEA
Break	
Opioid Risk: Benefit Contradiction	Arthur Lipman, Pharm.D., University of Utah
Opiate Use Data	Gianna Rigoni, Pharm.D., FDA
Misuse & Abuse of Opiate Analgesics in the Medical Setting	Steven Passik, Ph.D., University of Kentucky
Nonmedical Use of Pain Relievers: Data from the National Survey on Drug Use and Health	Joe Gfroerer, SAMHSA
Data on Treatment Admissions for Opiate Abuse	Deborah Trunzo, SAMHSA
Opiate Abuse Data	Judy Ball, Ph.D., M.P.A., SAMHSA
Lunch	
Diversion of Prescription Opiates	Elizabeth Willis, Ed.D., DEA
Existing Risk Management Plans	
Goals of Risk Management Plans/Non-Opiate Risk Management Plans	Anne Trontell, M.D., M.P.H., FDA

Break	
Current Opioid Risk Management Plans	Celia Winchell, M.D., FDA
Committee Discussion	
Adjournment	

September 10, 2003

Call to Order, Opening Remarks	Nathaniel Katz, M.D., Chair, ALSDAC
Conflict of Interest Statement	Johanna Clifford, M.S., Exec. Sec., ALSDAC
Committee Discussion	
Sponsor Presentation	
Palladone Capsules for the Management of Persistent Moderate to Severe Pain in Opioid-Tolerant Patients	J. David Haddox, D.D.S., M.D., Purdue
Palladone risk Management Program	J. David Haddox, D.D.S., M.D., Purdue
RADARS Surveillance System	Sidney Schnoll, M.D., Ph.D., Purdue
Prescription Drug Abuse	Herbert Kleber, M.D., Columbia University
Abuse Liability of Hydromorphone Extended Release Capsules	Silvia Calderon, Ph.D., FDA
Break	
Long Acting Opioids: Challenges in Pharmacotherapy	Mary Jeanne Kreek, M.D., Rockefeller University
FDA Presentation	Sharon Hertz, M.D., FDA
Open Public Hearing	
Lunch	
Committee Discussion	
Break	
Committee Discussion – Continued	
Adjournment	

***Questions to the Committee**:*

1. Please discuss the role of the potent, modified-release opioids in the management of chronic pain.

The committee found general agreement that modified-release opioids are appropriate for management for patients with moderate to severe pain and not mild pain, in the setting of cancer-related and nonmalignant chronic pain conditions. The decision to use any opioid or whether to use an opioid or nonopioid as the first analgesic depends on the clinical situation. There was also agreement that good comparative studies of opioids vs. nonopiods in chronic nonmalignant pain were not available in the literature.

The committee recognized the clear advantage of the convenience of MR opioid preparation over IR. Panel members discussed the generally accepted principle that continuous analgesia will result in less total amount of drug used, but a paucity of data on this subject was noted. In addition, panel members cited an accepted notion that flat serum levels of the drug may be less likely to cause addiction; again a paucity of data was noted.

In summary, the committee agreed that the management of chronic malignant and nonmalignant pain of moderate to severe intensity with modified release opioids was appropriate. The committee considered that advantages of modified-release products included possible better pain control with lower dosages, perhaps being less addictive either by not being associated with withdrawals or having reinforcing effects, and possibly an increased quality of life. The conclusions drawn by the panel and sponsor were supported by the results of small trials (not reviewed by FDA) and anecdotal evidence.

Further, in response to this question, the FDA asked the committee to provide some comment on the level of evidence to support the claim of lowered relative addictive potential of long acting vs. short acting opiates. In response, the committee admitted to a lack of direct and conclusive evidence on this subject.

2. In response to reports of abuse/misuse of modified-release opioids, the FDA changed the indication for OxyContin to "…for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." Please comment on the appropriateness of this indication and provide any specific recommended changes that may further enhance the safe and effective use of these products.

The majority of the committee felt that the wording of "moderate - severe" was appropriate. There was discussion that additional provisions could be placed in the label that a patient should have demonstrated opioid responsiveness of their pain syndrome with immediate release treatment first, or that patients whose pain was rated as moderate should also have evidence of impaired function to be candidates for treatment with these products. Those few that suggested limiting the wording to "severe" suggested that the language reflect "chronic" severe or "markedly" severe with functional impairment, but recognized difficulties that would arise with this type of wording. There was no clear consensus favoring either of these points.

With regard to labeling language outside the indication section, the committee also suggested that the labeling could address screening people for their risk of negative outcome, including addictive behaviors, and recommendations for routine periodic assessment. There was significant discussion surrounding the available tools that can be implemented in the clinical setting that would assist in the prediction of the addiction risk in the patient. It was specifically noted that physicians should ask the question of whether patients have had difficulty with taking such products in the past. The addictionologists identified that there is need for further study into the aberrant behaviors of chronic pain patients.

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Further, with respect to this matter, interventions proposed by the committee included a monitoring system for the entire population of candidates for opiate therapy, thus suggesting that the enhanced risk can be mitigated through appropriate monitoring system. The committee accepted the statement by Dr. Passik that safe and effective prescribing of opioid analgesics requires further data on the risk of addiction, risk factors, and diagnostic criteria.

3. The FDA is currently reviewing a number of proposed Risk Management Plans (RMPs) for modified-release opiate analgesics. In order to make informed and appropriate determinations in regard to these RMPs, we need to carefully consider which elements would most likely increase the safe use of these products for legitimate patient and result in a reduction in abuse, overdose, addiction, and misuse in the medical setting. In addition, we must also take into consideration the potential adverse impact of these various risk management elements on patients, prescribes, and pharmacists, as we do not wish to impede proper pain management. In light of these concerns, please discuss the following elements of risk management.

1. Restricted Access

Some RMPs have attempted to manage risk of drugs through various interventions that attempt to limit product use to appropriate patients. Examples of such interventions have include efforts to limit prescribing to a subgroup of physicians based on established expertise or completion of specific training in safe use of the drug or to limit prescribing to a subgroup of patients such as patients who have failed other available therapies or patients who have the most severe manifestations of the disease.

Discuss the role of restriction in access in addressing concerns about the abuse and misuse of modified-release opioid products and how any such measures may impact on the use of these products in appropriate patients.

There was a general agreement among the committee members that the prescribing of these products should not be limited to certain physicians having particular specialty training.

However, the committee encouraged that DEA licensure to prescribe these products be linked to a requirement for Continuing Medical Education related to the use of opioids. The DEA verified that there is currently no policy in place that requires a physician to have special qualifications, other than a medical license, to prescribe controlled substances. Further, the DEA is working in conjunction with the FDA and state medical boards to initiate the policy of mandating education for the renewal of DEA registration, although will not realistically be in place for another 3-5 years if at all.

A patient registry was suggested as a process to collect data for patient selection and appropriate treatment. Privacy issues were noted as a possible barrier.

There was consensus that for whatever measures were introduced, the impact on appropriate opioid prescribing should be measured.

2. Education

Education (directed at patients, prescribers, and pharmacists) is one element of risk management that is currently being used for modified-release opioids. Given the current educational efforts being undertaken by FDA, sponsors, and other government agencies and organizations regarding the safe use of modified-release opioids described earlier today:

Please comment on the adequacy of the current educational efforts and provide any suggestions for ways these efforts could be improved (either by the sponsors, FDA or other stakeholders).

Due to time constraints, the committee did not address this aspect of question 3.
However, education was discussed extensively during other portions of the discussion. The Committee felt that education was a measure that would have very little downside in terms of potential deleterious effects on pain management, and while robust data on the effectiveness of educational interventions in this area are lacking, the Committee felt strongly that requiring education as a condition of opioid prescribing would be a very positive step.

3. Surveillance

Sponsors of modified-release opioids have instituted active surveillance programs in attempt to detect misuse, abuse, and diversion of drug product as described in the presentations earlier today.

Please comment on the adequacy of current surveillance programs and provide any suggestions on how the surveillance programs could be improved (either by FDA, sponsors, or other stakeholders).

Consider in your discussion the fact that there is redundancy among attempts by different sponsors to capture similar surveillance information for different modified-release opioid products.

Please comment on the current situation of multiple, simultaneous surveillance efforts and whether there are alternatives that may be feasible and preferable.

Due to time constraints the Committee did not discuss this item as a separate component of the discussion.
However, surveillance systems were discussed extensively during other portions of the meeting. The Committee was

impressed by industry efforts to produce useful data on prescription opioid abuse. However, the Committee pointed out important limitations of current surveillance programs. The most important of these limitations were: (1) None of the current systems shed any light on the pathways to prescription opioids abuse, i.e., from what source do diverted drugs come? (2) None of the current systems shed any light on the proportion of patients prescribed opioids therapeutically for chronic pain who develop complications such as addiction. The Committee universally agreed that without such information any RMP for these medications would be of unknown usefulness, and the results of any RMP could not be determined.

4. Intervention

After surveillance programs identify a problem of misuse, abuse, or diversion of modified-release opioids, please discuss appropriate interventions that should be undertaken by the sponsor, FDA, other state or federal agencies, law enforcement agencies, or professional organizations.

Due to time constraints, the committee did not address as a separate agenda item this aspect of question 3. However, the Committee did express concern about the appropriateness of a pharmaceutical company on its own determining the point at which a pattern of opioid prescribing or opioid abuse becomes a problem, and also determining the appropriate intervention.

5. Other Strategies

Recognizing the roles of the many stakeholders involved in managing the misuse and abuse of modified-release opioids (including DEA, law enforcement, state medical boards, pharmaceutical companies, health care providers, patients, and patient advocacy groups):

What other types of risk management strategies are recommended in order to increase patient safety and to reduce the likelihood of misuse and abuse?

Due to time constraints, the committee did not address this aspect of question 3.

6. Research:

Please comment on the role of research on optimizing risk management of modified-release opioid products. What are the current gaps and what research would be best done to address these gaps?

Due to time constraints, the committee did not address this aspect of question 3. However, this question was directly addressed in other portions of the meeting. The Committee felt strongly that certain types of information must be gathered to inform safe and effective use of MR opioid analgesics. These include: (1) validated criteria for the diagnosis of addiction in the setting of opioid treatment; (2) rates of incidence/prevalence of addiction and similar complications among patients on chronic opioid therapy; (3) risk factors for these complications; (4) the effectiveness of management interventions on reducing these complications in high-risk patients; (5) characteristics and natural history of individuals with prescription opioid abuse; and (6) sources of abused prescription opioids.

Day 2 Question:

Based on the information that has been presented at this meeting, and taking into account your earlier discussion and deliberation about risk management plans for modified-release opioids, does the Palladone risk management plan (including its proposed labeling and indications) define a program that will likely result in safe use of the product and limit the potential for abuse and misuse of the product while assuring that appropriate patients are able to receive the medication?

The committee commended the Sponsor for the program that they submitted for review. In particular they endorsed the phased rollout of the plan. They did, however, have concerns about the 4-month time period identified for sufficient collection of data, particularly given the time required to gather and analyze sufficient data to have an understanding of potential problems. There was general agreement that approximately 12 months would be more reasonable. The Sponsor clarified that the goal of phase one is to evaluate "message integrity," which would be determined by the survey responses of the physicians, limited to oncologists and pain specialists. The committee noted that establishing message integrity was insufficient grounds to expand marketing, and recommended that sufficient time, perhaps a year, be allowed to collect and analyze the data from the surveillance program. Further, the committee addressed concerns about the lack of prespecified outcome measures and interventions that would address the problems that the data identifies. The sponsor argued that the program interventions will depend heavily on the nature of the signal and that such interventions include education, outreach, etc.

Suggestions for improvement of the current plan included, initiating the rollout with the lower doses and monitoring for substantial overdose or misuse at the lower dose, with the thought in mind that there would be more risk of death from abuse with the higher dosage formulation. In addition, it was suggested that the information collected reflect data on the outcomes of interest, such as abuse, diversion and appropriate treatment, particularly among patients, as opposed to message integrity alone. Another suggestion was to incorporate an educational component for physicians that discusses the risks of opioids in general and the unique issues with Palladone.
Questions to the Committee:

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The meeting was adjourned at approximately 5:00 p.m. on September 10, 2003.