

EXHIBIT 2

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AFFIDAVIT OF JAMES E. O'BRIEN, Ph.D., M.D.

I, James E. O'Brien, having been duly sworn, depose and say:

1. I am over eighteen years of age and believe in the obligations of an oath.
2. I have a B.S. in Pharmacy and an M.S. and Ph.D. in Pharmacology from the University of Connecticut, and obtained an M.D. from the University of Vermont. Upon completion of my internship and residency requirements in internal medicine at St. Francis Hospital in Hartford, Connecticut, I remained with the hospital as Director of the Intensive Care unit and as Clinical Pharmacologist. In addition to my work at St. Francis Hospital, I was also a member of the faculty at the University of Connecticut Medical School for over 17 years, where I was an Associate Professor with appointments in medicine, surgery, psychiatry and toxicology. I have served on numerous boards and commissions, including the Pharmacy Commission for the State of Connecticut where I was the board's chairman for 12 years. I am currently a toxicologist with the University of Connecticut Poison Control Center, and still consult on various drug-related issues with the United States Drug Enforcement Administration and the United States Attorney's Office for the District of Connecticut. (*See attached Curriculum Vitae*).
3. I have been asked by the Office of the Connecticut Attorney General to give my opinion, based on my education, training and experience as both a pharmacologist, pharmacist and a physician, as to the pharmacologic effects of OxyContin when an increase in the patient's total daily dose of oxycodone is accompanied by a decrease in

the time interval between doses from the manufacturer's recommended q12h guideline to q8h or more frequently.

4. The labeling for OxyContin specifically states that patients who experience breakthrough pain may require rescue medication or dosage adjustment. Rescue medications, if needed, should be prescribed in an immediate-release dosage form. Often, rescue medication is prescribed in 5mg or 10mg dosages. When the rescue medication does not adequately control a patient's pain between doses of OxyContin, the labeling recommends that the total daily dose of oxycodone should be increased by increasing the OxyContin q12h dose, not by increasing the dosing frequency.

5. It is my opinion that increasing the dosing frequency of OxyContin from q12h to q8h or more frequently, coincident with an increase in the total daily dose of oxycodone, will lead to a stepwise progression in the patient's plasma levels due to a greater accumulation of the drug in a relatively short time. This increase in oxycodone plasma concentration will significantly raise the potential for a patient to incur an increase in the frequency and severity of side effects and, possibly, adverse events. The risk for developing side effects and adverse events is greatest within the time it takes for the drug to reach steady-state, which is normally within the first few days after dose adjustment.

6. I base my opinion on the fact that OxyContin's AcroContin delivery system is constructed for a biphasic absorption pattern. Essentially this means that oxycodone is absorbed into the bloodstream in two phases. In the first phase, the drug's delivery system results in an initial absorption of approximately one-third of the total dose of oxycodone within the first two hours of administration. This initial phase is followed by a second prolonged phase, where approximately two-thirds of the remaining oxycodone

is slowly diffused through an acrylic matrix into the bloodstream. The prolonged phase of oxycodone absorption occurs over a 10-12 hour period.

7. Because of OxyContin's biphasic construction, in those instances when the total daily dose of oxycodone is increased and the frequency of drug administration is shortened to intervals of less than 12 hours, the subsequent one-third dose of oxycodone contained and absorbed during the initial phase will be superimposed on the dose of oxycodone still remaining in the patient's system from the prior dose's prolonged phase. This results in an increased accumulation of oxycodone and its less active metabolites in the plasma. The higher concentrations occur for the reason that not all of the drug from the first dose is eliminated prior to introduction of the second dose, and will lead to higher drug concentrations over at least the next several doses. The onset of accumulation is hastened by the drug's delivery system, since almost 40% of the drug is absorbed within the first one to two hours. This level of accumulation is beyond the level one would expect to see if a physician prescribed an immediate-release rescue dose rather than an additional dose of OxyContin. These risks are further magnified in OxyContin's higher strengths, the 40mg, 80mg and 160mg tablets.

8. On average, according to OxyContin's labeling, steady-state plasma concentration -- the point at which the amount of the drug eliminated during each dosing interval is equal to the amount of the dose -- will take place within approximately 24-36 hours of titration and dosing frequency adjustment. Time to steady-state is based on OxyContin's stated elimination half-life of 4.5 hours. For the average patient population using OxyContin, this will be the window when the potential for additional side effects and adverse events will most likely be expected to occur if the total daily dose of oxycodone

is increased in concert with a decrease in the time interval between administrations. If, however, the elimination half-life of OxyContin is actually closer to 10 hours rather than 4.5 hours, it will take longer for the patient to reach steady-state. If this were true, then the plateau concentration of the drug will be greater due to a continued accumulation from more frequent doses and the longer time it takes for one to eliminate the drug from their body. Further, although the drug's labeling indicates it is appropriate to adjust the dosage after one to two days, if the time to steady state is actually longer, the better practice would be to wait at least two or more days before making each dosage adjustment. This is so since the true therapeutic effect of a drug cannot be observed, and thus evaluated, until the drug has achieved its maximal response, which occurs only after maximum drug concentrations are reached. Adjusting the dosage again, prior to the preceding dosage adjustment reaching steady-state, may result in consecutively higher plasma concentrations of oxycodone than is warranted for proper pain relief, and will add to the potential for developing drug induced complications.

9. While average time to steady-state is an important factor in prescribing drugs for chronic conditions, there are essential variations in kinetics among different patients, either due to patient population or disease, that prescribers of OxyContin must take into account. For certain patient populations, many of which are prescribed this drug, the time to steady-state after dose titration and dosing frequency adjustment may be even longer. This is particularly true for those patients whose ability to eliminate the drug is compromised, leading to longer elimination half-lives. The longer it takes to achieve steady-state plasma concentration, the greater the prospect for a rapid and continued accumulation of oxycodone from the increased dosing frequency, leading to a heightened

potential for toxic concentrations. Among those patient populations most at risk are the elderly, those with respiratory disease, and/or renal, hepatic, or endocrine impairments, making them more susceptible to increased occurrence of side effects or adverse events such as central nervous system depression, orthostatic hypotension, hypoxia, and/or respiratory arrest when an increase in total daily oxycodone dosage is coupled with a decrease in the time interval between administrations.

10. Also of concern with the above-described prescribing practice is the problem of physical and psychological dependence. Although this is always an issue when prescribing opioids, this concern is amplified when an increase in the total daily dose of oxycodone, combined with more frequent dosing, is used in conjunction with OxyContin's biphasic delivery system. When oxycodone daily dosage is increased and the frequency of administration occurs in dosing intervals less than q12h, the absorption within a relatively short time of almost 40% of the drug will lead to a quick and marked increase in oxycodone plasma levels that will raise the likelihood of increased euphoria which will add to the specter of the potential for abuse and psychological dependence to the drug.

11. While the prospect for the occurrence of euphoria is certainly present during the first few days after titration, it is my opinion that long-term use of OxyContin at dosing frequencies of q8h or more frequently will enhance the chances of developing an iatrogenic-based psychological dependence and addiction to the drug as well. I reach this conclusion for several reasons. First, the frequency of administration of a drug, especially one as potent as OxyContin, is always a factor in a patient developing an addiction. Therefore, when a drug is taken on a more frequent and sustained basis it can

produce compulsive drug use. Second, under q12h administration the initial absorption phase of oxycodone delivery causes onset of drug effect within 42 minutes to an hour. The superimposing of a significant OxyContin dose on an already existing level will not only rapidly raise the peak concentration but will also intensify the euphoric effects and, thus, the potential for developing addiction. Finally, an increase in total daily oxycodone dose, combined with a more frequent administration of OxyContin will result in higher and more frequent peaks in oxycodone plasma concentration, which will invariably lead to greater drug effect and, consequently, greater gratification from drug use.

12. Assuming that prescribers are increasing a patient's total daily dose of oxycodone by adding one or more doses rather than increasing the q12h dose, it is my opinion that there is a marked need to better inform prescribers on the pharmacokinetics of OxyContin, and increase awareness of the serious adverse events that may occur when titration is effectuated by prescribing the drug for administration more frequent than q12h. I suspect that many q8h, q6h and q4h OxyContin prescriptions are inadvertently written as a substitute for immediate-release preparations to treat breakthrough pain. Obviously, because of the greater potential for side effects and adverse events that may result from this prescribing practice, more specific information relating to the issues involved in prescribing OxyContin in dosing intervals less than q12h should be disseminated to healthcare professionals as expeditiously as possible.

13. The logical place for more specific information related to the greater risks of prescribing OxyContin in dosing intervals less than q12h should be the drug's labeling and advertising. However, revisions to a drug's labeling require Food and Drug Administration approval, which can be time-consuming. Thus, it is my opinion as a

pharmacologist, pharmacist and physician, and in light of the potentially serious nature of this problem, that in addition to the manufacturer initiating steps to revise OxyContin's labeling, there is a clear need for the immediate issuance of a "Drug Warning" or "Dear Healthcare Professional" letter explaining OxyContin's pharmacokinetics, the dissimilarity of the drug's AcroContin delivery system from other controlled-release opiates, and the risks involved in prescribing this drug in dosing frequencies more often than every 12 hours.


James E. O'Brien, Ph.D., M.D.

STATE OF CONNECTICUT)

COUNTY OF Hartford)

ss: Hartford

Sworn and subscribed before me in Hartford, Connecticut, on this 5th day of December, 2003.

Debra L. Shea
Notary Public
My commission expires: 5/31/06

CURRICULUM VITAE

JAMES EDWARD O'BRIEN, Ph.D., M.D.

31 Surrey Drive
Wethersfield, CT 06109
(860)721-0121

Board Eligible – Internal Medicine

**Memberships – 1) Connecticut Medical Society
2) Hartford County Medical Society
3) American College of Clinical Pharmacology (Fellow)**

Education:

University of Connecticut, Storrs, Connecticut
B.S., Pharmacy – 1952
M.S., Pharmacology- 1955
Ph.D., Pharmacology – 1957
M.D., University of Vermont, Burlington, Vermont – 1961

Internship:

St. Francis Hospital, Hartford, Connecticut
Rotating Internship, July 1961 – July 1962

Residency:

St. Francis Hospital, Hartford, Connecticut
Surgical Resident, July 1962 – December 1962
Medical Resident, January 1962 – December 1966

Honors / Awards:

U.S. Department of Justice, Award for Significant Contributions in the Field of Drug Abuse

Distinguished Alumni, University of Connecticut

Connecticut Narcotic Enforcement Officers Association for Devoted Support and Assistance in Drug Education of Enforcement Officers and Civic Organizations

Milton Camilleri Award for Outstanding Contributions in Drug Education and Pursuit of Abolishment of Drug Abuse

New England Narcotic Enforcement Association for Exemplary Service Given in the Interest of Public Safety of People in New England

Narcotic Enforcement Association Award for Education and Training in Substance Abuse in Business and Industry

Consultantships and Committees:

**Capitol Region Council of Governments, Task Forces on Narcotics and Dangerous
Drugs, Sub-Committee Chairman for Treatment and Rehabilitation,
Sub-Committee Vice-Chairman for Law Enforcement**

**Connecticut Hospital Association – Council on Professional Services and
Committee on Alcoholism**

Research Advisory Committee, Department of Corrections, State of Connecticut

Board of Directors, Nutmeg Games

Governor's Task Force on Drug Abuse Education

**Appeals Officer & Consultant on Drug Education & Testing for Northeast Utilities
Nuclear Facilities**

Consultant on Drug Testing, University of Hartford Athletic Department

Chairman, Medical Committee for International Narcotic Enforcement Assoc.

**National Institute of Drug Abuse, Office of Extramural Project Review, Contract
Review Unit**

**State of Connecticut Medical Society, Joint Conference Committee on Pharmacy
and Medicine**

**Research Committee, State Methadone Program, Alcohol and Drug Division,
Department of Mental Health, State of Connecticut**

Past Consultant, U.S. Department of Justice Drug Enforcement Administration

U.S. Pharmacopoeia, Credentials Committee

Greater Hartford Chamber of Commerce Committee on Drug Legislation

Research Support:

Career Teacher, Alcohol and Drug Dependency, NIAAA#5T01 AA 07085,
July 1975 – September 1979, \$124,647

Alcohol Research Center, University of Connecticut, NIAAA#P50AA03510-3,
March 1978 – November 1982, Program Coordinator, \$2,000,000.

“Double Blind Study of Lorazepam versus Diazepam in the Treatment of the Acute Alcohol Abstinence Syndrome”, Wyeth Laboratories Grant, April 1979- September 1980, Principal Investigator, \$20,143.

“Double Blind Study of Halazepan (Paxim) versus Chloriazeposide (Librium) in The Symptomatic Relief of Acute Alcohol Withdrawal”, Schering Laboratories Grant, July 1, 1980 – June 30, 1981, Principal Investigator, \$51,788.

Professional Experience:

Assistant Professor of Medicine, University of Connecticut School of Medicine,
1974 -1992

Assistant Professor of Surgery, University of Connecticut School of Medicine, 1992
- present

Associate Professor Psychiatry, University of Connecticut School of Medicine,
1981 - present

Medical Director, LaMontagne & O'Brien, Assoc., L.L.C., 1995- Present

Medical Director, State of Connecticut Parole Program- 1998 – Present

Medical Director, Government Programs-Pharmacy and Therapeutic Affairs
Blue Cross/ Blue Shield of Connecticut- 1996 – 1999

Medical Director-Disability, The Hartford Insurance Company, 1992 - 1996

Consultant, Pharmacology, Rocky Hill State Hospital, 1970 – 1990

Clinical Pharmacologist and Assistant Visiting Physician, Department of Medicine,
St. Francis Hospital, Hartford, Connecticut, 1966 – 1975

Director, Methadone Detoxification Program, St. Francis Hospital, 1975 –1980

Medical Consultant and Lecturer, Blue Hills Hospital, Department of Alcohol and
Drug Dependence, State of Connecticut, 1968 – 1978

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Cirriculum Vitae

James E. O'Brien, Ph.D., M.D.

Professional Experience (Continued)

Medical Director, Combined Hospital Alcoholism Program, 1973 - 1975

Director, Hartford County Poison Control Center, 1966-1974

Professional Specialist, Alcohol and Drug Training Center, University of Connecticut School of Medicine, 1973 - 1975

Medical Director, St. Francis Hospital Intensive Care, 1966 -1973

Appointments:

Vice-President, Hartford Dispensary, 1990 - 1998

Medical Director, Member, Board of Directors, Hartford Dispensary Methadone Maintenance, 1986 - Present

Chairman, Medical Committee and Physician for State Boxing Commission, 1991 - 1998

Commissioner of Pharmacy, State of Connecticut, 19679- 1978;
Chairman, 1974 - 1976; appointed permanent Chairman, 1979 - 1988

Drug Advisory Council, State of Connecticut, 1967; Chairman, 1976 -1982;
Sub-Committee of Enforcement, Control and Criminal Administration,
Chairman, 1970 - 1982

Commission on Alcoholism and Drug Abuse, Hartford, Connecticut, 1974 -1982

Commissioner, Alcohol and Drug Abuse Commission, State of Connecticut,
1982 - 1991

Governor's Task Force on Alcohol and Driving, 1982

Governor's Task Force on Substance Abuse 1986

Faculty Appointments:

Medical Director, Alcohol and Drug Abuse Treatment Center,
John Dempsey Hospital, 1977 - 1992, 1993 to 2000

Assistant Professor of Medicine, University of Connecticut School of Medicine
1976 - 1992

Faculty Appointments: (Continued)

Associate Professor of Psychiatry, University of Connecticut School of Medicine
1981 – Present

Associate Professor of Surgery, University of Connecticut School of Medicine
1992 – Present

Associate Director, Poison Control Center, State of Connecticut, University of
Connecticut Health Center, 1993 – Present

Medical Director, Poison Control Center, State of Connecticut University of
Connecticut Health Center, 1986 – 1993

Research Associate, University of Vermont, Department of Pharmacology,
1957 – 1961

Consultant in Pharmacology, University of Connecticut, 1966 – 1973

Lecturer in Psychiatry, Yale University School of Medicine. 1971 – 1972

Assistant Professor of Psychiatry, University of Connecticut School of Medicine,
1974 – 1981

Publications:

O'Brien, James E. and Thomas, R.K., The In-Vitro Effect of Sodium Lauryl Sulfate
on Vaginal Pathogens. JA Ph A Sc Ed, XLIV, No. 4, 245-247, 1955

O'Brien, James E. and Thomas, R.K., The Antipyretic and Analgesic Activities of
Thymatic Acid. JA Ph A Sc Ed, XLVII, 258, 1958

Hanna, C and O'Brien, James E., The effect of HET on Early Histological Changes
in the Lens of Co=60 Gamma Radiated Rat, Fed Proc 18:400, 1959

Hanna, C and O'Brien, James E., Cell Production and Migration in the Epithelial
Layer of the Cornea. A.M.A. Arch Opth 64:536-539, 1960

Hanna, C and O'Brien, James E., Intracellular Distribution of Drugs, II. Cations and
the Intracellular Distribution of Mephentermine in the Isolated Rabbit Heart.
Arch Int Pharmacodyn, CXXVII 361-368, 1960

Publications: (Continued)

Hanna, C., Gecknell, D.S. and O'Brien, J.E., Cell Turnover in the Adult Human Eye. Arch Ophth 65:695-698, 1962

Jersey, Robert, M., M.D., Godar, Thomas, J., M.D., O'Brien, J.E. M.D., Ph.D., Liss, J.P., M.D., and Huszar, R.J., M.D., Experience with External Cardiac Resuscitation in a Community Hospital. ConnMedicine Vol 32 (3):193, 1968

O'Brien, James E., Pharmacological Principles of Drug Dependency, I.N.E.O.A. 13th Annual Conference report, pp. 13-15, 1972

O'Brien, James E., Clinical Pharmacy – A Requirement for Licensure? Proceedings of Annual Meeting, National Association of Boards of Pharmacy and American Association of Colleges of Pharmacy, District 1, pp. 70-73, 1970

O'Brien, James E., Medical and Psychiatric Aspects of Phencyclidine Intoxication. Medical Tribune. 21(87):1, 1980

Ladder, Ingrid, L., O'Brien, James E. and Voth, Harold, M., Answering Questions about Marijuana. Patient Care Vol. 14, No.10:112-148, 1980

O'Brien, James E., Behavioral Problems Due to Substance Abuse. Topics in Emergency Medicine, pp. 30-41, January 1983

O'Brien, James E., The Drug Scene Today and it's Effect on Mortality. Association of Life Insurance Medical Directors of America. Vol LXVII, 1984