On behalf of Dr Halfdan Mahler, Director-General of WHO, Dr Lu Rushan, Assistant Director-General of WHO, welcomed the participants in this meeting and expressed the concern of WHO regarding the process of reviewing substances for international control.

Dr Norman Sartorius, Director, Division of Mental Health WHO, discussed with the participants the conditions in the developing nations which must be considered in reaching decisions regarding the recommendation of substances for international control. He referred specifically to a gradual change in the attitude of people towards pain. No longer is pain accepted as a natural accompaniment of disease. The effective analgesics, widely available in the developed countries of the world, must become available for legitimate medical needs of patients in the developing countries. This availability of analgesic drugs must however take into account the fact that many such substances are capable of producing dependence and as a consequence significant public health and social problems. Therefore, regulatory arrangements must balance the legitimate medical need for psychoactive substances against their possible abuse.

The issue of this document does not constitute formal publication. It should not be reviewed, abstracted or quoted without the agreement of the World Health Organization. Authors alone are responsible for views expressed in signed articles.

Ce document ne constitue pas une publication. Il ne doit faire l'objet d'aucun compte rendu ou résumé ni d'aucune citation sans l'autorisation de l'Organisation mondiale de la Santé. Les opinions exprimées dans les articles signés n'engagent que leurs auteurs.
2. SCOPE OF THE MEETING

The charge given to the Group was:

2.1 The Director-General of WHO received a note verbale from the Secretary-General of the United Nations from the Government of Belgium (NAR/CL.24/1982 DND 421/11 (1-6)) on 8 November 1982 requesting consideration of alfentanil for placement in Schedule I of the Single Convention, 1961.

2.2 Psychoactive substances from two classes were to be reviewed:

1. Sedative hypnotics: chloral hydrate, potassium bromide and paraldehyde which were to be compared to phenobarbitone which is currently in Schedule IV of the Convention on Psychotropic Substances, 1971.

2. Agonist-antagonist opioids: butorphanol, buprenorphine cyclazocine, nalbuphine, pentazocine, with comparison to morphine, nalorphine and naloxone.

The review of pentazocine was in response to a request made to WHO during the seventh special session of the United Nations Commission on Narcotic Drugs (E/1982/13 E/CN.7/678).

3. SOURCES AND NATURE OF DATA REVIEWED

The participants were supplied with background documents covering the chemistry, pharmacology, toxicology, therapeutic usefulness, dependence potential, abuse liability, epidemiology of abuse, public health and social problems; the countries of the world where each substance is marketed, the nature of domestic controls in these countries, illicit manufacture and traffic for each of the substances under review. The background documents were supplied by various participants as well as the United Nations Division of Narcotic Drugs, INTERPOL, the International Narcotics Control Board and WHO.

In addition, information was obtained from the relevant pharmaceutical companies through the International Federation of Pharmaceutical Manufacturers Associations. This information was presented in written form for all of the participants and in addition a hearing was held on 2 March 1983 in which representatives of the concerned pharmaceutical houses (see Annex I for list of the companies participating) met with a core group of participants of the Review Group and the Secretariat.

The data presented for each substance were reviewed in the context of the criteria set forth for the inclusion of a substance in the Single Convention, 1961. If the Group decided that the substance did not meet the criteria for inclusion in Schedules I or II of the Single Convention it was next reviewed using the criteria for inclusion in Schedules I, II, III or IV of the Convention on Psychotropic Substances, 1971. The decisions reached by the Group will be reported on in this document in accordance with the above procedure.

4. REVIEW OF DRUGS FOR INTERNATIONAL CONTROL

4.1 Alfentanil

In response to a notification from the Government of Belgium requesting the addition of alfentanil to Schedule I of the 1961 Convention, the Group, in conformity with Article 3, paragraph 3 (iii) of that Convention, examined relevant evidence and found that alfentanil has a pharmacological profile closely resembling that of morphine.

The Group concluded unanimously therefore, that alfentanil is liable to similar abuse and productive of similar ill-effects as the drugs in Schedule I of the Single Convention, 1961.

The Group unanimously recommended that alfentanil be included in Schedule I of the Single Convention, 1961.
4.2 Chlormal hydrate

The Group, after reviewing the evidence unanimously concluded that chlormal hydrate did not satisfy the criteria for inclusion in either Schedules I or II of the Single Convention as set forth in Article 3, paragraph 3 (iii). Therefore, chlormal hydrate was not recommended for control in the Single Convention.

Chlormal hydrate was next considered for international control under the Convention on Psychotropic Substances, 1971. The Group unanimously recommended that chlormal hydrate not be controlled under the Convention on Psychotropic Substances since it did not satisfy the requirements as set forth in Article 2, paragraph 4 (b) for inclusion in either Schedules II, III or IV of that Convention.

4.3 Paraldehyde

The Group, after reviewing the evidence, unanimously concluded that paraldehyde did not satisfy the criteria for inclusion in either Schedules I or II of the Single Convention as set forth in Article 3, paragraph 3 (iii). Therefore, paraldehyde was not recommended for control in the Single Convention.

Paraldehyde was next considered for international control under the Convention on Psychotropic Substances, 1971. The Group unanimously recommended that paraldehyde not be controlled under the Convention on Psychotropic Substances since it did not satisfy the requirements as set forth in Article 2, paragraph 4 (b) for inclusion in either Schedules II, III or IV of that Convention.

4.4 Potassium bromide

The Group, after reviewing the evidence unanimously concluded that potassium bromide did not satisfy the criteria for inclusion in either Schedules I or II of the Single Convention as set forth in Article 3, paragraph 3 (iii). Therefore, potassium bromide was not recommended for control in the Single Convention.

Potassium bromide was next considered for international control under the Convention on Psychotropic Substances, 1971. The Group unanimously recommended that potassium bromide not be controlled under the Convention on Psychotropic Substances since it did not satisfy the requirements as set forth in Article 2, paragraph 4 (b) for inclusion in either Schedules II, III or IV of that Convention. Although only potassium bromide was formally considered, the Group noted that this conclusion would also apply to all the inorganic bromide salts since the actions of such preparations are those of the bromide ion.

4.5 Buprenorphine

The Group, after reviewing the data concluded that buprenorphine did not meet the criteria for inclusion in either Schedules I or II of the Single Convention, 1961 as set forth in Article 3, paragraph 3 (iii). In addition, the Group concluded that buprenorphine did not meet the criteria for scheduling in the Convention on Psychotropic Substances, 1971. The Group recognized, however that buprenorphine does produce a state of dependence and central nervous system depression resulting in disturbances of behaviour and hence satisfies the criteria set forth in Article 2, paragraph 4 (a). However, the Group concluded that there is currently not sufficient evidence that buprenorphine is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of buprenorphine under international control.
4.6 Butorphanol

The Group, after reviewing the data concluded that butorphanol did not meet the criteria for inclusion in either Schedules I or II of the Single Convention, 1961 as set forth in Article 3, paragraph 3 (iii).

In addition, the Group concluded that butorphanol did not meet the criteria for scheduling in the Convention on Psychotropic Substances, 1971. The Group recognized, however that butorphanol does produce a state of dependence and central nervous system depression resulting in disturbances of behaviour and hence satisfies the criteria set forth in Article 2, paragraph 4 (a). However, the Group concluded that there is currently not sufficient evidence that butorphanol is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of butorphanol under international control.

4.7 Cyclazocine

The Group, after reviewing the data concluded that cyclazocine did not meet the criteria for inclusion in either Schedules I or II of the Single Convention, 1961 as set forth in Article 3, paragraph 3 (iii). In addition the Group concluded that cyclazocine did not meet the criteria for scheduling in the Convention on Psychotropic Substances, 1971.

4.8 Nalbuphine

The Group, after reviewing the data concluded that nalbuphine did not meet the criteria for inclusion in either Schedules I or II of the Single Convention, 1961 as set forth in Article 3, paragraph 3 (iii).

In addition, the Group concluded that nalbuphine did not meet the criteria for scheduling in the Convention on Psychotropic Substances, 1971. The Group recognized, however, that nalbuphine does produce a state of dependence and central nervous system depression resulting in disturbances of behaviour and hence satisfies the criteria set forth in Article 2, paragraph 4 (a). However, the Group concluded that there is currently not sufficient evidence that nalbuphine is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of nalbuphine under international control.

4.9 Pentazocine

The Group, after reviewing the evidence, unanimously concluded that pentazocine should be placed under international control. Following extensive discussion, the Group considered how pentazocine should be controlled. It was then decided by vote that pentazocine did not satisfy the criteria for inclusion in Schedules I or II of the Single Convention, 1961 as set forth in Article 3, paragraph 3 (iii).

The Group next considered whether pentazocine should be placed in Schedule II of the Convention on Psychotropic Substances, 1971. By vote it was decided that pentazocine should not be included in Schedule II. By vote it was decided that pentazocine should be recommended for inclusion in Schedule III of the Convention on Psychotropic Substances. This recommendation was based on the evidence demonstrating that pentazocine did have the capacity to produce (a) a state of dependence and (b) central nervous system changes resulting in disturbances of mood and behaviour. In addition, pentazocine is being abused so as to constitute a public health and social problem warranting the placing of the substance under international control. The extent of the abuse of pentazocine, as well as its established medical usefulness was the basis for the Group's decision to recommend that pentazocine be included in Schedule III of the Convention on Psychotropic Substances, 1971.
WHO'S CANCER PAIN RELIEF PROGRAMME

Dr M. Swerdlow, a WHO consultant, outlined the WHO Cancer Pain Relief Programme and stressed the need for safe, effective analgesics. Of particular concern was the problem of providing such medications to patients in the developing countries where medical practitioners are only limitedly available. He cautioned the Group that these considerations must be taken into account when considering international regulations of analgesic drugs.

6. CONSIDERATIONS OF FUTURE PROGRAMMES

(i) WHO's Programme for Pain Relief in Cancer:

WHO's programme for international control and pain relief should have a close collaboration in the future. It will be helpful to know of the current use of analgesics in this programme and the relation of therapeutic use to abuse of analgesics in this context.

(ii) Drugs to be considered for future review:

The agenda for the next two reviews is established. At the review meeting to be held in September 1983 the benzodiazepines and certain related drugs will be reconsidered for possible international control. At the review meeting to be held in March 1983, amphetamine-like drugs not currently under international control will be reviewed. The subsequent review will consider uncontrolled barbiturates and related compounds. As stated in the report of the Sixth Review of Psychoactive Substances for International Control (MNH/82.44), the following list of topics were to be considered in future review meetings:

1. Derivatives and congeners of tetrahydrocannabinols with regard to their dependence potential, abuse liability and therapeutic usefulness.
2. Derivatives and congeners of sedative, hypnotic, anxiolytic and stimulant substances (e.g. amphetamine derivatives, khat) already scheduled or proposed for scheduling under both the 1961 and 1971 Conventions.
3. Analgesic drugs not subjected to international control.
4. Sedative, hypnotic and anxiolytic drugs not subject to international control.
5. Precursors and intermediates of drugs listed in schedules of both Conventions.
7. Antipsychotic and antidepressant drugs with dependence potential and abuse liability.

The Group also recommended that in preparation for the forthcoming review meetings, the United Nations agencies concerned, and particularly the United Nations Division of Narcotic Drugs, be requested to indicate, whether the substances:

(a) have been recently seized from illicit traffic, and
(b) have been put under national control because of their abuse potential and dependence liability.

(iii) The Group considered the report from the working group which met on 3 and 4 March 1983 for Consultation for the Development of Guidelines for the WHO Review of Psychoactive Substances for International Control. The Group concluded that the report would be of great value in standardizing WHO's procedures as well as providing detailed information on the procedures used by WHO to reach a recommendation for placing a substance under international control. This information may be helpful to the members of the United Nations Narcotics Commission, regulatory agencies in the countries of the world as well as to the pharmaceutical manufacturers. It was, therefore, recommended that this document be published and widely disseminated.
7. LIST OF PARTICIPANTS

Dr A. Anumonye, Professor and Head, Department of Psychiatry, University of Lagos, Lagos, Nigeria (Co-Rapporteur)

Dr Cai Zhi Ji, Associate professor, Vice-Director, Institute of Clinical Pharmacology, Beijing Medical College, Beijing, People's Republic of China

Dr A. Hamid Ghodse, Consultant Psychiatrist in charge of Drug Dependence Treatment Unit, Blackshaw Road, London, England (Chairman)

Dr H. I. Maghazaji, Assistant Professor, Baghdad University, Head of Neuropsychiatric Unit, Medical City Hospital, Baghdad, Iraq

Dr C. R. Schuster, Professor, Departments of Psychiatry, Pharmacology and Behavioral Sciences, University of Chicago, 950 East 59th Street, Chicago, Illinois, USA (Rapporteur)

Dr J. Woods, Department of Pharmacology, Medical School University of Michigan, Ann Arbor, USA (Co-Rapporteur)

Dr T. Yanagita, Director, Preclinical Research Laboratories, Central Institute for Experimental Animals, Kawasaki, Japan (Vice-Chairman)

Representatives of other organizations

United Nations

Mr P. K. Bailey, Chief, Treaty Implementation and Commission Secretariat Section, United Nations Division of Narcotic Drugs, Vienna International Centre, Vienna, Austria

International Narcotics Control Board

Dr S. Kaymakçalan, Vice-President INCB, and Chairman, Department of Pharmacology, Medical School of Ankara University, Ankara, Turkey

International Criminal Police Organization

Mr H. de Fine, International Criminal Police Organization, 26 rue Armengaud, Saint-Cloud, France

International Council on Alcohol and Addiction

Dr P. H. Connell, Director, Drug Dependence Clinical Research and Treatment Unit, The Maudsley Hospital, London, England

WHO Collaborating Centres for Research and Training in Drug Dependence

Tan Soo Choon, National Drug Dependence Research Centre, University Sains, Penang, Malaysia

Health Research Institute,* Chulalongkorn University, Bangkok, Thailand

Institute Mexicano de Psiquiatria,* Mexico

Dr J. Peachey, Addiction Research Foundation, 33 Russell Street, Toronto, Canada

* Invited but unable to attend.
National Institute on Drug Abuse

Dr. D. Jasinski, National Institute on Drug Abuse, Addiction Research Centre, P.O. Box 5180, Baltimore, Maryland 21224, USA

Mr. A. Duncan, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857, USA

WHO Secretariat

Dr. A. Arif, Senior Medical Officer in charge of Drug Dependence Programme, Division of Mental Health, WHO, Geneva

Mr. R. J. Gallagher, Legal Officer, Office of the Legal Counsel, WHO, Geneva

Dr. I. Khan, Senior Medical Officer, Division of Mental Health, WHO, Geneva (Secretary)

Dr. N. Sartorius, Director, Division of Mental Health, WHO, Geneva

Dr. M. Swerdlow, Consultant, Cancer unit, Division of Noncommunicable Diseases, WHO, Geneva

Observers

Dr. J. V. Brady, Professor of Behavioral Biology, Chairman CPPD, The Johns Hopkins University School of Medicine, 720 Rutland Avenue, Baltimore, Maryland 21205, USA

Dr. H. Coper, Institute of Neuropsychopharmacology, Free University of Berlin, 1000 Berlin, 19 Ulmen allée 30, Federal Republic of Germany

Mr. H. McClain Jr., Chief, Drug Control Section, Drug Enforcement Administration, 1405 Eye Street, N.W., Washington D.C., 20537, USA

Dr. L. Rossini, Head, Professor, Department of Pharmacology, WHO-ITA National Collaborating Drug Monitoring Centre, University of Ancona, Medical School, 601000 Ancona, Italy

ANNEX I

DISCUSSIONS WITH PHARMACEUTICAL COMPANIES

1. **Company presenting:** Bristol Myers (USA)
   - **Product:** Butorphanol
   - **Representatives:**
     - Dr Irwin Pachter, Former Vice-President of Research & Development at Bristol Laboratories - consultant
     - Dr Janice Wohltmann, Group Marketing Director at Bristol Laboratories

2. **Company presenting:** Sterling Drug Inc. (USA)
   - **Product:** Pentazocine
   - **Representatives:**
     - Dr George S. Goldstein, Vice-President and Medical Director, Sterling-Winthrop Laboratories, USA
     - Dr John B. Spooner, Medical Director, Sterling-Winthrop Group Ltd., UK
     - Dr J. Gene Hinson, Vice-President, Sterling Drug Inc., President, Sterling Africa, Middle-East, Southern Europe
     - Dr William R. Martin, Consultant, Professor and Chairman, Dept. of Pharmacology, University of Kentucky School of Medicine, Lexington
     - Mr Charles B. O'Keefe Jr., Consultant, 1907 Huguenot Road, Richmond, Virginia 23235, USA
     - Roger M. Rodwin, Esq., Assistant General Counsel, Sterling Drug Inc., 90 Park Avenue, New York, N.Y. 10016, USA

3. **Company presenting:** Reckitt and Colman (UK)
   - **Product:** Buprenorphine
   - **Representatives:**
     - Dr J. W. Lewis
     - Dr Varey, Medical Director

4. **Company presenting:** DuPONT de Nemours (USA)
   - **Product:** Nalbuphine
   - **Representatives**
     - Dr William K. Schmidt, Senior Research Pharmacologist
     - Dr Newton C. Birkhead, Director of Medical Research
     - Dr Robert I. Taber, Director of Research, DuPont Company, Glenolden Laboratory, Glenolden, Pa. 19036, USA
     - Dr Leonard Cook, Manager, CNS Disease Research.