UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

In the Matter of	)	
	)	Docket No. 84-48
MDMA SCHEDULING	)	
	)	

DIRECT TESTIMONY OF EDWARD CHARLES TOCUS, Ph.D.

I, Edward Charles Tocus, make the following statement:

I am a pharmacologist employed as Chief of the Drug Abuse Staff, Division of Neuropharmacological Drug Products, Center for Drugs and Biologics, United States Food and Drug Administration. I received my doctoral degree in pharmacology from the University of Chicago in 1959. From 1960 through 1966, I was employed as a Research Pharmacologist at Lederle Laboratories, Pearl River, New York. Since 1966, I have worked in the Division of Neuropharmacological Drug Products, Food and Drug Administration. I have served as a Reviewing Pharmacologist, Supervisory Pharmacologist, and Chief of the Drug Abuse Staff. A copy of my curriculum vitae is attached as Exhibit 1.

The Division of Neuropharmacological Drug Products evaluates the safety and effectiveness of new human drugs which affect the central nervous system. The Drug Abuse Staff is responsible for the evaluation of the safety and efficacy of drugs that are analgesics, narcotic antagonists,

hallucinogens, and drugs which are used to treat some form of drug dependency. The Drug Abuse Staff evaluates all drugs with an abuse liability which are submitted to the Food and Drug Administration. Evaluation normally occurs upon submission of an investigational new drug application (IND) or a new drug application (NDA). Approval of an IND allows the sponsor of a drug to legally administer that drug to humans.

The IND process is a continual monitoring and approval process which continues during the course of the studies conducted by the the sponsor. The Food and Drug Administration may stop the process at any time. The initial or original application for an IND must satisfy three elements. The first element concerns the chemistry of the drug. The sponsor must show the sources and purity of substances used in the manufacture of the drug. He must show how the drug is synthesized and that such synthesis is reproducible. The sponsor must show the composition of the drug, and must determine its purity. Any impurities must be identified and quantified. The second element involves submission of the results of animal toxicity studies. These studies are required to obtain information concerning the safety of the drug. The studies must show that the chemical in a biological system is not likely to produce irreversible damage at the doses proposed for human use. The third

element is a description of the clinical studies which will be conducted on humans. The studies must be defined in specific terms and include such things as the procedure to be followed, a definition of the population to be used, the dosages to be administered, the variables to be measured, the control observations, the statistical analyses to be used and provisions to prevent harm to the patients. The scientific qualifications of the investigators must be documented as well. The results of the human studies must be submitted to the Food and Drug Administration on an ongoing basis. The studies continue until terminated by the sponsor, stopped by FDA, or until sufficient scientific data is available for the sponsor to prepare a new drug application (NDA).

An NDA must be approved by the Food and Drug Administration prior to marketing a drug in the United States. The NDA generally consists of data which has been collected as part of the investigational new drug (IND) process. The data in the new drug application must include carcinogenic studies in animals, reproductive studies in animals, stability determinations of the product, side effects in humans, samples of labeling, and sufficient results from controlled studies to show that the drug is safe and effective in humans for the therapeutic purpose advanced by the sponsor. If the drug which is the subject

of the NDA has any chemical or pharmacologic properties which indicate that it might have an abuse liability, the NDA submission must include specific drug abuse studies.

New drug applications have been required prior to drug marketing since 1938. The statutory requirements for new drug applications and procedures regarding submission, approval, withdrawal, and revocation are found in Section 505 of the Food, Drug and Cosmetic Act. 21 U.S.C. § 355. A copy of this section is attached as Exhibit 2.

The Drug Abuse Staff of the Food and Drug Administration evaluates data included in the NDA submission, the published literature and information received from other sources such as the Drug Enforcement Administration in order to determine whether a drug has an actual and/or relative potential for abuse. After evaluation of a compound for abuse potential, the Drug Abuse Staff makes a recommendation to the Division Director, then to the Commissioner of the Food and Drug Administration (FDA) and finally with concurrence of the National Institute on Drug Abuse, to the Assistant Secretary for Health of the Department of Health and Human Services as to the propriety and necessity of scheduling such a substance under the Controlled Substances Act. As part of my duties I initiate and prepare control recommendations to be submitted to the Drug Enforcement Administration by the Assistant Secretary

for Health for drugs which have been approved in the NDA process. There are occassions when drugs which have not been evaluated by the Drug Abuse Staff as part of the NDA process come to the attention of the staff. This occurs primarily when the Drug Enforcement Administration submits a control recommendation to the Assistant Secretary for Health for a scientific and medical evaluation and recommendation as required by the Controlled Substances Act. As part of my duties I evaluate control recommendations submitted to the Assistant Secretary for Health by the Drug Enforcement Administration and prepare the control recommendations which will be sent to the Administrator of DEA by the Assistant Secretary for Health.

In March, 1984 the then-Administrator of the Drug Enforcement Administration sent a letter and a document entitled, "Schedule I Control Recommendation Under the CSA for 3,4-Methylenedioxymethamphetamine (MDMA)" to the Assistant Secretary for Health. The DEA Administrator asked for a scientific and medical evaluation and a scheduling recommendation for MDMA in accordance with 21 U.S.C. § 811(b). The control document sent by DEA contained information concerning the abuse potential, references from the scientific literature and statistics on the illicit trafficking of MDMA which had been collected by DEA staff. The March 13, 1984 letter to the Assistant

Secretary for Health and the control document were forwarded to me for evaluation. Prior to the receipt of information from the Drug Enforcement Administration, I had had no specific knowledge or information concerning the drug MDMA. I reviewed the data contained in the DEA document, and searched the files of the Food and Drug Administration for information concerning the drug 3,4-methylenedioxymethamphetamine (MDMA). I found no reference in the files of the Food and Drug Abministration to this drug. There were no investigational new drug applications or approvals, there were no new drug applications or approvals, and there was no indication that any sponsor had informed FDA that such submission would be forthcoming. Based on the review of the files of the Food and Drug Administration, I was able to conclude that the substance or drug 3,4-methylenedioxymethamphetamine had not been approved for human research studies, or for marketing in the United States. I then applied the eight factor analysis required by the Controlled Substances Act using the data which had been submitted by the Drug Enforcement Administration in their control document. My conclusions based upon the application of the data supplied by DEA to the eight factor analysis are as follows:

1. The actual or relative potential for abuse of MDMA is evidenced by its chemical and pharmacological similarity

to the Schedule I controlled substance MDA. Actual abuse of MDMA has been shown by submissions of MDMA to DEA laboratories, seizures of MDMA, evidence of clandestine manufacture of MDMA, and mentions of MDMA in the Drug Abuse Warning Network. MDMA has been identified in 34 submissions to DEA laboratories from 12 states in an 11 year period. Clandestine laboratory seizures involving the manufacture of MDMA have been identified in four states. MDMA has received 8 Drug Abuse Warning Network (DAWN) mentions and one medical examiner report since 1972. These mentions indicate the existence of human use of MDMA.

2. Scientific studies have shown that the pharmacological effect of MDMA is similiar to that of MDA. MDMA and MDA both have analgesic activity in several procedures in mice, and both substances have been shown to produce increased motor activity or stimulant activity in mice. When tested in dogs and monkeys MDMA produced a spectrum of central nervous system, autonomic nervous system and motor activity similar to that obtained with MDA and mescaline, also a Schedule I controlled substance. Tests in humans have shown MDMA to be similar to MDA. Both substances produced a change in consciousness without hallucination, a decrease in tension, a heightening of mood, and an increase in acoustic, visual and tactile perception. Both MDMA and MDA cause increased heart rate and mydriasis.

3. The current scientific knowledge concerning MDMA is that it is chemically and pharmacologically related to the substance 3,4-methylenedioxyamphetamine (MDA) which is currently a Schedule I controlled substance under the Controlled Substances Act. This relationship is the same that amphetamine bears with methamphetamine, both Schedule II controlled substances, which is that there is a methyl group on the nitrogen of the amine. This difference is reflected in the chemical names of the substances methamphetamine and 3,4-methylenedioxymethamphetamine, which contain "meth" for the methyl group. MDMA can be synthesized easily using readily available materials. Several alternative pathways for the synthesis of MDMA have been described in the scientific literature. Several synthetic methods of making MDMA have also been identified through the chemicals seized in clandestine laboratories.

4. The history and current pattern of abuse of MDMA was shown by DEA in its document describing laboratory submissions, seizures, clandestine laboratory operations, and DAWN mentions.

5. The scope, duration, and significance of abuse were shown in the DEA document by describing evidence of consistent illicit trafficking since 1970.

6. MDMA can produce harm to the public health. Studies in experimental animals which were included in the

DEA document indicate that MDMA is more toxic than mescaline and less toxic than MDA on a milligram basis.

7. There was no specific data available concerning the psychic or physiological dependence liability of MDMA.

8. MDMA is not an immediate precursor of a substance already controlled under the Controlled Substances Act.

After reviewing the eight factor analysis I concluded that MDMA satisfies the three criteria for Schedule I control. MDMA has a high potential for abuse. This is evidenced by its pharmacological similarity to the Schedule I substance MDA and evidence of its actual abuse. MDMA has no currently accepted medical use in treatment in the United States. This is because MDMA has not been approved by the FDA for marketing in this country. It is not a grandfathered drug, it does not have an approved NDA, and it has not been approved for over-the-counter use. MDMA lacks accepted safety for use under medical supervision. A substance cannot be deemed safe unless FDA has determined that there is scientific data which demonstrates that a substance can be given to humans without irreversible harm. No scientific data has been supplied to FDA which would demonstrate the safety of the drug, MDMA. A review of the available scientific literature on MDMA does not support the safety of the drug for use under medical supervision. If the safety of a drug cannot be established, then the drug lacks accepted safety.

After review and evaluation of the DEA document in conjunction with the eight factor analysis, finding that MDMA has not been approved by the Food and Drug Administration for marketing in the United States, and in the interest of preventing actual and significant harm to the public health, I concluded that MDMA should be controlled in Schedule I of the Controlled Substances Act.

I declare under penalty of perjury that the foregoing statement is true and correct.

Executed on April 22, 1985.

Edward Charles Tocus

Edward Charles Tocus, Ph.D.

EXHIBIT 1

PROFESSIONAL RESUME

EDWARD C. TOCUS, A.B., M.S., Ph.D.

EDUCATION:

Iowa State College, Ames Iowa, 1942-1944, 1946-1947
Two years completed in Chemical Engineering.

Grinnell College, Grinnell, Iowa, 1947-1950
Three years completed in Biology and Chemistry in a Pre-Med program.
A.B. degree.

Washington University, St. Louis, Missouri, 1950-1951
One year graduate school in Chemistry.

University of Chicago, Chicago, Illinois, 1953-1956
Three years completed in graduate school in Pharmacology.
M.S. degree.

University of Chicago, Chicago, Illinois, 1956-1959
Three years completed in graduate school in Pharmacology.
Ph.D. degree.

EXPERIENCE

Washington University School of Medicine, Department of Radiology, Research Assistant, 1951-1953.

Receive, assay and dispense radioisotopes. Assist in developing medical uses of isotopes. Perform thyroid function studies using I-131. Assist gynecologist in treating cervical cancer with Au-198.

University of Chicago School of Medicine, Department of Medicine, Research Associate, 1953-1960.

Perform wet combustion of tissues and determine C-14 content. Develop a continuous expiratory C-14CO_2 analyzer for <u>in vitro</u> analysis of the rate of oxidation of C-14 labelled metabolic intermediates to humans. Liaison between biologist and mathematician for applying IBM and UNIVAC computers to biological problems. Transport CO_2 apparatus to Geneva, Switzerland, 1958, and exhibit for U.S. at 2nd International Conference on Peaceful Uses of Atomic Energy.

University of Chicago School of Medicine, Department of Pharmacology, Research Associate, 1953-1959.

Establish and operate an isotope pharmacy, train pharmacists at Argonne Cancer Research Hospital. Synthesize and label octoiodofluorescein

(OIF). Determine toxicity of OIF in mice. Transplant mouse brain tumors and determine efficacy of OIF in tumor localization. Establish a human brain tumor localization program with Department of Neurosurgery. Develop equipment and technique for brain tumor scanning with OIF I-131. Receive and analyze clinical data concerning toxicity distribution and excretion of OIF I-131. Report results in dissertation.

Lederle Laboratories, American Cyanamide Company, Pearl River, New York, Department of Endocrine Research, 1960-1966.

Plan, organize and develop a screening program for detecting hypoglycemic activity of chemicals in experimental animals. Train personnel in efficient operation of screening program. Develop program for evaluation of compounds found to possess hypoglycemic activity. Develop new assay methods and automate existing methods when possible. Plan and execute experiments in diabetes research. Maintain records and report all findings.

Lederle Laboratories, American Cyanamide Company, Pearl River, New York, Department of Toxicology Research, 1966.

Plan protocol for 30, 60, 90, days, 6 months or one year's preclinical toxicity studies in rats or dogs. Collect and evaluate pre-dose, during-dose and recovery data from clinical observations, function studies and clinical chemistry studies in animals. Coordinate during life with postmortem pathology studies. Maintain all records and report all results for assigned preclinical toxicity tests. Develop new tests and apply new methods for the study of toxic responses to drugs. Supervise and schedule professional and technical personnel associated with specific projects.

Food and Drug Administration, Center for Drugs and Biologics, Division of Neuropharmacological Drug Products, Washington, D.C., 1966 to present.

1. Review pharmacological data in IND and NDA applications. Evaluate studies for design, performance and results. Prepare written reports and recommend additional studies based on proposed clinical trials. Confer with company representatives concerning toxicity, pharmacological, metabolic and reproduction studies in animals.

2. Lecturer in training course for FDA Inspectors. "Reviewing INDs and NDAs, one-hour presentation to inspectors, 1968, 1969. "Investigating Preclinical Studies", one-hour presentation 1969.

3. FDA representative to the Post Office as an expert witness for the Office of the General Counsel. Case against Ama-Tol Industries, December 18, 1967 resulting in a fraud order. Case against Dalidex, Inc., August 14, 1968 resulting in a favorable decision.

4. Classified as Expert by FDA June 19, 1968 in the field of pharmacology. Representative of Bureau of Medicine at scientific and committee meetings.

5. Acting supervisory pharmacologist in Division of Neuropharmacological Drug Products from November 1968 to May 1969 involving the supervision and evaluation of work of three Ph.D. pharmacologists, GS-12 and 13, from May 1970-1972 supervising five Ph.D.s and two M.S. pharmacologists.

6. Advisor and consultant to medical officers, chemists and pharmacologists on matters pertaining to the performance and evaluation of pharmacological research.

7. Chief of the Drug Abuse Staff of the FDA, Center for Drugs and Biologics from November 1971 to present. Responsible for coordinating the activities and information on drug abuse research for FDA. Representative for the FDA with officials of other government agencies, industry, educational institutions and professional societies in the area of drug abuse.

SERVICE:

U.S. Army Air Force 1944-1946

AWARDS AND ACTIVITIES:

Abbott Fellow for Radioisotope Research
Argonne Cancer Research Hospital
Chicago, Illinois 1953-1955

Member of the U.S. Delegation to the Second International Conference for the Peaceful Uses of Atomic Energy. Geneva, Switzerland, 1958.

FDA representative in the area of drug abuse at regular committee meetings of the American Medical Association, National Academy of Science, Drug Enforcement Administration, National Institute on Drug Abuse, and American College of Neuropsychopharmacology.

Consultant to the World Health Organization on Drug Abuse Treatment and Control.

Consultant to the Pan American Health Organization on Developing Drug Abuse Prevention Programs.

Consultant to various state drug abuse authorities.

Advisor to Congressional Committees in the area of drug abuse.

Member of White House working groups to develop a national strategy on preventing drug abuse.

FDA Commendable Service Award, 1981.

Bibliography

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"An Historical Perspective on Delta-9-tetrahydrocannabinol and Cannabis sativa L.", Chapter 4, Treatment of Nausea and Vomiting in Cancer Chemotherapy. Eds. D.S. Poster, et al, 1981, Masson Press, New York, New York.

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"The Effects of Tripelennamine Alone and in Combination with Opiates to Produce Antinociception in Mice." Life Sciences 32, 14, 1983.

3. Leroy, G.V., Okita, G.T., Tocus, E.C., Charleston, D.
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"Continuous Measurement of Specific Activity of $C^{14}O_2$ in Expired Air". International Journal of Applied Radiation and Isotope, 7, p. 273-286, 1960.

5. Sherman, A.I., Ter-Pogossian, M., Tocus, E.C.
"Lymph-Node Concentration of Radioactive Colloidal Gold Following Interstitial Injection. Cancer 6, #6, November 1953.

6. Tocus, Edward C.
"Clinical Use of Narcotic Antagonists in Opiate Addiction", Chapter 30, Drug Addiction, 2. Eds. Singh, Miller, Lal, Futura Publishing Co., Mt. Kisco, New York, 1972.

7. Tocus, Edward C.
"FDA Requirements for the Study of Endorphines." Endorphines in Mental Health Research, Chapter 45. Eds. Earl Usdin, et al, 1979, The Macmillan Press Ltd., London.

8. Tocus, Edward C.
"Food and Drug Administration's Requirements for Markers." Controlled Clinical Trials 5, #4, December 1984.

9. Tocus, Edward C.
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10. Tocus, Edward C., Bauer, V.J.
U.S. Patent 3,341,413 "Compositions Containing Pyrazolylpyridinium Salts and Method of Administration." September 12, 1967.

11. Tocus, Edward C., Boshart, C.R.,
"A New Class of Hypoglycemic Agents". J. of Medicinal Chemistry, Vol. 11, p. 981, September, 1968.

12. Tocus, Edward C., Cavallo, M.
"The Production of Alloxan Diabetes in Mice." Federation Proceedings 20, #1, March 1961.

13. Tocus, Edward C., Morris, L.A., Nightingale, S.L.
"Patient Information Program of the FDA." J. Psychoactive Drugs 15, #1-2, January-June 1983.

14. Tocus, Edward C., Nelson, R.C., Vocci, F.J.
"Regulatory Perspectives and the Benzodiazepines." J. Psychoactive Drugs 15, #1-2, January-June 1983.

15. Tocus, Edward C., Okita, G.T.
"Localization of Mouse Brain Tumors with Octoiodofluorescein 1-131."
"Federation Proceedings 18, #1, April 1959.

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"Protein Binding of Octoiodofluorescein 1-131." Federation Proceedings 19, #1, March 1960.

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18. Tocus, Edward C., Okita, G.T., Evans, J.P., Mullan, S.
"The Localization of Octoiodofluorescein 1-131 in Human Brain Tumors." Cancer Research 15, #1, January-February 1962.

19. Tocus, Edward C., Tonelli, G.
"Lack of Hypoglycemic Activity of Insulin After Intestinal Administration to the Rabbit." Diabetes 14, p 696-699, November 1965.

EXHIBIT 2

§ 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

(b) Filing application; contents

Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary

finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j) of this section or to comply with the notice requirements of section 360(j)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals or the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28. The commencement of proceedings under

this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section.

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any control used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which approval of an application filed pursuant to subsection (b) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: *Provided, however,* That regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(June 25, 1938, ch. 675, § 505, 52 Stat. 1052; 1940 Reorg. Plan No. IV, § 12, eff. June 30, 1940, 5 F.R. 2422, 54 Stat. 1237; 1953 Reorg. Plan No. 1, § 5, eff. Apr. 11, 1953, 18 F.R. 2053, 67 Stat. 631; June 11, 1960, Pub. L. 86-507, § 1(18), 74 Stat. 201; Oct. 10, 1962, Pub. L. 87-781, title I, §§ 102(b)-(d), 103(a), (b), 104(a)-(d)(2), 76 Stat. 781-783, 784, 785; Aug. 16, 1972, Pub. L. 92-387, § 4(d), 86 Stat. 562.)