ANESTHETIC & LIFE SUPPORT DRUGS
ADVISORY COMMITTEE MINUTES
JANUARY 30 & 31, 2002
Holiday Inn Gaithersburg

ALSDAC MEMBERS
Nathaniel P. Katz, M.D. Chairman
Winston C.V. Parris, M.D., FACPM
Richard M. Smiley, M.D., Ph.D.
Joseph R. Tobin, M.D.
Janice Bitetti, M.D.
Madelyn Kahana, M.D.
Thomas Vetter, M.D.

CONSULTANT (voting)
Michael A. Ashburn, M.D., M.P.H.
Amanda S. Carlisle, Ph.D., M.D.
Eric S. Holmboe, M.D.
Terese T. Horlocker, M.D
Llyn A. Lloyd, R.Ph.
Edward Lowenstein, M.D.
Mitchell B. Max, M.D.
Laura F. McNicholas, M.D., Ph.D.
Marcus M. Reidenburg, M.D.

GUESTS & GUEST SPEAKERS (non-voting)
Jim Anthony, Ph.D.
Howard Chilcoat, M.D.
Kathleen M. Foley, M.D.
Debra Friedman, M.D.
Bruce Allen Levy, M.D., J.D.
Steven Passik, M.D.
Russell Portenoy, M.D.
Richard G. Roberts, M.D.
Charles Schuster, M.D.
Neil L. Schechter, M.D.
Mark S. Schreiner, M.D.

EXECUTIVE SECRETARY
Kimberly L. Topper, MS

PATIENT ADVOCATE (non-voting)
Jeff Bloom

INDUSTRY REPRESENTATIVE (non-voting)
Charles H. McLeskey, M.D.

CONSUMER REPRESENTATIVE (voting)
Maria K. Connolly, D.N.Sc

INDUSTRY SPEAKER
J. David Haddox, M.D., D.D.S.

FDA PRESENTERS
Gerald DalPan, M.D.
Sharon Hertz, M.D.
Sandra Kweder, M.D.
Sharon Hertz, M.D.
Deborah Leiderman, M.D.,
Bob Rappaport, M.D
Bill Rodriguez, M.D.

FEDERAL AGENCY PRESENTERS
Howard Davis
Judy Ball, Ph.D.

I certify that I attended the January 30 & 31, 2002 meeting of the Anesthetic and Life Support Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/S/	**22 Apr 02**	**/s/**	**22 Apr 02**
Kimberly L. Topper, MS	Date	Nathaniel P. Katz, M.D.	Date
Acting Executive Secretary		Chairman	

A verbatim transcript of this meeting is available for more detailed information.

Anesthetic and Life Support Drugs Advisory Committee
January 30, 2002

The meeting opened at 8:00 with a welcome from the chair and an introduction of all members at the table. Dr. Rappaport introduced the day's topic and provided the format for discussion.

The Open Public Hearing (OPH) was held with the following presenters:
John D. Giglio, M.A., J.D., American Pain Foundation, Chris Mullikin, RNC, CPP, MHS, Pain Management Center, Nancy Kowal MS, NP, American Society of Pain Management Nurses, Lorraine Reeves, Executive Director, Chronic Pain Advocacy League, Cheryll Cusimano RN , Touro Rehabilitation Center / Touro Infirmary, Chronic Pain Unit, Rhonda Garrett, Interstitial Cystitis Association of America, Paul Swerdlow, M.D. , National Institutes of Health, Chair, Sickle Cell Advisory Committee, Dan Handel M.D., National Institutes of Health, Chief of Pain and Palliative Care Service, James W. Broatch, MSW, Reflex Sympathetic Dystrop Syndrome Association, Kathleen Anderson, American Society for RSD/CRPS (ASRSD), Kathryn A. McLaughlin RN, BSN, CHPN, Hospice and Palliative Nurses Association, Michael H. Levy, M.D., Ph.D., Fox Chase Cancer Center, Peter Wilson, M.D., American Society of Anesthesiologists, Jeffrey Ramirez, Pharm.D., Veterans Health Administration, Randolph V. Merrick, M.D., UVA Health Services Foundation, Jeff Stoffler, Patient, Najib Babul, M.D., TheraQuest Biosciences, Art Van Zee, M.D., St. Charles, Virginia, and Glenda Dahlquist, M.D., Pain Management, Ohio. Dr. Katz thanked all the presenters and closed the OPH.

Dr. Rappaport then introduced the morning session on opiate analgesic development and the use of opiate analgesics. He reaffirmed the framework within which the FDA makes its decisions based on scientific evidence from the available data.

Dr. Bruce Allen Levy presented on Pain Treatment Guidelines. He provided proper prescribing definitions for non-therapeutic prescribing and prescribing pharmaceuticals or practicing consistent with the public health and welfare. His definition of intractable pain is a state in which the cause of the pain cannot be removed or otherwise treated and which in the generally accepted course of medical practice no relief or cure of the cause of the pain is possible or none has been found after reasonable efforts. He laid out the proper prescribing for pain guidelines and described practices warranting board scrutiny. He stated the challenge to State Medical Boards is to protect the medical use of controlled substances and simultaneously prevent drug diversion and abuse and ensure public access to effective pain.

Dr. Russell Portenoy presented the Evolving Trends of Opioid Therapy. The evolving consensus shows safe and effective therapy requires knowledge and skills in addiction medicine sufficient to judge risks, monitor treatment, and handle problems and a commitment to documentation and infrastructure. It also requires pain management specialists as consultants educated in both pain management and the principals of addiction medicine. He concluded that the treatment of pain with opioid therapy can probably be effective for any type of pain syndrome but the data are limited, responsiveness varies across individuals and subpopulations and responsiveness cannot be assessed unless therapy is optimized by individualization of the dose. He concluded by stating that opioid therapy is an approach to pain treatment with extraordinary promise and substantial risks and there is a clear obligation upon the prescribers to assess and reassess, be skillful in the drug administration, have knowledge of addiction medicine principals and to provide documentation and communication.

Dr. Gerald Dal Pan discussed the Opiate Analgesic Trials and Drug Development Plans. He stated the choice of the patient population in clinical trials is a crucial element in the development of opiate agents. Considerations for patient populations include the intensity of the underlying pain, the underlying disease that's the cause of the pain, the pathophysiologic mechanisms of the pain and the duration of the treatment needed. He then discussed the drug utilization data from the National Prescription Audit Plus and the National Disease and Therapeutic Index from the IMS Health. He concluded by presenting the two questions to the committee for discussion.

1. Discuss the target population for various opioid formulations and what factors you consider in making this determination?

- In the some patients with chronic non-cancer pain, opioids may be the best drug for treatment. There is a belief that there is not enough data to eliminate a specific patient class from using opioids. Consideration should be exercised to eliminate the under treatment of pain. Pain treatment decisions should be based on the nature of the pain, the pain intensity, and a response to treatment whether the cause of pain is malignant or nonmalignant.
- Previous history of substance abuse should be considered but should not necessarily exclude the patient from treatment with opioids. The patient should be followed much more closely, including with more frequent visits to the office. In considering treatment the patient's home environment should be considered.
- There is a role for specialists in pain and the primary care physician to work together to develop a patient history, diagnosis, treatment plan, evaluation of the treatment plan and adjusting this plan to benefit the patient. It is important that the primary physician has the skills necessary to diagnosis and treat pain. Consider the patient as a whole and consider conducting research where the patients are - in the primary care arena. Include the nursing staff in the treatment team.
- Industry should look at long-term opioid outcomes and collect acute pain data relevant to the pediatric population.
- The label information does not currently drive the use of the drug in specific populations. Guidance should be issued with each new pain medication.

2. In the context of clinical trials to support an indication for chronic pain, discuss the need to assess sustained efficacy over the duration of the trial.

- Labeling for opioids should be very broad if it is not a new novel drug delivery system but FDA should encourage industry to do more studies on covariates. There is a need for better long term surveillance data and post marketing studies of specific disease groups to help define the covariates.
- The health literacy level of the patient must be taken into consideration when including them in a clinical trial.
- Consideration of efficacy versus effectiveness must be looked at in clinical trials. Efficacy is shown in the trial but effectiveness includes many factors or influences relatively independent of the drug's pharmacology. Focusing on a specific population would help to show efficacy.
- A traditional efficacy program should be sufficient to achieve broad labeling, and that should be the goal of the development program but there should be studies of various types to identify responses in subpopulations and to further inform the clinical utility of the drug.
- The durability of response, or tolerance, in response to opioid analgesics, should be studied.

Dr. Rappaport introduced the topic of Opiate use in the pediatric population and provided a brief introduction to the topics each of the speakers will address in the afternoon.

Dr. Debra Friedman discussed the use of analgesics in the Pediatric population. She discussed the administration, evaluation, patient and family concerns, and standards and policies related to the administration of opiates within the pediatric population. Dr. Friedman addressed pain assessment in pediatrics and discussed the issues of oral, intramuscular and intravenous pain resolution techniques. She provided a format for discussion of pediatric pain resolution.

Dr. Bill Rodriquez covered the changes in the FD&C Act with regard to the Food and Drug Modernization Act (FADMA). The 1994 Pediatric Rule applied to approved drugs and biologics and the pediatric indication may be based on adequate and well-controlled trials in adults, with other information supporting pediatric use. It also provided for when the course of the disease and the effects if the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations, it may be permissible to extrapolate the adult efficacy data to pediatric patients. The 1998 Final rule requires pediatric studies for certain new and marketed drugs and biological products. The rule became effective April 1, 1999 and the compliance date was December 2, 2000. Effective on this date the FDA could require submission of pediatric studies and all applications being submitted need to comply with the rule. The important parts of the rule are that it will not delay approval for adult indications, it limits requirements to indications under

review or in development, and it promotes early consideration of pediatric use and drug development plans. The Best Pharmaceuticals for Children Act was signed into law on January 4, 2002. This Act renewed pediatric exclusivity, required FDA to review pediatric supplements under the 6 month priority review, and required the sponsor to submit with IND a statement about intent to study the pediatric population.

Dr. Bob Rappaport provided three hypothetical situations for opiate analgesic pediatric drug development to assist the committee in the discussion of the following questions.

Opiate Analgesic Use in Pediatric Patients

1. The FDA is aware that there are still significant unmet needs in pediatric pain management. In the context of the Agency's new mandate to require studies of drugs in children, discuss these unmet pharmacotherapeutic needs in current pediatric pain management and how they might be met with regard to opioid drug products.

- Industry should make lower dose pills for use in pediatric patients
- A better infrastructure for pediatric clinical trials and symptom relief needs to be researched and incentives provided to encourage the research
- Collection of PK/PD data for recurrent, persistent, procedural or pathologic pain due to a disease state
- There are specific subpopulations of pediatric patients where more data is needed.
- Pain management is limited due to restrictions or extensive paperwork on prescribing opiates. Pharmacy availability many times determines the pain medication prescribed.

2. Discuss the significance of barriers to opioid analgesic trials in children (ethical, safety, scientific, practical, etc). What strategies might be used to overcome barriers?

- Parents are surprisingly willing to enroll their child in a clinical trial and we need to consider if the child is able to realistically give assent.
- Should consider non-invasive dosing. If a child has to get a shot to relieve pain they might not tell you about the pain.
- The amount of liquid needed to get an appropriate dose should be minimal as pediatric patients do not want to or may not be able to drink large amounts of fluids. It must also taste good to the child. Sweet or thick gritty liquids reduce compliance.
- Consider the size of the pill or capsule. Smaller is better.
- Be cautious with abuse liability and do not make medications look like candy.
- Designing the clinical trial follow-up can be arduous for the patient. Requiring multiple visits to the clinic for a patient with mobility problems could be prohibitive. Consider making the follow-up care where the patient is located (i.e., home, hospice, hospital)

3. Many different opioid formulations, delivery methods, and drug-device combinations are currently available on the market or may be available in the future. Discuss the age appropriateness and limitations of these various methods of administration, as well as any others that may be useful or particularly hazardous in pediatrics. Are there particular delivery systems that have found a useful niche in pediatric pain management that should be encouraged?

- Ensure consideration of the size, taste and invasiveness of the delivery system of the pain medication is considered.
- Neonates present issues with the size of a needle and/or extremely sensitive skin when using a patch dosing system and many of the patches do not have a small enough dosing system.
- We need more options that do not use a needle or subcutaneous delivery systems. Experience has shown that patients will not request the medication for pain as frequently if it requires a painful dosing method.
- We need more medications that may be used in the pediatric population and in developing these we need to consider the abuse and diversion potential.

4. It has been historically accepted that the mechanisms of action of opioid analgesics are sufficiently similar between adults and children that large controlled studies demonstrate efficacy, of the nature conducted in adults, have not been required for a pediatric indication. Instead, pediatric trials have been largely focused on investigating safety, pharmacokinetics and appropriate dosing in children. Discuss the shortfalls, if any, to this approach in the ways it has been used to guide and inform the clinical use of opioid analgesics in pediatric patients.

- There is insufficient information to make that assumption. If the pediatric patient is older than 6 years this method would generally work.
- The efficacy and mechanism of action should be tested in pediatric patients and not extrapolated particularly for new agents. We need to do efficacy trials in pediatric populations just like we do in adults.
- We should consider the minimum dose for minimal effect. Respiratory depression, side effects such as constipation should be considered. In many cases we don't always know what we are looking for so we need to find the minimum dose and move forward from that point.

5. Discuss approaches to dose finding and the evaluation of pain in the very young.

- We should look at safety issues in both acute pain and long-term pain patients. Safety is assessed in relationship to something else.
- Compare patient reaction on pain using facial reactions, body language and other non-verbal cues.

6. As new products become available for home use in younger patients, there may be a risk to family members of accidental ingestion, overdose, or deliberate abuse and diversion of these medications. Discuss the strategies for risk communication and risk management that should be considered at the time of pediatric opioid drug approval.

- Counseling for patient and family members needs to be improved and is a very important part of pain management. In general parents ask better questions on the behalf of a child than for themselves.
- A written mechanism such as a "Medi-Guide" would be useful to highlight the pediatric dosing and potential side effects to watch for in the pediatric patient.
- Discussion with family members on where the medication should be placed, a safe haven for the drug and precautions and recognition of an overdose and the required actions if that occurs.
- Consider a "use contract" when the drug is used chronically.

Anesthetic and Life Support Drugs Advisory Committee
January 31, 2002
Questions to the Committee

Prescription Drug Abuse

January 31, 2002

Dr. Katz welcomed everyone to the meeting and asked the committee and guests to introduce themselves.

The Conflict of interest statement was read into the record.

Dr. Bob Rappaport thanked the participants for their work yesterday and introduced the topic for today's discussions on risk management and addiction.

The Open Public Hearing was started with the following making presentations: Catherine Underwood, American Pain Society, Randall C. Cork, M.D., Ph.D., LSU Health Sciences Center, Mary Baluss, Palliative Care Law Project, Ellen Battista, DNS, ANP, PNP, Pain Treatment Consultants of Western New York, Rollin M. Gallagher, M.D., MPH, American Academy of Pain Medicine, Rick Lieb, The National Pain Foundation, Michael Cinque, American Pharmaceutical Association, Rebecca Burkeholder, National Consumers League, Dennis Buede, Ph.D., Kerry W. Cranmer, MD, CMD, Jim Monahan, Houston Hospice, Michael Gloth, M.D., Johns Hopkins University School of Medicine, John Coleman, MA, MS,Dennis Fisher,MD, Durect Corporation of California, Dorothy Steffler, Parent of Pain Patient, Randolph V. Merrick, M.D., UVA Health Services Foundation, Paul Desjardins, MD, Scirex Corporation. Dr. Katz thanked everyone for their presentations and then provided a brief overview of the previous day's discussions.

Dr. J. David Haddox, representing Purdue Pharma, presented an industry view of risk management development, the disease burden of pain, treatment of chronic pain and addiction management. When researching the disease burden of pain they found that there were not many studies to provide data so they did a brief study of their own and discovered that 10% of those surveyed contemplated suicide as a means to end their pain, 77% had been in pain for more than 1 year and 13% had been denied pain medication. He explained that Purdue's risk management plans include the education of health care professionals, education of care givers, surveillance activities and stepped interventions.

Dr. Bob Rappaport introduced the topic of prescription drug abuse and reminded the committee that what we put in the label may be used for marketing claims which may have a profound impact on drug prescribing and use.. Dr. Kweder clarified that once the drug is on the market it is used however the prescribing physician desires and not always within the labeling guidelines.

Dr. Judy Ball, Substance Abuse and Mental Health Services, discussed the findings from the drug abuse warning network. She explained the DAWN system, the systems strengths and weaknesses, how the data is gathered and provided examples of the data available from this system.

Dr. Deborah Leiderman, Director Controlled Substance Staff, FDA provided the regulatory background in which they work. She explained that potential abuse assessment is mandated by two distinct acts. She explained each act and what the FDA does to fulfill the requirements of the acts.

Mr. Howard Davis, Chief, Domestic Drug Unit, Office of Diversion and Control, Drug Enforcement Agency, provided n overview of the role of the DEA in the Diversion of prescription Drugs. He explained there were six categories of opiate analgesic abuse. These included: "Doc" shopping, prescription drug rings with prescription forgery; employee thefts, infividual theft (realestate agent stealing from homes they show), robbery, and intratransit thefts.

Dr. Howard Chilcoat from Johns Hopkins University provided an epidemiologic overview of prescription drug misuse. His findings showed there is a prevalence of abuse of Rx drugs that is comparable to that of cocaine with analgesics being most commonly misused, ages 18 - 25 have the highest risk, girls 12 - 17 ar particularly vulnerable. They also showed there is a hight level of comorbidity with other psychiatric disorders, a strong relationship with antisocial personality disorders and cocaine abuse and the lifetime prevalence of Rx drug dependence is similar to that of cocaine.

Dr. Steven Passik, Director, Oncology Symptom Control and Research Community Cancer Care discussed substance abuse issues in chronic pain management. He explained substance abuse issues are complex during pain management and they defy simple solutions and these issues require tactical and humane approaches that combine thoughtful diagnosis, structure and a team approach.

Dr. Sharon Hertz, FDA discussed the regulatory approaches to Risk Management of prescription opioid drug abuse. She explained there are many approaches to managing abuse potential and amoung these are scheduling under the Controlled Substances Act, labeling, risk management plans, formulation changes, and restricted distribution. Risk management plans provide key messages, identify risk potential, utilize prograns to identify abuse, misuse, and diversion, develop prevention and intervention prograns and develop monitoring efforts. She then presented five vignettes for the committee to use in the discussion of the questions.

The Agency is aware of the growing problems of abuse, misuse and diversion prescription drugs, including the opioid analgesics, among patients and non-patients.

1. Discuss the adequacy of the available data to determine the prevalence of addiction among patients treated with opioids for chronic pain. What can we currently say about the prevalence?

- There is a difficulty in getting patients to do reliable self reporting - urine toxicology testing or spousal reporting are potential ways to determine prevalence of addiction
- Consider observational data or behavioral data to inform studies of addiction, such as prescription monitoring programs.
- Most patients on chronic therapy develop physical dependence on opioids yet are not addicted. An unknown proportion develop clinically significant tolerance which is also distinct from addiction. The incidence of true addiction to chronic opioid therapy is unknown.
- The phenomenon of addiction must be better characterized and assessed in clinical trials in order to conduct risk-benefit analysis of long-term opioid therapy.

2. Discuss how addiction in a chronic pain patient on opioid therapy can be accurately assessed in the office setting.

- Behaviors that raise suspicion of addiction include selling prescription drugs, prescription forgery, stealing or borrowing another patient's drugs, injecting oral formulations, obtaining prescription drugs from non-medical sources, concurrent use of illicit drugs, multiple unsanctioned dose escalations, and recurrent prescription losses. The physician must be aware of this and watch for these problems.
- Be cautious of labeling a patient as addicted because it does imply criminal consequences and what appears to be addiction could be shopping to gain adequate pain control
- Patient self-report alone is probably inadequate.

3. Discuss the pros and cons of excluding patients with a prior history of substance abuse from clinical trials.

- There is not enough data to exclude anyone from opioids when medically indicated
- Failure to treat pain adequately may increase the appearance of addiction when patient visits multiple physicians to get adequate pain relief leading to "pseudo-addiction"
- When treating a patient with a history of drug abuse the physician must be more aware of the home situation and provide extra contact with the patient to limit potential for abuse
- Treatment of the patient’s pain until reduced to an acceptable level is primary; the prior history of abuse is secondary

4. Discuss the methods of monitoring for addiction in the clinical setting that may be extended to the Clinical Trials setting.

- Ensure the program is concrete and doable and not overly fanciful or conceptual
- Antisocial personality disorder appears to pose a 15 fold greater risk of addiction

- Determine if the drug is going to become the "Drug of the Day" and be prepared to adjust the risk management program to accommodate the abuse potential
- Track psychiatric or psychological comorbidities in clinical trials for chronic pain
- Track the use of other medications and the use of alternative therapies
- Consider external sources of information about drug-taking behavior.
- Other potential side effects of opioids, including neuropsychological and endocrine effects, may be important.

5. In the context of increasing awareness of the problems of diversion and addiction to prescription opioids among patients and non-patients, comment on what measures might be appropriate to consider in the development of an overall risk management strategy that could reduce abuse and diversion without restricting access to drugs by patients in need of treatment. Comment on what components should be incorporated into such programs.

- Consider a program such as Kentucky's that has an electronic measurement program that collects data on the prescriptions filled at each pharmacy and for what patient.
- Survey existing pain centers to gather data on pain control and the methods used since they already have an established cohort
- Continuous review by experts of data being collected
- Ensure data collection methods are consistent and validated
- Consider competence based prescribing
- Use web based training for users and prescribers
- Consider a shared decision making program
- Develop Medi Guide for opiate drugs
- The usefulness of present "abuse liability testing" should be revisited. Alternative and valid methods for such testing should be considered.

The chair thanked everyone for the intensely constructive discussion on such important issues and the meeting closed at 4:42PM.