

April 30, 2002

Dockets Management Branch
HFA – 09305
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

4370 02 MAY -2 AM 3/

Re: International Drug Scheduling: Convention on Psychotropic Substances, 67 Fed. Reg. 17074 (April 9, 2002)

The Pharmaceutical Research and Manufacturers of America (PhRMA) herein provides comments on the Department of Health and Human Services' (DHHS') request for comments on the World Health Organization's (WHO's) critical review of several drugs marketed in the United States (U.S.) and throughout the world, 67 Fed. Reg. 17074 (April 9, 2002). PhRMA is a voluntary, non-profit association that represents America's leading research-based pharmaceutical and biotechnology companies. PhRMA member companies invested over \$30 billion in 2000 alone here in the United States, and around the world, to discover and develop new medicines. In an industry that is increasingly multi-national in scope, these companies are the source of nearly all new drugs that are discovered and marketed throughout the world.

In May 2000, PhRMA commented on procedures used in the last round of international drug scheduling and raised issues concerning the inadequacy of those procedures. With regret we note that nothing has been done to ameliorate the problems that we identified.

In this cycle, WHO has five drugs under critical review: amfepramone, amineptine, buprenorphine, tetrahydrocannabinol, and tramadol. One of these drugs, amineptine, is not marketed in the United States. Each of the others is approved for use in the United States and is currently marketed in this country. How these drugs might be scheduled in the international system is very important to patients and medical practice in this country; scheduling and changes in scheduling create regulatory requirements and affect availability of medicines for their use, in the United States.

Our government is the voice of the American people in the scheduling process. PhRMA believes that our government therefore has an obligation to assure that this process will take cognizance of the fullest set of sound data available. The WHO questionnaire will not commit the agency to an information-

02N-0101

Pharmaceutical Research and Manufacturers of America

C1

based decision; instead, it invites anecdotal information and therefore decisions that are of poor quality and likely arbitrary and capricious.

The WHO Questionnaire is Inadequate

Dr. Frank Hurley's declaration is enclosed. He makes the point, as he did in the last scheduling cycle, that WHO's questionnaire cannot be expected to yield information to justify a scheduling decision that is methodologically adequate. The questionnaire asks questions that will elicit anecdotal information that cannot be used to make scientific evaluations concerning drug abuse. WHO and the U.S. government both strongly endorse the need for good data when making health care decisions; this questionnaire will not yield data that support an information-based decision.

In the last scheduling cycle, PhRMA made the same criticism of the questionnaire, and our comments were passed to the WHO secretariat. The WHO secretariat responded, saying: "Re the WHO questionnaire, the more detailed the questions are the greater the burden on the governments to respond. For this reason we are always requested to make our questionnaire as simple as possible." It appears that "simple" has been chosen as a substitute for "adequate." When the issue is the public health, how can such an answer be acceptable?

Also, as in the last scheduling cycle, the WHO questionnaire does not ask for information concerning the therapeutic value of the drugs; that is, the relative value of the medicine in light of its uses and the availability of other medicines. Rather, the questionnaire asks about the impact of scheduling and its impact on the "availability for medical use." This does not provide for data on the importance of the drug or the availability of therapeutic alternatives, vitally important bits of information when considering scheduling. Given the dramatic differences in availability of adequate health care among countries, such information is critical for WHO to make an informed decision on these drugs. WHO's own *Guidelines* document identifies therapeutic use as an important factor. How reviewed medicines fit into the medical scheme of the countries receiving the questionnaire should not be ignored.

We recognize that, because of the inadequacies of the questionnaire, most of the information garnered from around the world will be anecdotal, useless for making information-based scheduling decisions. We also are aware that the response rate for the questionnaire is poor. The data however will be cited as a basis for some action, and the citizens of the United States will be affected as a consequence.

In light of the foregoing, PhRMA believes the U.S. government has a special burden to go beyond the inadequate questionnaire and provide a proper review of the subject medicines. A full presentation of the available information, especially including data that provide context, can greatly assist the WHO to conduct a full and adequate review.

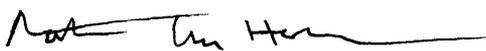
The Role of DHHS

Just as in the last cycle, the current Federal Register notice states that DHHS "... will not now make any recommendations to WHO regarding whether any of these drugs should be subjected to international controls. Instead, DHHS will defer such consideration until WHO has made official recommendations to the Commission on Narcotic Drugs" This language declares that DHHS is prepared to make no effort to affect the medical/scientific decision made at WHO until it is too late to be effective.

The WHO's medical and scientific findings are binding on the Commission on Narcotic Drugs when control assessments are made under the Psychotropic Convention. So, once the WHO recommendation is made to the Commission on Narcotic Drugs, any recommendations our government might make relating to the medical and scientific issues would be out of order. Given that the United States is indisputably the repository of the great proportion of collected drug abuse data, this hesitance on the part of DHHS to express its views so they might be known at the time of the medical and scientific review is inexplicable. PhRMA strongly encourages DHHS to adopt a more active role while it may influence WHO's decisions with full information that – to repeat – puts the reviewed medicines in context of their medical use.

The FDA process is not timely or adequate

This Federal Register announcement was published 38 days before the U.S. is supposed to submit its answers to the WHO questionnaire. Comments can be received until eight days before the submission date. DHHS, FDA, NIDA, DEA, ONDCP, and SAMHSA all are participating in the process. There is no way that these agencies can receive, absorb, and prepare an adequate response in the time allotted. This is also too short a time for the public to prepare meaningful comments. This means that the U.S. response will be prepared without the consideration that an important issue such as this should have. PhRMA urges FDA to develop procedures that will provide for timely intervention by interested parties and permit U.S. agencies to develop proper responses to WHO questionnaires.


Matthew B. Van Hook

DECLARATION OF FRANK L. HURLEY, PH.D.

I, Frank L. Hurley, Ph.D., declare and state as follows:

1. I make this declaration to provide my expert opinion in clinical epidemiology regarding the World Health Organization's ("WHO's") Questionnaires used for the collection of information and data for the WHO's review and ultimate scheduling recommendation for Amfepramone (diethylpropion), Amineptine, Buprenorphine, Delta-9-tetrahydrocannabinol (dronabinol) and Tramadol. The questionnaires were published in the Federal Register on April 9, 2002, 67 Fed. Reg. 17074. The facts contained herein are true to the best of my knowledge, information and belief.

CREENTIALS

2. I have worked in the field of clinical epidemiology for approximately 30 years. I received a Bachelor of Science degree in Mathematics and Pre-Medical Sciences from Georgetown University in 1966 and a Ph.D. in Biostatistics from Johns Hopkins University in 1970. I currently serve as an Adjunct Associate Professor for the Georgetown University School of Medicine. I am affiliated with a number of professional organizations, including, but not limited to, The Johns Hopkins University Health Advisory Board of the Bloomberg School of Hygiene and Public Health, the Commonwealth of Virginia Biotechnology Research Park Authority Board of Directors;

DECLARATION OF FRANK L. HURLEY, PH.D.

the Food and Drug Law Institute, the Society for Clinical Trials, the Society for Epidemiologic Research, the Regulatory Affairs Professional Society, the American Statistical Association, and the Drug Information Association. A true and accurate copy of my *curriculum vitae* is attached hereto as Tab A.

3. As an employee of a major contract research company and independent consultant I have been responsible for regulatory and clinical research policy, identification of areas of importance for scientific development and senior scientific staff requirements. I work with clients to develop regulatory research strategies designed to minimize the time for Food and Drug Administration ("FDA") approval, review protocols, analyze and interpret results for clinical studies, and develop presentation of results for FDA. I routinely interact with investigators and medical consultants on issues of research design and interpretation of results; and review quality control procedures and client clinical data processing systems. I present seminars for Research and Development staff on designing and conducting clinical research for regulated products.

4. I have been involved in over 300 clinical studies of pharmaceuticals, medical devices, and diagnostic products; occupational health studies; as well as a number of epidemiological studies on the long-term effects of drugs and medical devices. I have assisted in the design and implementation of computerized occupational health information systems.

DECLARATION OF FRANK L. HURLEY, PH.D.

5. I have authored or co-authored over 100 technical reports on epidemiologic and clinical research. These reports have included the health effects of various occupational exposures, as well as reports on clinical studies of drugs and devices. I also have presented these reports to a variety of FDA advisory panels.

WHO Questionnaires

6. On April 9, 2002, the FDA published a notice in the Federal Register requesting the submission of data or comments concerning the abuse potential, actual abuse, medical usefulness, and trafficking of five drug substances, "Docket 02N-0101": International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Amfepramone (diethylpropion); Amineptine; Buprenorphine; Delta-9-tetrahydrocannabinol (dronabinol); Tramadol, 67 Fed. Reg. 17,075 (April 9, 2002) ("Fed. Reg. Notice"). A true and accurate copy of the "Fed. Reg. Notice" is attached hereto as Tab B.

7. The notice asked for information in response to a WHO Questionnaire containing the following items:

- (1) Availability of the substance (registered, marketed, dispensed, etc.);
- (2) Extent of the abuse or misuse of the substance; and Degree of seriousness of the public health and social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.); and

DECLARATION OF FRANK L. HURLEY, PH.D.

- (3) Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.).

In addition to the above, with regard to Amfepramone (INN) report on:

- (4) The impact of transferring Amfepramone from Schedule IV to Schedule III of the Convention on Psychotropic Substances, 1971, and its effect on availability for medical use.

In addition to items 1 through 3 above, with regard to Amineptine (INN) report on:

- (5) The impact of placing amineptine in Schedule IV of the Convention on Psychotropic Substances, 1971, and its effect on availability for medical use.

In addition to items 1 through 3 above, with regard to Buprenorphine (INN) report on:

- (6) The impact of transferring buprenorphine from Schedule III of the Convention on Psychotropic Substances to Schedule I or II of the Single Convention on Narcotic Drugs and its effect on availability for medical use.

In addition to items 1 through 3 above, with regard to Tramadol (INN) report on:

- (7) The impact of placing Tramadol in Schedule IV of the Convention on Psychotropic Substances, 1971, and its effect on availability for medical use.

“Fed. Reg.” Notice, 67 Fed. Reg. 17,074 – 17,075 (April 9, 2002) (footnote omitted).

8. I have reviewed the WHO Questionnaires for Amfepramone (diethylpropion), Amineptine, Buprenorphine, Delta-9-tetrahydrocannabinol (dronabinol) and Tramadol. In my opinion, based on thirty years of experience in epidemiology, the questionnaires are entirely inadequate to capture valid data and information about the nature and extent of substance abuse. The structure of the current questionnaires

DECLARATION OF FRANK L. HURLEY, PH.D.

precludes collection of quantifiable data amenable to analysis. The format of the questionnaires encourages anecdotal responses, which will not provide the type of data required to assess the potential problems associated with abuse, or the extent of the problems. The lack of specific definition of terms means that "substance abuse" will be subject to a wide variety of interpretations. This will render the collective responses meaningless without specification of what each individual respondent defines as substance abuse.

Indeed, if abuse or misuse is defined as use not in accordance with a product's label or instructions for use, it is likely that the vast majority of products in all consumer categories would require a "yes" response to question 2a.

9. In order to be accurate, information on abuse or misuse should come from structured studies or surveys. The studies should include specific definitions for categories of substance abuse, information on the sources of reports of abuse and protocols for primary data capture. The only useful information to be elicited by the questionnaire would come from protocol driven studies or reports from structured registries submitted as supplements to the questionnaire.

Signed this 15th day of May, 2002,

A handwritten signature in black ink, appearing to read "Frank L. Hurley", written over a horizontal line.

FRANK L. HURLEY, Ph.D.

EDUCATION:

- 1970 Ph.D., Biostatistics, Johns Hopkins University
- 1966 B.S., Mathematics and Pre-Medical Sciences, Georgetown University

WORK SKILLS:

Development of regulatory research strategies; Drug development requirements; Review of preclinical and clinical information; Preparation of regulatory documents; Presentations to Government regulatory agencies; Regulatory requirements, training/consulting.

WORK EXPERIENCE:

July 1, 2000 – *HD Consulting, LLC, Washington, DC & Bethany Beach, DE*
Present Chief Scientific Officer and Managing Member

1999 – *Quintiles Transnational Corporation, Arlington, VA*
June 30, 2000 Senior Scientist

1996 - 1999 *Quintiles Transnational Corporation, Arlington, VA*
Chief Scientific Officer

1995 - 1996 *BRI International, Inc., Arlington, VA*
Chairman and Chief Scientific Officer, Senior Technical Adviser
As Chairman & Chief Scientific Officer, has overall responsibility for FDA regulatory and clinical research policy, identification of areas of importance for scientific development and senior scientific staff requirements.

As Senior Technical Adviser, works with clients to develop regulatory research strategies designed to minimize the time for FDA approval; reviews protocols, analysis and interpretation of results for clinical studies, and develops presentation of results for FDA; interacts with investigators and medical consultants on issues of research design and interpretation of results; reviews quality control procedures for BRI and client clinical data processing systems; and gives seminars for client R&D staff on designing and conducting clinical research for regulated products.

Projects have included over 300 clinical studies of pharmaceuticals, medical devices, and diagnostic products, as well as a number of epidemiologic studies of long-term effects of drugs and medical devices, occupational health studies, and

design and implementation of computerized occupational health information systems.

Recognized, published educator and authority on research strategy and study design for pharmaceuticals, biologics, and medical devices. Preeminent in formatting data presentation to communicate clinical outcomes. Has presented applications to every FDA division and seen them through approval. Strong background in regulatory research strategy and implementation.

1991 - 1995 Chairman and Chief Executive Officer, Senior Technical Adviser

1989 - 1991 President and Chief Executive Officer, Senior Technical Adviser

1976 - 1989 Executive Vice President, Senior Technical Adviser

1971 - 1976 Senior Partner

As Senior Biostatistician and Project Director, was responsible for clinical and epidemiological research protocol designs and their presentation to regulatory agencies; implementation and maintenance of cooperative studies; and coordinating center functions for a variety of research contracts. As Director of Quality Assurance and Regulatory Affairs, was responsible for design and implementation of systems that assure data accuracy and completeness consistent with FDA regulations.

1976-Present *Georgetown University School of Medicine, Washington, DC*
Adjunct Associate Professor

1971 - 1976 *Georgetown University School of Medicine, Washington, DC*
Assistant Professor, Department of Community Medicine

1970 - 1973 *The George Washington University School of Medicine, Washington, DC*
Assistant Professor, Department of Epidemiology and Environmental Health

1966 - 1970 *Loyola College, Baltimore, MD*
Instructor

PROFESSIONAL AFFILIATIONS:

The Johns Hopkins University Health Advisory Board of the Bloomberg School of Hygiene and Public Health

The Johns Hopkins University Bloomberg School of Public Health Dean's Alumni Council

The Johns Hopkins University Washington DC Alumni Advisory Committee

Commonwealth of Virginia Biotechnology Research Park Authority Board of Directors – Vice Chairman

Coagulation Diagnostics, Inc. Board of Directors

The BRI Foundation Board of Directors

AnVil Informatics, Inc. Board of Directors

Nascent Pharmaceuticals, Inc. Board of Directors

American Statistical Association

Association for Advancement of Medical Instrumentation

Biometrics Society

Drug Information Association

Food and Drug Law Institute

New York Academy of Sciences

Non-Prescription Drugs Manufacturer's Association

Regulatory Affairs Professional Society
International Coordinating Committee, 1984
Vice President, International Section, 1985 – 1987
RAPS Certification, October 1991

Society for Clinical Trials

Society for Epidemiologic Research

PUBLICATIONS:

Dr. Hurley has authored or co-authored over 100 technical reports on epidemiologic and clinical research. These reports have included health effects of various occupational exposures as well as reports on clinical studies of drugs and devices. Dr. Hurley also has presented these reports to a variety of advisory panels for FDA.

Leung, H., Hurley, F., Strand, V., "Heterogeneity in RA Radiographic Trials: Issues to consider In a Meta-analysis," *The Journal of Rheumatology* (February 2000).

Cohen, S., Schiff, M., Weaver, A., Caldwell, J., Kaine, J., Fleischmann, R., Cannon, G., Fox, R., Moreland, L., Olsen, N., Furst, D. for the Leflunomide RA Investigators Group; Sharp, J., Hurley, F., Strand, V. "Treatment of Active Rheumatoid Arthritis with Leflunomide Compared to Placebo and Methotrexate," *Archives of Internal Medicine* (November 1999).

Sharp, J., Strand, V., Leung, H., Hurley, F., Loew-Friedrich, I. on behalf of the Leflunomide Rheumatoid Arthritis Investigators Group, "Treatment with Leflunomide Slows Radiographic Progression of RA – Results from Three Randomized Controlled Trials of Leflunomide in Patients with Active Rheumatoid Arthritis," *Arthritis & Rheumatism*, **43**, 495-505, (March 2000)

Hurley, F., "Multinational Clinical Trials," *RAPS RA Focus Magazine* (March 1997).

Hurley, F., West, D., "The Logistics of Conducting Clinical Studies," in the Clinical Trials for Medical Devices series, *Medical Device & Diagnostic Industry Magazine* (May 1996).

Hurley, F., "Statistical Approach to Subgroup Analyses: Patient Compliance Data and Clinical Outcomes," in Patient Compliance in Medical Practice and Clinical Trials (1991).

Hurley, F., "Clinical Trials of Biomaterials and Medical Devices," in Handbook of Biomaterials Evaluation - Scientific, Technical, and Clinical Testing of Implant Materials (1986).

Hurley, F., "Planning Research and Development of New Drugs to Assure Regulatory Approval," *Food Drug Cosmetic Law Journal*, **39**, 312-317, (1984).

Wong, O. and F. Hurley, "A Biostatistical and Epidemiologic Perspective of an Occupational Health Record System," *Journal of the American Medical Record Association*, **52**, 57-62, (1981).

Hurley, F., "Design and Management of Device Clinical Trials," *Medical Device and Diagnostic Industry*, **3**, 44-49, (1981)

PRESENTATIONS:

Dr. Hurley has made over 50 presentations to FDA Expert Advisory Panels.

Hurley, F., "Research Questions About Means in Three Groups," Georgetown University School of Medicine, Biostatistics and Epidemiology, May 2001

Hurley, F., "A 30 Year Perspective on Biostatistics," presented at Johns Hopkins University, August 1999.

Hurley, F., Participated as a member of the Roundtable on Research and Development of Drugs, Biologics, and Medical Devices for the Institute of Medicine, National Academy of Sciences, "Assuring Data Quality on Validity in clinical Trials for Regulatory Decision Making," May 1999.

Hurley, F., "Resolving FDA/Sponsor Disputes", presented at FDLI/FDA Annual Educational Conference, Washington, DC, December 1998.

Hurley, F., "Multinational Clinical Trials", presented at BIO '98 International Biotechnology Meeting and Exhibition, June 1998.

Hurley, F., "The Evolution of the Multicenter Trial & The Critical Position of the Clinical Research Coordinator", presented for the Japanese Ministry of Health, United Kingdom, March 1998.

Hurley, F., Munsey R., "FDA Modernization Act", presented at Quintiles BRI Quality Systems & Hyman, Phelps, McNamara, P.C. Workshop, March 1998.

Hurley, F., Participated as member of the Roundtable on Research and Development of Drugs, Biologics, and Medical Devices for the Institute of Medicine, National Academy of Sciences, "Assuring Data Quality on Validity in clinical Trials for Regulatory Decision Making," April 1998.

Hurley, F., Participated in Forum on "Clinical Trials: Looking to the Future," for the National Institutes of Health, November 1997.

Hurley, F., "FDA and Legal Issues of Genetic Tests and Therapeutics," presented at the Cancer and Genetics Conference, Portsmouth, NH, October 1997.

Hurley, F., "Multinational Clinical Trials," presented to the Massachusetts Biotech Council in the Bioprocessing Development Center at University of Massachusetts Lowell, Lowell, MA, May 1997.

Hurley, F., "Multiplicity - Combination Endpoints," presented at DIA Workshop entitled "Statistical Issues in the Pharmaceutical Industry: Multiplicity in Clinical Trials," Hilton Head, SC, March 1997.

Hurley, F., "Multinational Clinical Development Programs," presented at DIA Biotechnology Workshop entitled "Clinical Trials in Biotechnology" Dana Point, CA, February 1997.

Hurley, F., "Prevention of Structural Damage: Statistical/Study Design Issues," presented at Food and Drug Administration Rheumatoid Arthritis Workshop, Rockville, MD, March 1996.

Hurley, F., "Assessing Equivalence to an Active Treatment Control: Use of Placebo Control Results," presented at Biologic Agents in Autoimmune Disease IV, San Francisco, CA, March 1995.

Hurley, F., "Multinational Clinical Development Programs," presented at BIOEAST '94, Washington, DC, January 1994.

Hurley, F., "Managing Clinical Development: From Start to Finish," presented at the Eighth International Biotechnology Meeting, Toronto, Canada, May 1994.

Hurley, F., "Avoiding the Perils of Clinical Trials," presented at the Suburban Maryland Technology Council Biotechnology Network, Gaithersburg, MD, October 1994.

Hurley, F., "The Review Process: Kudos and Concerns - An Industry Viewpoint," presented at FDLI's 38th Annual Educational Conference, Washington, DC, December 1994.

Hurley, F., "Biostatistics of Clinical Trials and Presentation of Study Results", presented at CPA, 1993 & 1994.

Hurley, F., "Medical Device Approvals: Strategies and Tactics", presented at RAPS, 1993.

Hurley, F., "Biotechnology Reimbursement: Integrated Regulatory Reimbursement Development", presented at ABC, 1993.

Hurley, F., "FDA Regulations and Policy for Accelerated Approvals", presented at Massachusetts Bioprocess Development Center, October 1993.

Hurley, F., "The Business of Consulting", February 1993.

Hurley, F., "Approvable Indications and Surrogate Endpoints," presented at Regulatory Affairs Professional Society, San Diego, California, January 1993.

Hurley, F., "What Do You Want To Be: Drug, Device or Biologic?" presented at Getting Your Combination Products Approved and to Market, The Institute for International Research, Washington, DC, January 1993.

Hurley, F., "Combination Products", presented at IIR, January 1993.

Hurley, F., "Post Market Surveillance and Adverse Event Reporting", presented at RAPS, 1992.

Hurley, F., "Clinical Trials for Drugs and Devices", presented at Georgetown University, January 1992.

Hurley, F., "Practical Aspects of Clinical Trials for FDA Approval Requirements", presented at ABC, 1991.

Hurley, F., "Related Regulations" presented at FDLI, 1991.

Hurley, F., "Regulatory Strategies, "Product Approval: Understanding the FDA," presented at the International Biotechnology Expo & Scientific Conference, San Francisco, California, October 1991.

Hurley, F., P. Levitch, "Welcome to Regulated Research and Approvable Indications:" Practical Aspects of Clinical Trials for FDA Approval Requirements, presented at the Association of Biotechnology Companies' Fifth International Biotechnology Meeting & Third Annual CBC Meeting, Washington, DC, May 1991.

Hurley, F., "Subgroup Analyses: Statistical Concerns," presented at Threats to Interpreting the Clinical Experiment: Occult Noncompliance American Society for Clinical Pharmacology and Therapeutics, San Francisco, California, March 1990.

Hurley, F., "Effective Interaction with the FDA", presented at CPA, 1990.

Hurley, F., "Approaches to the Handling of Clinical Trial Data in the Presence of the Accurate Compliance Records" presented at Noncompliance as a Source of variance in Drug Response, American Association of Pharmaceutical Scientists 4th Annual Meeting and Exposition, Atlanta, Georgia, October 1989.

Hurley, F., "Do Drugs or Devices Move More Quickly through the FDA?" presented to the Department of Continuing Medical Education of the New York Medical College, Washington, DC, October 1989.

Hurley, F., "Statistical Approach to Subgroup Analyses," presented at "The Impact of Partial Compliance in Clinical Trials," Drug Information Association, Philadelphia, Pennsylvania, September 1989.

Hurley, F., "Difference Between Drug and Device Trials," presented at Clinical Trials with Drugs and Devices: A Rational Approach, Regulatory Affairs Professionals Society, Nice, France, May 1989.

Hurley, F., "Industry Regulatory Perspective," presented to the Pharmaceutical Manufacturers Association, San Diego, California, April 1989.

Hurley, F., "Planning Research and Development of New Drug to Assure Regulatory Approval", presented at CPA, 1988.

Hurley, F., "Clinical Study Design," presented at How to Prepare for and Conduct a Clinical Investigation, Regulatory Affairs Professional Society, Rockville, Maryland, May 1988.

Hurley, F., "Biosafety and Biocompatibility of Medical Devices," presented at the Regulatory Affairs Professional Society Symposium, Nice, France, April 1988.

Levitch, P., A. Ghignone, and F. Hurley, "Overview of Medical Device Development: From Concept to FDA Approval," presented to The Center for Professional Advancement CLIN-REG Conference, New Brunswick, New Jersey, March 1988.

Hurley, F., "Non-U.S. clinical Studies to Support U.S. Premarket Approval Applications", presented at RAPS, 1987.

Hurley, F., "FDA Regulatory Process", presented at the Washington Orientation Meeting, October 1987.

Hurley, F., "The IND Rewrite Comments and Questions," presented at Food and Drug Law Institute Pharmaceutical Update, Chicago, Illinois, May 1987.

Hurley, F., "Management of Foreign Clinical Device Trials presented to Pfizer, Aspen, Colorado, August 1987.

Hurley, F., "Clinical Studies in Europe," presented at the International Section Annual Meeting, Regulatory Affairs Professional Society 11th Annual Meeting, Alexandria, Virginia, September 1987.

Hurley, F., "When, How and Why Do Cost-Benefit Analysis?," presented at Drug Information Association Conference, June 1986.

Hurley, F., "Industry's Role in Resolving PMA Problems," presented at Food and Drug Law Institute Device Update, June 1986.

Hurley, F., "Multicenter Trials - A Statisticians Perspective", presented at RAPS, 1985.

Hurley, F., "Understanding the NDA Rewrite - The Impact on Clinical Investigations," presented to the Food and Drug Law Institute, Washington, DC, March 1985.

Hurley, F., J.M. Minnis, and D. Wilson, "Quality Control Systems for Clinical Trial Research," presented to the Medical Devices and Diagnostic Industry, Expo '84, New York City, New York, May 1984.

Hurley, F., "Planning Research and Development for Regulatory Approval," presented to the FDLI 27th Annual Educational Conference, Washington, DC, December 1983.

Hurley, F., "IDE Research: Current Problems and Future Trends," presented to the Medical Device and Diagnostic Industry, Expo '83, New York City, New York, June 1983.

Hurley, F., "Epidemiologic Evaluation of the Relationship Between Reye's Syndrome and the Use of Salicylates," presented at the American Academy of Pediatrics Meeting, New York City, New York, October 1982.

Hurley, F., "Evaluation of Epidemiologic Studies of Reye's Syndrome," presented to the National Council on Drugs, Washington, DC, October 1982.

Hurley, F., "Review of Epidemiologic Studies of Reye's Syndrome, Phase I," presented to the US Congress, Committee on Science and Technology, Subcommittee on Natural Resources, Agriculture Research & Environment, September 1982.

Hurley F., "Practical Considerations in the Design and Management of Clinical Studies," presented to the Small Manufacturers Medical Device Association, September 1981.

Hurley, F., "Epidemiologic Considerations for an Occupational Health Information System," presented to the American Chemical Society Meeting, New York City, New York, August 1981.

Hurley, F., "What Happened to All That Paper?," presented at the Second US Intraocular Lens Symposium (Sponsored by the American Intraocular Implant Society), Los Angeles, California, April 1979.

Implant West 77: Instructional Symposium for Intraocular Lens Implantation.

2/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 02N-0101]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Amfepramone (diethylpropion); Amineptine; Buprenorphine; Delta-9-tetrahydrocannabinol (dronabinol); Tramadol

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is requesting interested persons to submit comments concerning abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of five drug substances. These comments will be considered in preparing a response from the United States to the World Health Organization (WHO) regarding the abuse liability and diversion of these drugs. WHO will use this information to consider whether to recommend that certain international restrictions be placed on these drugs. This notice requesting comments is required by the Controlled Substances Act (CSA).

DATES: Submit written or electronic comments by May 9, 2002.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-09305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: James R. Hunter, Center for Drug Evaluation and Research (HFD-9), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1999, e-mail: hunterj@cder.fda.gov.

SUPPLEMENTARY INFORMATION: The United States is a party to the 1971 Convention on Psychotropic Substances. Article 2 of the Convention on Psychotropic Substances provides that if a party to the convention or WHO has information about a substance, which in its opinion may require international control or change in such control, it shall so notify the Secretary General of the United Nations and provide the Secretary General of the United Nations with information in support of its opinion.

The CSA (21 U.S.C. 811 *et seq.*) (Title II of the Comprehensive Drug Abuse

Prevention and Control Act of 1970) provides that when WHO notifies the United States under Article 2 of the Convention on Psychotropic Substances that it has information that may justify adding a drug or other substances to one of the schedules of the convention, transferring a drug or substance from one schedule to another, or deleting it from the schedules, the Secretary of State must transmit the notice to the Secretary of Health and Human Services (the Secretary of HHS). The Secretary of HHS must then publish the notice in the Federal Register and provide opportunity for interested persons to submit comments that will be considered by HHS in its preparation of the scientific and medical evaluations of the drug or substance.

I. WHO Notification

The Secretary of HHS received the following notices from WHO:

Ref: C.L.4.2002

WHO QUESTIONNAIRE FOR COLLECTION OF INFORMATION FOR REVIEW OF DEPENDENCE-PRODUCING PSYCHOACTIVE SUBSTANCES

The Director-General of the World Health Organization presents her compliments and has the pleasure of informing Member States that the Thirty-third Expert Committee on Drug Dependence (ECDD) will meet from 17 to 20 September 2002 to review the following substances:

1. Amfepramone (International Nonproprietary Name (INN))¹
2. Amineptine (INN)
3. Buprenorphine (INN)
4. Delta-9-tetrahydrocannabinol²
5. Tramadol (INN)

One of the essential elements of the established review procedure is for the Secretariat to collect relevant information from Member States to prepare a Critical Review document for submission to the Expert Committee on Drug Dependence. The World Health Organization invites Member States to collaborate, as in the past, in this process by providing pertinent information mentioned in the attached questionnaire concerning the substances listed above.

Further clarification on any of the above items can be obtained from Quality Assurance and Safety: Medicines (QSM), Essential Drugs and Medicines Policy (EDM), WHO, Geneva, to which replies should be sent not later than 17 May 2002.

GENEVA, 7 February 2002

1. AMFEPRAMONE (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? (Yes/No)

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

1.2 Is there other legitimate use of the substance? (No/Yes, it is used for ____.)

¹ If the reply to the questionnaire provides sufficient information for a critical review.

² Including dronabinol (INN).

1.3 How is the substance supplied? (Imported/Manufactured in the country)

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No/No information)

2.2 If yes, is the abuse increasing? (Yes/No/No information)

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

4. IMPACT OF TRANSFER TO A HIGHER SCHEDULE

4.1 If amfepramone is transferred to Schedule III of the Convention on Psychotropic Substances, do you think that its availability for medical use will be reduced? (Yes/No/No opinion)

4.2 If yes, would the reduction adversely affect the provision of medical care? (Yes/No/No opinion)

Please elaborate:

2. AMINEPTINE (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? (Yes/No)

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

1.2 Is there other legitimate use of the substance? (No/Yes, it is used for ____.)

1.3 How is the substance supplied? (Imported/Manufactured in the country)

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No/No information)

2.2 If yes, any information on the extent of abuse?

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

4. IMPACT OF SCHEDULING

4.1 If amineptine is placed under international control, do you think that its availability for medical use will be reduced? (Yes/No/No opinion)

4.2 If yes, would the reduction adversely affect the provision of medical care? (Yes/No/No opinion)

Please elaborate:

3. BUPRENORPHINE (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? (Yes/No)

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

1.2 Is there other legitimate use of the substance? (No/Yes, it is used for ____.)

1.3 How is the substance supplied? (Imported/Manufactured in the country)

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No/No information)

2.2 If yes, is the abuse increasing? (Yes/No/No information)

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

4. IMPACT OF TRANSFER TO SCHEDULE I/II OF THE SINGLE CONVENTION ON NARCOTIC DRUGS, 1961, ON MEDICAL AVAILABILITY

4.1 If buprenorphine is transferred from Schedule III of the Convention on Psychotropic Substances to either Schedule I or II of the Single Convention on Narcotic Drugs, do you think that its availability for medical use will be reduced? (Yes/No/No opinion)

4.2 If yes, would the reduction adversely affect the provision of medical care? (Yes/No/No opinion)

Please elaborate:

4. DELTA-9-TETRAHYDROCANNABINOL³

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? (Yes/No)

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

1.2 If the answer to 1.1 is no, is there other legitimate use of the substance? (Yes/No)

If yes, please describe the purpose of use.

1.3 If there is legitimate use of the substance, how is the substance supplied? (Imported/Manufactured in the country)

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No)

2.2 If yes, any information on the extent of abuse?

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

5. TRAMADOL (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? (Yes/No)

Please indicate trade name(s), dosage form(s) with strength(s) and indication(s):

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? (Yes/No/No information)

2.2 If yes, any information on the extent of abuse?

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the

substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

4. IMPACT OF SCHEDULING

4.1 If tramadol is placed under international control, do you think that its availability for medical use will be reduced? (Yes/No/No opinion)

4.2 If yes, would the reduction adversely affect the provision of medical care? (Yes/No/No opinion)

Please elaborate:

II. Background

Amfepramone, also known in the United States as diethylpropion, is classified as an anorexiant with pharmacological effects similar to the amphetamines. It is marketed in the United States for short term (8 to 12 weeks) use, in conjunction with a regimen of weight reduction based on caloric restriction, in patients with obesity and who have not responded to an appropriate weight reducing regimen (diet or exercise) alone. It is controlled domestically in Schedule IV of the CSA and internationally in Schedule IV of the Psychotropic Convention.

Amineptine is classified as a tricyclic antidepressant. It is not marketed in the United States. It has been marketed in other countries for the treatment of major depressive disorders and has also been studied for its potential use in the treatment of amphetamine withdrawal. In 1999, amineptine products were voluntarily removed from the market in France and Portugal due to risks of misuse and addiction. It is not controlled in the United States under the CSA or internationally under the Psychotropic Convention or the Single Convention on Narcotic Drugs.

Buprenorphine is a semisynthetic opium derivative with partial mu-opioid receptor agonist activity. In the United States buprenorphine is currently only available as a parenteral product and is marketed for the relief of moderate to severe pain. Buprenorphine is also marketed for the treatment of pain in several other countries in both sublingual and parenteral dosage forms. A high-dose formulation of buprenorphine is also marketed in other countries for use in the treatment of opiate dependence. It is currently controlled domestically in Schedule V of the CSA as a narcotic and is controlled internationally in Schedule III of the Psychotropic Convention. In the *Federal Register* of March 21, 2002 (67 FR 13114), the Drug Enforcement Administration published a proposed rule to increase the regulatory controls placed on buprenorphine by rescheduling buprenorphine from a Schedule V narcotic to a Schedule III narcotic.

Delta-9-tetrahydrocannabinol (delta-9-THC), the active component of marijuana, is currently controlled in Schedule I of the CSA. Synthetic *delta-9-THC*, or dronabinol, is the active component of the drug product Marinol, which is marketed in the United States as an antiemetic in the setting of cancer chemotherapy and for treatment of AIDS wasting syndrome. Dronabinol in sesame oil and encapsulated in an FDA-approved product is controlled in Schedule III of the CSA. Marinol is the only product that meets this definition. Dronabinol (which is the synthetic equivalent of the natural active component of marijuana, *delta-9-THC*) in any other form is controlled in Schedule I of the CSA. The drug substance dronabinol is controlled internationally in Schedule II of the Psychotropic Convention.

Tramadol is a centrally acting synthetic analgesic. At least two complementary mechanisms of action appear applicable: binding of parent and metabolite to mu-opioid receptors and weak inhibition of the reuptake of norepinephrine and serotonin. It is marketed in the United States for the treatment of moderate to moderately severe pain. Cases of abuse and dependence of tramadol have been reported. It is not controlled in the United States under the CSA or controlled internationally under the Psychotropic Convention or the Single Convention on Narcotic Drugs.

III. Opportunity to Submit Domestic Information

As required by section 201(d)(2)(A) of the CSA (21 U.S.C. 811(d)(2)(A)), FDA, on behalf of the Department of Health and Human Services (DHHS), invites interested persons to submit comments regarding the five named drugs. Any comments received will be considered by DHHS when it prepares a scientific and medical evaluation of these drugs. DHHS will forward a scientific and medical evaluation of these drugs to WHO, through the Secretary of State, for WHO's consideration in deciding whether to recommend international control/decontrol of any of these drugs. Such control could limit, among other things, the manufacture and distribution (import/export) of these drugs and could impose certain recordkeeping requirements on them.

DHHS will not now make any recommendations to WHO regarding whether any of these drugs should be subjected to international controls. Instead, DHHS will defer such consideration until WHO has made official recommendations to the Commission on Narcotic Drugs, which

³ Including dronabinol (INN)

are expected to be made in late 2002. Any DHHS position regarding international control of these drugs will be preceded by another Federal Register notice soliciting public comments as required by section 201(d)(2)(B) of the CSA.

IV. Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding the drugs by May 9, 2002. This abbreviated comment period is necessary to allow sufficient time to prepare and submit the domestic information package by the deadline imposed by WHO. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 29, 2002.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02-8493 Filed 4-8-02; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity; Public Workshop

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop.

The Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER), in cooperation with the Department of Defense (DoD), is announcing the following public workshop: "Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity." The workshop will discuss possible strategies for the efficacy testing of investigational anthrax vaccines.

Date and Time: The public workshop will be held on April 23, 2002, from 8 a.m. to 5 p.m.

Location: The public workshop will be held at the Jay P. Sanford Auditorium on the campus of the Uniformed Services University of Health Sciences (USUHS), 4301 Jones Bridge Rd., Bethesda, MD 20814.

Contact: Kerry Davis, Science Applications International Corp. (SAIC), 5340 Spectrum Dr., suite N, Frederick,

MD 21703, 301-619-7078, FAX 301-698-6188, e-mail:

kerry.davis@det.amedd.army.mil.

Registration: Preregistration is required and must be completed by April 12, 2002. Contact Kerry Davis (see "Contact" for address) for information about registration, including registration fees. Seating is limited.

If you need special accommodations due to a disability, please contact Kerry Davis at least 7 days in advance of the meeting.

Transcripts: You may request public workshop transcripts in writing from the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A-16, Rockville, MD 20857. The transcripts will be available approximately 15 working days after the meeting at the cost of 10 cents per page. The public workshop transcript will also be available on the Internet at <http://www.fda.gov/cber/minutes/workshop-min.htm>

SUPPLEMENTARY INFORMATION: CBER, in cooperation with DoD, is holding a public workshop entitled "Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity." The workshop will discuss: (1) Pathogenesis of *Bacillus anthracis*, (2) animal models of anthrax, (3) immunogenicity data available from human clinical trials of anthrax vaccines, and (4) identification of surrogate markers and possible strategies. The workshop's goal is to expedite the development of anthrax vaccines by providing additional information about efficacy testing of these vaccines.

Dated: March 29, 2002.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02-8463 Filed 4-8-02; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 02N-0037]

Public Informational Meeting on Antimicrobial Resistance

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of meeting; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing the following meeting: "Public Informational Meeting on Antimicrobial Resistance." The purpose of this public

meeting is to provide the general public the opportunity to hear speakers from the agency, industry, and others to provide information on the issue of antimicrobial resistance so the public can fully participate in the public dialogue about the issue. Attendees will be invited to ask questions during the meeting.

Date and Time: The meeting will be held on April 26, 2002, from 9:30 a.m. to 4:30 p.m. Walk-in registration will begin at 9 a.m. You may submit written or electronic comments at any time, but in order for your comments to be included with others in conjunction with this meeting, please submit comments no later than 180 days after the meeting. Please include the Docket No. 02N-0037 on your comments.

Addresses: The meeting will be held at the Capital Hilton Hotel, Congressional Room, 1001 16th St. (16th and K Sts.), Washington, DC, 202-393-1000. Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. Comments should be identified with the full title and the Docket No. 02N-0037 on your comments.

For General Information Contact: Vash Klein, Center for Veterinary Medicine (CVM) (HFV-12), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, e-mail: cvmmeet@cvm.fda.gov.

For Information About Registration Contact: Ben Horsley, The Shipley Group, at 888-270-2157, FAX 888-270-2158.

Registration: Registration is required. There is no registration fee for the meeting. Limited space is available, and early registration is encouraged.

Information about the meeting and the registration form are available on the Internet at www.fda.gov/cvm, click on Antimicrobial Resistance, then scroll down to PUBLIC MEETINGS, April 26, 2002 — *Consumer Meeting on Antimicrobial Resistance*. Please mail or fax the registration form to: FDA/CVM Enrollments — The Shipley Group, Inc., 1584 South 500 West, suite 201, Woods Cross, UT 84087; Ben Horsley at 888-270-2157 or 801-298-7800, FAX 888-270-2158 or 801-298-7820. Additional information about the meeting and the agenda will be available on the Internet (www.fda.gov/cvm) before the meeting.

Oral Presentations: Please submit requests for oral presentations by April 22, 2002, to FDA/CVM, Attn: Consumer Meeting, Docket No. 02N-0037, 7500 Standish Pl., (HFV-12), rm. 3503,