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HEALTH CONSEQUENCES OF MARIHUANA ABUSE: RECENT FINDINGS AND THE THERAPEUTIC USES OF MARIHUANA AND THE USE OF HEROIN TO REDUCE PAIN

A REPORT

OF THE

SELECT COMMITTEE ON NARCOTICS ABUSE AND CONTROL

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PREFACE

The Select Committee, in addressing its primary mission, "narcotics abuse and control," is, of course, principally directed to the harmfulness of drugs through use or abuse—whether licit or illicit, or whether of natural origin or synthetic. The Committee, however, is not unmindful of the continuing research of drugs to seek health benefits. This present research involves substances which are illicit, principally marihuana.

The Committee sought to determine the status of present research to determine the harmfulness of marihuana. The results of the Committee's hearing on this subject are set forth in Part I of this report.

Recognizing the controversy surrounding the therapeutic uses of marihuana, and to assure a balanced perspective in considering the issue, the Committee held a subsequent hearing to determine the status of the current research on the therapeutic uses of marihuana and to examine the factors forming the basis of the controversy. The hearing also included an examination of the issue to allow the use of heroin to relieve pain and suffering for the terminally ill. The results of this hearing are set forth in Part II of this report.

The purposes of both hearings and this report are not only to examine objectively the medical research and findings of the harmfulness of drugs and other substances, but also to examine any medical benefits recognizing that the main and sole purpose to be served is the health and well-being of our citizens.

CONTENTS

PART I.—HEALTH CONSEQUENCES OF MARIHUANA: RECENT FINDINGS

	Page
Introduction	1
Testimony of Dr. Gabriel Nahas	1
Testimony of Dr. Norman Zinberg	3
Testimony of Dr. Sidney Cohen	4
Panel discussion of marihuana's health hazards	7
Testimony of Dr. William Pollin, Director of the National Institute on Drug Abuse	9
Testimony of Dr. Snyder	13
Panel discussion	14
Findings and conclusions	15
Recommendations of the Select Committee	16
Appendix	17

PART II.—THERAPEUTIC USES OF MARIHUANA AND THE USE OF HEROIN TO REDUCE PAIN

Introduction	23
Background	24
Patient Panel	25
Ann Guttentag	25
Richard Csandl	26
Robert Randall	26
Cancer Researchers Panel	27
Dr. Phillip Schein	27
Dr. Steven Sallan	30
Dr. Solomon Garb	30
Discussion	31
Communications	33
Glaucoma Panel	34
Dr. John Merritt	34
Dr. Carl Kupfer	34
Heroin Panel	35
Judith Quattlebaum	35
Dr. Allan Mondzac	35
Discussion	36
Federal Panel	36
National Cancer Institute (NCI)	36
Food and Drug Administration (FDA)	37
National Institute on Drug Abuse (NIDA)	39
Drug Enforcement Administration (DEA)	40
National Eye Institute (NEI)	41
Interagency Committee on Pain and Discomfort	42
Discussion	43
THC	43
Marihuana	44
Heroin	46
Recommendations	47
Appendix	49

PART I.—HEALTH CONSEQUENCES OF MARIHUANA: RECENT FINDINGS

INTRODUCTION

Intent upon clarifying the health hazards of marihuana use, the Select Committee held two hearings on this drug which is smoked by an estimated 30 million to 50 million Americans. On July 17 and 19, 1979, the opinions of private researchers and government experts were sought in hopes of achieving a consensus on the effects of marihuana in relation to: psychomotor function, learning ability, pulmonary/respiratory function, endocrine and reproductive systems, immune systems, genes and chromosomes, and brain function.

TESTIMONY OF DR. GABRIEL NAHAS

Dr. Gabriel Nahas of the Columbia University Medical School began his testimony by stating that marihuana or *Cannabis savita* consists of over 380 chemicals, 60 of which are cannabinoids unique to the cannabis plant. In addition to the psychoactive cannabinoid delta-9-tetrahydrocannabinol (THC), there are nonpsychoactive cannabinoids such as cannabinol. Because cannabinoids are fat soluble, it takes 30 days to eliminate a dose of THC from the body.

The brain is the target organ for THC. A billionth of a gram of THC affects the brain, producing euphoria and detachment. THC also disrupts the production of certain brain transmitters in the hypothalmus which control the hormones regulating sexual function. These hormones in turn control the maturation of ovum or sperm which are impaired by the use of cannabis. Any concentration of psychoactive cannabinoids will impair the ability of cells to produce protein and nucleic acids, thereby inhibiting cell function and cell division.

Clinical evidence indicates that chronic marihuana smoking, in a controlled environment, is associated with abnormal standard lung function tests, and early symptoms of airway obstruction. Experimental studies indicate that marihuana impairs the immunity defense that protects the lung against bacteria. Other studies have shown that 6 months' exposure to marihuana smoke produces disseminated, organized lesions of the lung and cholesterol deposits, which are signs of tissue destruction. Therefore, there is now ample evidence to indicate that the smoking of marihuana induces some changes in the lung which, on a long-term basis, might be accompanied by alterations. Although these alterations can only be detected through long-term epidemiological studies, present research indicates that severe abnormal pathology might develop, according to Dr. Nahas.

Marihuana affects both male and female reproductive functions. It has been observed in many subjects studied in a controlled environment that heavy marihuana smoking is associated with a decrease in

sperm count, a decreased sperm motility, and an increased appearance of abnormal forms of sperm.

In a discussion of the mechanism involved in marihuana's affect on reproductive function, Dr. Nahas noted that in especially heavy smokers, the byproduct of the drug and other cannabinoids might accumulate in the testes. He defined a heavy smoker as an individual who smokes from 1 to 10 cigarettes a day.

Dr. Nahas acknowledged that different individuals respond variably to large or small doses of marihuana. "There are some individuals who are able to take a lot of marihuana and present relatively minimal side effects, while others with small doses would have even greater effects." However, he warned that the drug's effects on young "growing individuals" are more far-reaching due to the fact that their central nervous system is developing and structuring itself.

Dr. Nahas concluded his discussion of marihuana's affect on male reproductive function by saying that the disruption of this function can be attributed to a direct mechanism produced by the effect of small amounts of marihuana on the brain, and a secondary mechanism due to the production of the product in the sex glands themselves.

Although research on marihuana's affect on the female reproductive function has not been performed on humans (due to a Food and Drug Administration ban on drug research with females of child-bearing age), studies on primates indicate that a single dose of THC produces a decrease in the hormones controlling the ovarian cycle. Observation studies conducted by Drs. Kolodny and Bauman found that young women who smoke daily or at least 3 times a week have a 36 percent increase in irregularities of their menstrual cycle as well as a disruption of prolactin, a hormone controlling female reproduction and cycling. These women also experienced an increase in testosterone.

Dr. Nahas raised the specter of potential damage to the children of a marihuana user: "But one can imagine that maybe there might be also a chance, if an impaired ovum or sperm were fertilized, there might be some damage to the offspring."

Studies with rodents, rats, mice, rabbits, and primates have shown that marihuana products administered to pregnant females are associated with embryo and fetal toxicity. The surviving offspring of these animals also have a lighter body and brain weight, and their brains are deficient in certain nucleic acids.

In his discussion of marihuana's affect on the brain, Dr. Nahas reported on research conducted by Dr. Heath who found persistent brain wave changes in monkeys exposed to marihuana smoke. Dr. Heath found that brain tissue viewed under an electron microscope shows structural changes in the synapses (switches which transmit signals to the nerve cell).

Dr. Heath's research also indicated that there are other alterations of brain structure—such as inclusion of the nucleus of the cell. Dr. Nahas stressed that these studies have yet to be confirmed by clinical observations which are very difficult to carry out.

Dr. Nahas provided the Committee with a brief summary of various studies on marihuana's affects on the brain:

> Rodents chronically fed THC exhibit specific impairment of learning a specific motor skill.

Dr. Reese Jones in California reported irritability, discomfort, hyperkinesia, nausea, and abdominal distress in subjects withdrawing from large amounts of THC.

It has been reported that THC triggers epileptic seizures in experimental models and, thus, should not be used by epileptics.

Acknowledging that the potent pharmacological properties of THC have led researchers to use it in the experimental treatment of asthma, glaucoma, and nausea associated with cancer therapy, Dr. Nahas testified that the latest medical panel on this subject concluded that marihuana is not a medicine—and should not be used as such. However, he clarified that THC and Nabilone might become medicines if controlled clinical trials prove them more effective than drugs currently in use.

In a report on specific studies in this regard, Dr. Nahas indicated:

Dr. Walter Jay of the University of Chicago found that glaucoma patients using Nabilone presented a decrease in intraocular pressure. However, it has not been proven that Nabilone is more effective than Pilocarpine or Timerol, the drugs currently in use for ocular pressure.

Studies of marihuana's affect on asthma indicate that THC, although capable of causing significant bronchodilation, has a locally irritating effect on airways.

Dr. Frytak of the Mayo Clinic, in a comparison of 9-THC with phenothiazine and prochlorperazine on patients who were having cancer chemotherapy, shows that while THC evidences antiemetic activity, it is not superior to a standard phenothiazine antiemetic. However, THC induces "significantly more toxicity," said Dr. Nahas, and, thus, is undesirable for treatment.

Dr. Nahas concluded his testimony by stating that only longitudinal, epidemiological studies of marihuana-smoking populations may document the pathological effects of long-term cannabis usage. Thus, it will take 2 to 3 decades to write the human pathology of marihuana.

Subsequently, Dr. Nahas testified that there are four groups of people who should be warned, "forthwith," of the health risks associated with marihuana usage:

(1) Adolescents, whose brains and neurohormonal regulatory systems are still developing and integrating;

(2) Epileptics who may experience seizures upon ingesting THC;

(3) Persons with a tendency to schizophrenia and mental illness;

(4) Women who wish to have children.

TESTIMONY OF DR. NORMAN ZINBERG

Dr. Norman Zinberg of Harvard University testified that every culture with the possible exception of the Eskimos has used intoxicants, and marihuana has been one of the most popular. He feels the debate over the use of marihuana has been more intense than that concerning alcohol and cigarettes. This is because pot has been introduced in a relatively short period of time—15 or 16 years—just when the other two intoxicants have been discovered to be very dangerous. He said, "We have to try to separate the effects of the illicitness of marihuana

per se from the effects of the drug itself; and that is not an inconsiderable problem . . ."

Dr. Zinberg acknowledged the existence of certain of marihuana's effects, but declined to specify the extent of any resulting hazards. "For example, I think it is absolutely true that THC does not dissolve in aqueous solution, and stays in the body longer than other substances . . . Whether or not the fact it stays in the body, per se, causes any difficulty is another issue entirely."

According to Dr. Zinberg, there is not a single known fatality caused by marihuana alone among those millions who have used the drug. He considers this a remarkable record considering the deaths caused by other active substances such as aspirin. Dr. Zinberg summarized briefly his opinion of some of the recent scientific research on marihuana: (1) Marihuana as a cause of psychoses is no longer an issue; (2) marihuana does not cause crime; (3) regarding marihuana's effect on testosterone levels, he questioned the significance of lowered levels; (4) there is little substantial evidence that marihuana causes brain damage. This important area requires further study; (5) there is still no definitive statement on marihuana's impact on immune bodies; (6) regarding the drug's affect on the lungs, Dr. Zinberg said, "The idea that smoking a great deal of anything would be bad for your lungs, I think, is absolutely true; and I have no question about it, etc." Dr. Zinberg added that the drop in age of first use is a very serious occurrence.

In a discussion of the legalization of marihuana, Dr. Zinberg said that he was not in favor of legalizing marihuana. ". . . if you tried to legalize marihuana, you would have another gun control issue, another abortion issue. You would have a tremendous polarization; and I think polarization only leads to heat. It doesn't lead to light."

TESTIMONY OF DR. SIDNEY COHEN

Dr. Sidney Cohen, University of California in Los Angeles, disagreed with Dr. Nahas' view that marihuana is not a medicine. He said, "If we think of it as a drug, as a medicine, that has a potential for harm and a potential for good, we might be on the right track in resolving this biased impasse that we are at." Dr. Cohen acknowledged that there are "great gaps" in the research knowledge on marihuana. Good research on this drug has only existed for the past dozen years, he said.

Dr. Cohen reviewed his shifting position on marihuana over the years. Compared to the casualties from LSD, amphetamine, and heroin, marihuana was a relatively "trivial weed" in the 1960's. Domestic marihuana had practically no THC in it, he said, and Mexican pot had about 1 percent. Adults used the drug a couple of times a week and, as far as Dr. Cohen was concerned, "very few people were getting hurt." Emerging research reports and a change in the street scene caused Dr. Cohen to shift his views in the 1970's. These new patterns of marihuana usage include: (1) younger children becoming involved, (2) increased numbers who smoke daily and often many times a day, and (3) more potent marihuana (from 5 to 7 percent THC) readily available from Colombia, Thailand, and the United States. All of these trends, he said, compel a reevaluation of our attitudes concerning the hazards of the drug. Consistent preteenage consumption of

marihuana is far more serious than occasional adult smoking for two reasons, according to Dr. Cohen: the preteenager and teenager is involved in an intensive learning period, "struggling to develop techniques of coping with life's frustrations and stresses . . . A youngster who spends this time in an intoxicated state remains psychologically immature," he said.

Second, this developmental period in a young person's life is the time when the habits of a lifetime are established. To start a "career" of smoking marihuana during elementary or junior high school places these individuals at great risk.

Later, during the panel discussion, he said that although there are some individuals who feel that almost all hard drug use begins with marihuana, "the only connection between marihuana and heavier drugs is that marihuana may be the first illicit drug used . . ."

Dr. Cohen's testimony emphasized the affects of marihuana on pulmonary, hormonal, and mental functions. Chronic daily smoking will eventually produce a narrowing of the medium and large sized airways, resulting in a decrease in of the diameter of the bronchial tubes. The airway resistance of smokers increases about 25 percent over that of nonmarihuana smokers. However, this airflow reduction should not produce symptoms except during maximal exercise. An individual would not notice any effect until he tried to assert himself, added Dr. Cohen. This narrowing of the airways, however, is secondary to an inflammation of the lining of the trachea and bronchi. Dr. Cohen stated that it has been recognized clinically that sustained smoking of marihuana or hashish results in chronic bronchitis and pharyngitis.

It is the coal tars present in marihuana smoke that produce the inflammation. Although marihuana tars could be compared to tobacco with a high tar content, Dr. Cohen cautioned that there are two important differences. First, although a heavy tobacco smoker would smoke 30 or more cigarettes a day, a "pothead" uses one or more "joints" a day. This difference would appear to decrease the risk for the marihuana user, according to Dr. Cohen. However, the technique of inhaling marihuana is different from smoking a tobacco cigarette. The marihuana smoke is deeply inhaled, retained in the lungs for as long as possible, and then exhaled. "This method of smoking exposes the hundreds of substances in the coal tar to direct contact with the cells of the tracheobronchial tree for much longer periods during each inhalation than tobacco smoking does," he said.

Chronic coal tar exposure may also lead to possible cancer production. Dr. Cohen noted that Hoffman's research suggests that cannabis smoke contains about 50 percent more co-carcinogens, tumor initiators, and cilia-toxic agents than tobacco smoke.

Although nothing is yet known of the combined effects of tobacco and marihuana smoking—a frequent occurrence—Dr. Cohen's guess is that they are additive in carcinogenicity.

As for sex hormone changes, the significance is not always clear regarding changes in sex hormone levels. Many questions have arisen as a result of the studies concerning the effects of marihuana on animal sexuality. "The animal work is highly suggestive that profound effects are possible, but changes in an animal should not be directly translated to the human experience," according to Dr. Cohen.

He advised, however, that it would be prudent to abstain or reduce marihuana use to a minimum during critical phases of psychosexual development—such as pregnancy and adolescence.

Regarding psychological effects, Dr. Cohen warned that it is the long-term, heavy juvenile consumer who seems to be at particular risk. Adolescent potheads who lose drive, ambition and goal-direction as a result of their smoking practices are often described as having the "antimotivational syndrome." Dr. Cohen cautioned that for some of these adolescents, marihuana has played only a secondary role in their dropout from society—the drug—simply reinforced their withdrawal and passivity.

It is Dr. Cohen's impression that the antimotivational syndrome is a special name for the sedative quality of marihuana. "Any young person who takes other sedatives during the day—alcohol, volatile solvents, sleeping pills, tranquilizers, etc., will also develop the so-called antimotivational syndrome." The pleasant, dreamy state invoked by marihuana can produce a desire to continue using the drug. Dr. Cohen noted that there are some highly-motivated youths who can smoke a great deal of pot and still overcome the loss of drive that can be induced by heavy marihuana use.

Of greater consequence than the antimotivational syndrome is the "burnout," according to Dr Cohen. This condition can occur after months or years of heavy marihuana usage. Even when the "burnout" is experiencing a period of non-drug use, the person appears dulled, mildly confused, and seems to have a diminished attention span. "Their mood is flat, thinking ability impaired, and the psychiatric diagnosis is usually 'organic brain dysfunction' or some variant thereof," said Dr. Cohen.

If these burnouts can be persuaded to stop using marihuana, many make progress toward recovery after several weeks or months. Some of these individuals may recollect their "burnout" days, recognizing their former impairment. Dr. Cohen expressed doubt that all of these burnouts would recover if they stopped their marihuana use. "It may be the pot equivalent of the chronic brain syndrome of the alcoholic—actual tissue damage due to the toxins involved."

In a brief statement of his current position on the health hazards of marihuana, Dr. Cohen offered the following points:

(1) Pregnant women should not use cannabis.

(2) Driving under the influence of this drug can be hazardous to one's health and to the health of those in the vicinity. Later in the hearing, Dr. Cohen stated that marihuana impairs immediate memory, peripheral vision, reaction time, and certain aspects of perception. Furthermore, a lot of youths who smoke pot, also drink beer with it, causing an additive effect on driving.

(3) Young people should be discouraged from its use, particularly heavy use.

(4) Those individuals with lung disease should avoid the drug.

(5) People with heart disorders may be further impaired by the acceleration of the heart that cannabis produces.

(6) Preschizophrenic and schizophrenic people may develop or exacerbate a psychotic break in connection with marihuana use.

(7) The infrequent adult use of marihuana (less than once a week) will probably not result in ill effects unless the smoker

happens to experience one of the uncommon, acute reactions, or gets into his car and drives.

(8) Continued study of the therapeutic potential of cannabis is desirable, particularly for the management of intractable nausea and vomiting for the wide angle glaucoma.

Later during the hearing, Drs. Zinberg and Nahas agreed with each of the above eight points. During the second hearing, Dr. William Pollin, Director of the National Institute on Drug Abuse expressed general agreement with these points. Dr. Pollin suggested a few modifications:

For example, point No. 6, when it speaks of "preschizophrenic and schizophrenic people may develop or exacerbate a psychotic break in connections with the effects of THC," I would broaden that a bit to say that there are a variety of types of severe psychotic pathology, so that any type of relative unstable personality structure, really, a neurotic personality structure, is, I think, at risk, and a greater risk to the effects of THC.

PANEL DISCUSSION OF MARIHUANA'S HEALTH HAZARDS

In a discussion of decriminalization versus legalization, Dr. Zinberg reaffirmed his support for the former and his opposition to making marihuana smoking legal. He compared the prospect of legalization to the gun control issue—a step that would result in polarization. He added that society would need between 10 and 15 years of trial decriminalization before a decision could be made on the possibility of legalization.

Dr. Cohen noted that, "from a purely public health standpoint, it may be that the decriminalization of small amounts for personal use may be desirable, because it avoids the kids getting arrest records which follow them through their lives."

Congressman Neal asked the panelists to compare marihuana with some of the other drugs widely used by the young, such as PCP.

Although Dr. Nahas preferred to make this comparison on a pharmacological basis, he noted that socially, a drug is most dangerous in relation to its potential to be abused.

Dr. Nahas said that, although alcohol has a very powerful potential for abuse, an individual can use alcohol moderately without any physical damage. One of the great differences between the use of marihuana and alcohol, he added, is that an individual pays for the abuse of alcohol later in life, possibly after establishing a successful career. A marihuana abuser, however, is usually young and is shifted out of the main stream of society early—before making any social contribution.

Although Dr. Zinberg acknowledged the pharmacological aspects involved in comparing drugs, he felt that the psychosocial aspects must be considered. Both personality and the existing cultural climate are necessary factors in making a comparison, he said.

Valium, Librium, and the other minor tranquilizers were introduced, according to Dr. Zinberg, because of the potential for suicide with the barbiturate depressants. Thus, the relatively low toxicity of these drugs provide them with an immense medical advantage over the barbiturates.

PCP, according to Dr. Zinberg, is a very difficult drug to control or use. Reports from users, he added, indicate that the drug is not a highly pleasurable one.

Dr. Cohen chose PCP and tobacco as the subjects of his discussion on the relative dangers of drugs. Although PCP abuse is a disaster in a city like Los Angeles with violence and many overdoses, 95 percent of the people who take the drug never get into trouble with it, he said. These individuals take small doses or take extreme care with the drug. On the other hand, enormous numbers of people smoke pot, with a relatively small percentage getting into visible trouble (evidenced by their visits to clinics).

In his comparison of tobacco and marihuana, Dr. Cohen recalled his medical days prior to World War II when a relationship had not yet been established between tobacco and eventual lung cancer. "The concern that I have for the pulmonary effects of marihuana is not today, but what will happen when we have sufficient numbers of people who are using heavily over many years. Will we have a repetition of the tobacco carcinogenesis information?" he asked.

Congressman Gilman then asked the panelists what each one would do as director of NIDA to get the message to our young people about the dangers of using marihuana. Dr. Zinberg replied ". . . the most effective thing you could do with marihuana would be to teach people how to use it safely and effectively."

Dr. Nahas disagreed, arguing that such an approach is unrealistic and impossible to achieve in any society. His view was that young people should be straightforwardly informed about the dangers of marihuana to their brain, their reproductive function, and to their lungs.

Dr. Cohen called for "a bit of a revolution; a revolution in how we bring our children up; how we educate them, how we give them gratifying goals and ambitions. This is the answer to not only marihuana, but to many other juvenile problems." Necessary changes, according to Dr. Cohen, include modifying the school system; reconstituting the family so that hopes and aspirations are instilled in the young; and eradicating negative and pessimistic attitudes. Perhaps educational programs should be for the parents rather than the children, added Dr. Cohen, so that they will once again take the responsibility for their child's upbringing.

"Nobody wants 12-year-olds to smoke," said Dr. Zinberg, "but what we may not agree on is what we think is the most effective way to keep 12-year-olds from using it." He also said that studies indicate that the use of education/prevention materials, rather than reducing drug use, consistently result in an upsurge in use.

Dr. Nahas said that he felt that the general consensus of the panel—and of the Committee—is to place a top priority on discouraging marihuana use among the young. His plan for accomplishing this includes education, setting an example for the young, and curtailing the glamorization of drug use by the media and certain publications.

Congressman Gilman then asked the panelists for their suggestions on the direction of future marihuana research and policy. Dr. Cohen replied that research projects designed to answer specific problems are necessary. He added that some of the studies currently being conducted by NIDA on specific topics, such as toxicology and reproduction, may turn out to be very valuable. However, since the marihuana problem is growing, research activity should be accelerated in the next 5 years.

Furthermore, much of the marihuana research has used a standard 2 percent level of THC on the subjects. If it is currently common practice to smoke marihuana with a 5 percent level of THC, then, according to Dr. Cohen, the research should attempt to duplicate that level in order to achieve an accurate understanding of the situation.

Dr. Cohen then commented that even after 50 or 60 years of research we won't know the "final truth" about marihuana's physiological effects. We will, however, keep increasing our knowledge.

Dr. Nahas outlined the four main areas of research he would like to see emphasized:

Studies should be undertaken to find out to what extent marihuana would produce cancer in animals similar to the research on cyclamates and saccharin substances.

Studies should be undertaken to find out to what extent marihuana smoke will produce changes in lung tissues.

Marihuana's affects on the offspring of users should be studied.

Research should be conducted in countries where marihuana has been used on a daily basis by native populations.

Dr. Zinberg would like to see a study on the process by which one learns to become a marihuana user in this culture. He would also like to see studies undertaken in States that might decriminalize marihuana use so that following decriminalization, a comparison could be made of smoking rates, etc.

Congressman Railsback then asked whether marihuana-caused impairments could be reversed if an individual stopped using the drug. Dr. Nahas responded that impairments could be reversed and the former marihuana user could live a normal, healthy life. However, he said, there is a point of no return with marihuana—as there is with any other drug.

The second day of the Committee's marihuana hearing focused on the position of the National Institute on Drug Abuse regarding the following areas:

(1) The known health hazards of marihuana;

(2) The eight points of agreement reached by the panel assembled for the first day of hearings;

(3) The extent to which the Federal Government provides educational material on marihuana to the drug's users and parents of users;

(4) The extent of marihuana research supported by NIDA.

TESTIMONY OF DR. WILLIAM POLLIN, DIRECTOR OF THE NATIONAL INSTITUTE ON DRUG ABUSE

Dr. Pollin testified that the Secretary of HEW had recently announced the Department's intent to undertake a comprehensive review of the existing scientific evidence on marihuana in order to identify the most urgently needed types of studies. The review would include research into the biological effects of chronic marihuana use and behavioral research on such topics as ways to help adolescents resist peer pressure to use the drug. The review would be implemented by an independent scientific group which would produce a report within 12 months.

Over 1,000 individual marihuana research projects have been conducted by the Federal Government since 1967 at a cost of $35 million. During fiscal year 1979 NIDA will support approximately 100 research studies costing $3.8 million. These studies include research into the effects of marihuana on the heart and lungs; on psychological, social and physical development; on pregnancy; as well as research into possible medical use.

Dr. Pollin then summarized the hazards of marihuana use for adolescents in nine key areas as determined by the National Institute on Drug Abuse: intellectual function; driving and skills performance; effects on the heart; effects on the lungs; on the immune system; on the brain; endocrine glands; reproduction; chromosome abnormalities.

Intellectual function

Acute marihuana intoxication, according to the Director of NIDA, impairs learning, memory, and intellectual performance. "Less familiar, more difficult tasks are interfered with more than well-learned performance, and the extent of the effect depends on the amount used and the tolerance for the effect." Being high on marihuana interferes with driving, flying, and other complex psychomotor performance.

Studies indicating impairment of driving skills

Driving skills studies have included laboratory assessments of driving-related skills, driver simulator studies, test course performance, and street driver performance. Dr. Pollin said that limited surveys indicated that between 60 and 80 percent of marihuana users questioned said they sometimes drive while high. Many of the respondents also combine marihuana with alcohol—this may be of greater risk than using either drug alone.

Research has indicated, said Dr. Pollin, that flying an aircraft while marihuana-intoxicated should be considered dangerous. "A continuing danger common to both driving and flying is that some of the perceptual or other performance decrements resulting from marihuana use may persist for some time, possibly several hours . . . the individual may attempt to fly or drive without realizing that his or her ability to do so is still impaired although he or she no longer feels 'high.' "

Effects on the heart

According to Dr. Pollin, the acute effects of marihuana use on heart function in healthy young male volunteers thus far appear to be benign. However, those with heart conditions, or at high risk, should not use marihuana due to the increased heart rate produced by the drug.

Effects on lung functioning

Both clinical observation and laboratory measurement have shown that marihuana can interfere with lung function and produce bronchial irritation in habitual users. Dr. Pollin referred to various reports indicating that: marihuana smoke contains more carcinogens than tobacco; smoke residuals produce skin tumors in animals; and human lung tissue exposed in the test tube to marihuana smoke shows more cellular changes than when exposed to similar amounts of standard tobacco

smoke. However, he cautioned, as yet, there is no direct clinical evidence that marihuana smoking causes lung cancer.

Dr. Pollin also said that heavy smoking by healthy young male subjects causes airway obstruction. From animal studies it appears that daily use of marihuana may lead to lung damage similar to that resulting from heavy cigarette smoking. "Since marihuana smokers often smoke both tobacco and marihuana," he said, "the effects of the combination require additional study."

Effects on the immune system

Research findings are unclear regarding the effect of marihuana on the human immune response. However, most of the studies reviewed, said Dr. Pollin, have shown that marihuana use adversely affects the body's natural defense against infection and disease.

Brain damage research

Research findings are also unclear regarding marihuana's potential for brain damage. Dr. Pollin stated that the quality of studies in this area is "highly variable" and clearly additional research is needed.

Effects on the endocrine system

Studies indicate that marihuana affects the glands and hormones involved in such functions as growth, energy levels, and reproduction. Some studies have found reduced levels of the male hormone testosterone. Furthermore, said Dr. Pollin, there is preliminary animal and human evidence which indicate that relatively heavy use of marihuana may reduce fertility in women. Of 11 studies on this subject, 7 reported endocrine changes, 4 reported no such change. However, the long term significance of these results remains to be determined.

Dr. Pollin acknowledged that concern has been expressed over possible effects on adolescent development and possible interference with sexual differentiation of the male fetus whose mother smokes marihuana during pregnancy.

Reproductive effects

A variety of animal and human studies suggest that the daily use of substantial amounts of marihuana may adversely impair aspects of the reproductive function, said Dr. Pollin. He noted, however, that there are no clinical reports directly linking marihuana use and birth abnormality.

Dr. Pollin summarized the results of several studies in this area:

Sixteen healthy male chronic marihuana users smoking from 8 to 20 standard marihuana cigarettes a day for 4 weeks in a hospital environment showed a significant decline in sperm concentration and motility. Abnormalities in the structure of the sperm were also detected.

Three animal studies found adverse effects of marihuana concerning testicular functioning and the production of sperm.

A recently completed study of 26 females who used street marihuana three times a week or more for at least 6 months found that these women had three times as many defective monthly cycles as non-using women. However, the results are inconclusive because the marihuana users also used more alcohol.

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The results from five recent animal studies administering high doses of marihuana or THC included early death of embryos and their reabsorption; higher reproductive losses among marihuana-treated rhesus females than among nontreated females, lower birth weight of male infants born to treated female monkeys, reductions in ovary and uterine weight, estrogen production, and the production of a number of important pituitary hormones.

Dr. Pollin concluded that these and other studies which use higher marihuana/THC doses underscore the undesirability of marihuana use—particularly during pregnancy.

Chromosome abnormalities

"Overall," said Dr. Pollin, "there continues to be no convincing evidence that marihuana use causes clinically significant chromosome damage. However, it should be emphasized that the limitations of the research to date preclude definitive conclusion."

Following his exposition of health hazards in nine key areas, Dr. Pollin discussed the comparative hazards of marihuana use versus other recreational drugs. It is misleading, he said, to compare marihuana with alcohol and tobacco because these three substances have great differences in social acceptability, period of use, and degree of availability. Furthermore, the hazards of alcohol and tobacco are reasonably well known—certainly more is known about them than marihuana.

"We have known what the active component and concentration of alcohol is for hundreds of years. We have known about the presence of nicotine and have studied nicotine for over 60 years. We only identified the psychoactive component in marihuana some 12 or 15 years ago. And the amount of research done on marihuana, though it is a much more complex substance than the two others with which it is usually compared, is quantitatively much less than the amount of research that has been conducted on those other substances with which we would like to compare marihuana."

The wealth of information on alcohol abuse includes the fact that 10 percent of users have a "problem" and that alcohol has been implicated in half of the automotive facalities in the United States. Dr. Pollin added that the health costs of alcohol as measured by the levels of cirrhosis, mental illness, crime, and industrial accidents can be documented. Similar problems caused by tobacco can also be documented.

The relatively recent popularity of marihuana prohibits a similar analysis. Only 5 percent of college students queried in 1965 indicated that they had any marihuana experience. Presently, said Dr. Pollin, between 60 and 70 percent of college students would respond affirmatively to that question.

Furthermore, he advised that any determination of marihuana's hazards must take into account the drug's future use as well as its present popularity. "At present," he said, "this involves many imponderables such as the parameters of risk for various groups in our society at different levels of use, the likely circumstances of use, effects on user functioning and motivation of heavier use patterns, degree of use restriction possible, combined use with other drugs—to name but a few."

Thus, for all of these reasons, summed up Dr. Pollin, any comparison of marihuana's health impact with that of alcohol and tobacco would certainly minimize the dangers of pot.

He strongly asserted, however, that no such controversy exists with respect to the hazards of use by children and young people. ". . . although there is still much to be learned about the impact of heavier use on the physical functioning of the child or adolescent, studies indicate that use may cause alterations in endocrine functioning which are more serious than endocrine involvements in older, mature users."

"Unfortunately," said Dr. Pollin, "the hesitancy of the scientific community in not drawing unwarranted definitive conclusions from what are preliminary research findings has led many to conclude that marihuana is without serious medical hazard, even for the very young."

"Although experimental evidence concerning the implications of use in this group is not easily obtained, there is little serious question that regular use of an intoxicant that blurs reality and encourages a kind of psychological escapism makes growing up more difficult."

He then noted the "worrisome" findings on the number of high school students using marihuana. According to an ongoing study of high school seniors, 1 in 9 smoked marihuana daily in 1978—nearly twice as many as in 1957. Independent surveys conducted in Maryland and Maine indicate that nearly 1 in 6 high school students use marihuana daily or nearly daily.

TESTIMONY OF DR. SNYDER

Dr. Snyder, acting director, division of research, National Institute on Drug Abuse, provided the Committee with a look at NIDA's projected research plans for the next 5 years, which included the following activities:

A major longitudinal study of the effects of marihuana by several researchers who would perform a series of psychological and biological examinations on a group of marihuana users over a projected period of time. Individuals would be followed to ascertain the development of problems in endocrine functioning, school performance, learning, and psychosocial development.

Studies examining the effects of marihuana and alcohol taken in combination.

Research targeted specifically at the areas of complex performance, such as learning and memory, and how this affects the ability of high school age youths.

A study of the effects of marihuana on human female endocrine function.

A major study to assess the effects of marihuana on lung pathology and to look at the carcinogenic effects of constituents of marihuana.

Plans to issue an invitation for applications from major neuroscience centers to use recent techniques developed for the study of brain structure in the infant animal. The purpose of this project would be to assess more specifically the effects of marihuana on the chemical and physical structure of the animal brain in order to relate this to human effects.

Further development of roadside methods for the detection of marihuana in cases of erratic operation of a vehicle.

Examination of the role PCP plays in producing schizophrenic-like reactions.

Efforts to synthesize the 300-odd different chemicals which make up the composition of marihuana.

Examining the use of marihuana for therapeutic purposes. Currently, there are 31 clinical studies on marihuana use for therapeutic uses including treatment of types of spasticity associated with multiple sclerosis, anorexia nervosa, and pain.

Dr. Snyder also reported that NIDA's fiscal year 1979 marihuana research program is $3.8 million. The projected fiscal 1980 budget is approximately $5.2 million. In order to fully carry out the program, as outlined above, the Institute would require an additional approximately $4 million each year, he added.

Although Dr. Peterson did not prepare a formal statement, he stressed that the area of psychosocial implications of marihuana use is of considerable concern for possible behavior toxicities of marihuana as they affect the way youngsters deal with the social realities of their own world. Furthermore, early marihuana use often leads to dropping out phenomena, to association with other youngsters who may be in some sense delinquent or truant or have other problems which, although not directly caused by the drug, may be the influence of the drug-using subculture.

PANEL DISCUSSION

In a discussion of the relative safety of various drugs, Dr. Pollin said that one of the "yardsticks" by which drugs are measured is the percentage of users who encounter side effects. Another measure of drug safety would be the nature and severity of those side effects.

He then noted that the number one drug listed in the national drug treatment network is heroin—accounting for about 45 percent of the people in treatment. Marihuana is the second most common drug of abuse listed in this network.

When asked specifically about the relative safety of alcohol vs. marihuana, Dr. Pollin stated that his personal opinion is that eventually the two substances may turn out overall to be comparably dangerous. NIAAA estimates that there are between 150,000 and 200,000 excess deaths each year attributable to alcohol. Such a statement cannot be made regarding marihuana, because there have not been longitudinal followup studies. Regarding Librium and Valium, Dr. Pollin said that these drugs have not been shown to cause the type of acute panic attack, nor to have some of the hallucinogenic-like properties that marihuana sometimes has for certain users.

In order to clear up any confusion that may have resulted from his testimony, Dr. Pollin stated that he did not intend to suggest that intoxicant use of other drugs is preferable to intoxicant use of marihuana. Furthermore, he added, "any type of frequent, regular drug use to the point of intoxication is highly undesirable, particularly among adolescents . . ."

In response to questioning from Congressman Gilman, Dr. Pollin said that NIDA requested $3.7 million for marihuana research in 1978, $3.9 million for 1979 and $5.5 million for 1980. Most of the research money goes for grants. The research proposals that are submitted to NIDA have been shaped to some extent by the Institute's priorities which are publicized in announcements distributed to the scientific community.

Mr. Gilman quoted from a May 31, 1979 letter, from then HEW Secretary Joseph Califano, to all school administrators seeking "your help in fighting alcohol and alcohol abuse."

"If drug abuse is so important," said Congressman Gilman, "why haven't you included that in your message to school administrators?" According to Dr. Pollin, the letter reflected the Secretary's concern with the health consequences of alcoholism. It was not intended, he said, to diminish the importance of drug abuse. NIDA's Director agreed that more information on the dangers of marihuana smoking could and should be distributed. Two projects currently underway in this area include a book for parents and teachers and a film geared to parents.

Congressman Gilman questioned whether there is any research underway comparable to Dr. Heath's research on the effects of marihuana on the brains of monkeys. Although Dr. Pollin said there are no studies which precisely duplicate Dr. Heath's research protocol, there are a variety of studies which are examining both the biological and psychological effects of marihuana on animal behavior.

When asked about the status of NIDA's 1979 drug prevention campaign, Dr. Pollin said that the television spots were recently audience-tested. NIDA was awaiting at the time of the hearing a report from HEW on whether to proceed with the campaign. The TV spots are part of a multimedia approach which also includes radio announcements, print media, and school-based contests. Approximately $250,000 has been spent on the campaign.

FINDINGS AND CONCLUSIONS

(1) Pregnant women should not use cannabis.

(2) Driving under the influence of this drug can be hazardous to one's health and to the health of those in the vicinity.

(3) Young people should be discouraged from marihuana use, particularly heavy use.

(4) Those individuals with lung disease should avoid the drug.

(5) People with heart disorders may be further impaired by the acceleration of the heart that cannabis produces.

(6) Preschizophrenic and schizophrenic people may develop or exacerbate a psychotic break in connection with marihuana use.

(7) The infrequent adult use of marihuana (less than once a week) will probably not result in ill effects unless the smoker happens to experience one of the uncommon, acute reactions, or get into his car and drives.

(8) Continued study of the therapeutic potential of cannabis is desirable, particularly for the management of intractable nausea and vomiting and for wide angle glaucoma.

RECOMMENDATIONS OF THE SELECT COMMITTEE

(1) Marihuana research should concentrate on the psychosocial factors which influence individuals to abuse this drug.

(2) The media should stress the possible harmful effects of marihuana with emphasis on youth based on recent clinical research.

(3) Trends regarding the abuse of marihuana, however, should be publicized as potential areas of concern.

(4) Parents and community groups should take deliberate action to warn youth of the potential for harm resulting from the abuse of marihuana.

(5) Innovative drug prevention programs—beginning as early as the fourth grade—should be instituted in local communities.

APPENDIX *

The following is a summary of the conference on "Marihuana: Biomedical Effects and Social Implications" co-sponsored by the New York University Post-Graduate Medical School and the American Council on Marijuana and Other Psychoactive Drugs. The conference was held in New York City on June 28–29, 1979.

Dr. D. Fredrickson of New York University opened the meeting by indicating that this conference appeared to be the most comprehensive review of the biomedical effects of marihuana ever presented.

Dr. N. A. Pace then presented statistics documenting the tremendous rise in the use of marihuana among youth. According to a report released by the Department of Health, Education and Welfare, between 1976–1977 the number of 12-to-17-years-olds who were current users of marihuana jumped by almost one-third. During that same time period, 16.1 percent of all adolescents in the United States reported using marihuana; 9 percent of high school seniors reported daily marihuana use.

Dr. G. G. Nahas, Columbia University, presented a paper on "Marihuana—Pharmacology and Cellular Effects." Dr. Nahas reviewed the pharmacokinetics (absorption, distribution, biotransformation and elimination) of the psychoactive substance of marihuana, delta-9-THC, and of its by-products.

Dr. Nahas reported that when marihuana is used daily or several times weekly, there is a high accumulation in the body of THC. A single dose of THC remains in the body for 30 days before being eliminated.

Dr. Nahas indicated that smoking marihuana results in bioavailability 9 to 10 times greater than by ingesting it. He also referred to various methods that have been devised to test clarification and identification of THC in body fluids. He showed that both THC and its non-psychoactive metabolites adversely affect cell division in vitro as well as in vivo by impairing the formation of nucleic acids and proteins. The cytotoxic effect of all cannabinoids on nucleic acid and protein synthesis occurs in concentrations that are easily reached in the tissues of chronic users. The mechanism of this cytotoxic effect was attributed to the action of the cannabinoids on the cell membrane which is dissolved, thereby preventing the transport of chemicals required for DNA, RNA, and protein synthesis.

In addition, THC and other cannabinoids also interfere with the synthesis of chromosomal proteins and the proteins that regulate gene expression and enzyme synthesis, namely histones and non histones.

As part of a session on marihuana's effects on the lungs, Dr. H. Rosenkrantz, EG&G Mason Research Institute, presented a paper

*To conform with Select Committee style, "marihuana" has been spelled with an "h" rather than a "j" throughout this appendix with the exception of the organization cited in the introductory paragraph.

entitled "Experimental Studies of Long-Term Effects of Marihuana Smoke on the Lung."

Dr. Rosenkrantz's animal experiments used a specially designed smoking apparatus so that subjects would inhale NIDA cigarettes in standardized delta-9-THC doses. After exposure to marihuana for 87–360 days, the subjects showed dose-related pulmonary pathology. The pulmonary pathology included alveolitis or pneumonitis which progressed from extensive mobilization of alveolar microphages and foreign body cell inflammation to pronounced focal proliferative aberrations associated with focal granulomatous and cholesterol clefts. These are all signs of tissue destruction. The extent of the lesions depended on the duration of the experiments and the dose inhaled.

Dr. G. Huber, Harvard Medical School, presented a paper entitled "Marihuana and the Defense System of the Lung." He indicated that marihuana smoke is significantly more destructive than tobacco smoke to the lung's defense system against bacteria.

Dr. D. Tashkin, UCLA School of Medicine, discussed "Clinical Studies of Chronic Marihuana Users." He showed that smoking an average of five marihuana joints per day for a period of 47–59 days caused statistically significant decreases in several indices of lung function, decreases in maximal mid-expiratory flow rate and specific airway conductance correlated with the quantity of marihuana smoked. When these marihuana users ceased their smoking for one week, they experienced only partial improvement in their mid-expiratory flow rate, with further improvement after 1 month of cessation.

The results of a controlled study conducted in Los Angeles by Dr. Tashkin concur with the findings of Henderson, Tennant and Guerry that severe upper airway and tracheal lesions occur in heavy users of hashish and that the habitual marihuana smoker has a greater risk of functional impairment involving the large airway of the lungs.

In the session on marihuana and the brain, Dr. A. Jacubovic, University of British Columbia, presented a paper entitled "Ultrastructure and Biochemical Changes in the Central Nervous System Induced by Marihuana." Dr. Jacubovic indicated that various cannabinoids inhibited the protein and nucleic acid synthesis in animal brain cells and that the most psychoactive cannabinoids—delta-9, delta-8 and 11 OH delta-9-THC—each caused highly significant morphological changes in the brain cells. These changes included reduction in the nuclear membrane-attached ribosomes (NMRi). The changes in the NMRi provide evidence to support the existence of biochemical effects of cannabinoids on protein and nucleic acid synthesis in the CNS.

Dr. H. Kalant, University of Toronto, Addiction Research Foundation, presented a paper entitled "Residual Effects of Cannabis on Learning." He conducted two experiments with young male rats who received a THC dose of 20 mg/kg in the stomach for about 6 months. This produced observable intoxication in the rats for about 4 hours each day. Other groups were given ethanol 6 g/km in a control solution. He showed that during the second month—after the last intubation—the cannabis and alcohol group showed significantly slower learning of a complex motor task than did the control group.

Dr. L. Chapman, University of California School of Medicine, presented a paper on the "Effects of THC on Primate Behavior." He

studied the social behavior of monkeys after exposure to daily doses of delta-9-THC for a period of up to several years. Dr. Chapman showed that given 2.4 mg./kg. of THC, the monkeys showed reduced social interaction, relaxed postures, and reduced general activity for the first 2–3 months. However, some animals have intermittently exhibited a form of behavior activity with increased pacing and other repetitive stereotyped behavioral patterns. With the treatment schedule held constant, tolerance to these behavioral effects was apparent.

As the acute effects diminished, irritability and aggressiveness in treated animals increased significantly. This behavioral change was apparently not a withdrawal effect. At this stage, previously lower-ranked animals began to rise in the dominance heirarchy. Overt aggression increased in treated animals and submissive behavior increased in non-treated cagemates. Under high stress conditions, previously low-ranking THC-treated animals initiated overt fighting episodes leading to elevated stress hormone levels in undrugged cagemates as well as injuries. These observations indicated that repeated exposure to moderate amounts of THC over long periods of time resulted in a biologically serious impairment in the subjects' ability to exhibit appropriately adaptive behavior. This impairment apparently represented a slip in baseline behavioral characteristics rather than the effects of acute intoxication or withdrawal.

Dr. Robert Heath of the Tulane University School of Medicine presented "Chronic Marihuana Smoking: Effects on Structure and Function of Primate Brain." Monkeys under rigid controls who were smoking active marihuana showed induced blood levels equivalent to the blood levels in human subjects who smoked three joints a day. Pathological changes were induced in electrical recordings from subcortical brain sites after 2–3 months. Scalp electroencephalograms of these monkeys were not affected. The monkeys were exposed to active cannabis ingredients for 6 months. They then rested for an additional 8 months, followed by the administration of serial electroencephalograms. Subcortical recordings continued to show persistent abnormalities.

Autopsies of these monkeys after 8 months of rest showed distinct structural changes at many synapses, disruption of the rough endoplasmic reticulum, and the presence of significantly increased numbers of intranuclear inclusion bodies at many brain sites.

These experiments were repeated with the intravenous administration of 0.7 mg/kg of delta-9-THC and showed the same results. Monkeys, on the other hand, exposed to marihuana smoke devoid of the psychoactive material (delta-9-THC), included in the study for control purposes, showed no changes in subcortical recording or brain structure.

Dr. R. Jones, University of California Medical School, showed in his paper on "Cannabis Tolerance and Dependence in Humans" that cannabis can produce rapid tolerance and dependence—both physiologically and psychologically.

Dr. Jones' controlled double blind study tested over 100 subjects. These individuals developed tolerance to most of the cardiovascular, autonomic, neurophysiologic, and perceptual motor effects. When the subjects were given smaller but more frequent doses, tolerance appeared more rapidly.

The cannabis withdrawal syndrome is similar to the one produced by stopping moderate doses of sedative hypnotics. The symptoms include irritability, anger, disturbed sleep, restlessness, decreased appetite, increased perspiration, chills/fevers, nausea and other abdominal distress, tremulousness, weight loss, salivation, tremor, increased body temperature, and increased intraocular eye pressure. Dr. Jones' subjects began experiencing symptoms of withdrawal a few hours after the last dose of THC.

Dr. D. Feeney of the University of New Mexico in his paper on "Marihuana and Epilepsy" showed that the psychoactive constituent of cannabis, delta-9-THC possesses both convulsant and anticonvulsant properties. He has shown that delta-9-THC provokes myoclonus, psychomotor and grand mal seizures in naturally epileptic beagle dogs. Thus, epileptics should be counseled against using marihuana as there is a risk of inducing seizures. However, one of the constituents of cannabis, cannabadiol, shows considerable promise as an anticonvulsant and does not have any convulsant or psychoactive action as delta-9-THC. It is hypothesized that there is some relationship between the convulsant and psychotropic actions of the psychoactive cannabinoids.

Dr. A. Zimmerman of the University of Toronto discussed "Marihuana and Spermatogenesis." He showed that mice given cannabinoids had a statistically higher incidence of abnormal sperm than untreated controls.

The induction of abnormal sperm morphology was transient since 72 days following the administration of THC, the incidence of abnormal sperm in the mice was comparable to the untreated controls. There was a twofold increase in the incidence of chromosome abnormalities in the cannabinoid-treated mice. Cytogenetic effects were observed in micronuclei assessments and in chromosomal analysis of bone marrow mitosis.

A paper on the "Effects of Prenatal Exposure to Cannabinoids on Sexual Differentiation" was presented by Dr. Dalterio of the University of Texas Health Center. He said that marihuana and its primary psychoactive constituent—THC—has been shown to reduce plasma testosterone levels, spermatogenesis, and androgen-dependent behavioral responses, including aggression and copulatory activity.

Female mice were treated with cannabinoids on the last day of pregnancy and for 6 days post-partum in order to expose their male progeny to THC during the perinatal period of sexual differentiation. This treatment resulted in long-term alterations in male reproductive functions. Dr. Dalterio's experiment indicated that constituents of marihuana affect development of the male mouse reproductive system as a result of exposure during critical periods of sexual differentiation.

Dr. W. Hembree of Columbia University described the "Effects of Marihuana Smoking on Male Gonadal Function." He noted that there is a diminution in the spermatogenesis of young marihuana smokers after unrestricted smoking for 4 weeks. This oligospermia was accompanied by an increase in abnormal sperm forms and by a decrease in sperm motility.

Dr. C. G. Smith of the Uniformed Services University of the Health Sciences in Bethesda, Md., presented a paper on the "Effects of THC on Female Reproduction Function." Dr. Smith showed that a single

intramuscular administration of THC leads to a decrease in FSH and LH in rhesus monkeys.

Dr. Smith indicated that primates treated with THC during one menstrual cycle will fail to ovulate during the following cycle. Thus, the effects of THC on the menstrual cycle are disruptive causing absence of ovulation, absence of normal hormonal cycling, elevated prolactin levels as well as increased length of time until the next menses.

Dr. J. Bauman of the Masters and Johnson Institute compared 26 women who were frequent marihuana users with a similar group of women who had never used marihuana. Dr. Bauman showed that 40.4 percent of the marihuana using group were either anovulatory or had a marked inadequate luteal phase compared to 15.6 percent in the control group. Prolactin levels were consistently and significantly lower while testosterone levels were consistently and significantly higher in marihuana users on all sampling days during the menstrual cycle.

Dr. H. Rosenkrantz of the EG&G Mason Research Institute showed that cannabis was embryotoxic in rodents treated either orally or parenterally. Using plasma levels correlated to human levels, Dr. Rosenkrantz demonstrated the embryocidal effect of marihuana and THC. Embryotoxicity could be induced following between 2 and 5 treatments on days 7 through 9 of gestation. The surviving offspring were hypotropic.

Dr. E. N. Sassenrath of the University of California found that when THC was administered before mating to female rhesus monkeys, the incidence of absorption and neonatal mortality was 4 times higher than in controlled animals. Cannabis also affected surviving offspring. The THC treated mothers were smaller than the controls and reacted abnormally to certain stimuli.

Dr. W. Jay of the University of Chicago reported on the use of marihuana in treating glaucoma. In discussing nabilone, a synthesized crystalline resembling the cannabinols, Dr. Jay noted that doses of nabilone capable of lowering intraocular pressure did not lead to associated euphoria, tachycardia or orthostatic hypertension. He added that THC and nabilone are potentially valuable in the treatment of glaucoma. However, he cautioned that further testing is required to discover whether these compounds are more effective and have fewer side-effects than currently employed anti-glaucoma medications.

In further discussion of Dr. Jay's remarks, Dr. A. de Roeth, Jr. of Columbia University, discussed a study published by Dr. Dawson. Dr. Dawson had completed a 10-year study on marihuana smoking Costa Ricans. These subjects had a higher incidence of eye problems, particularly glaucoma. Dr. de Roethe added that Eli Lilly had suspended its study of nabilone because of its extreme toxicity. Nabilone caused convulsions and the death of all the animals in which it was used.

Dr. D. Tashkin of the UCLA School of Medicine presented a paper on marihuana and asthma. He indicated that when an individual smokes marihuana there is an initial dilatation of the airways which lasts as long as 60 minutes. However, smoking marihuana is not therapeutically usable, he said, since the drug contains (in addition

to THC) hundreds of chemicals with a variety of effects on the respiratory system.

Dr. Tashkin also indicated that aerosolized THC, although capable of causing significant bronchodilatation with minimal systemic side effects, has a local irritating effect on airways which makes it unsuitable for therapeutic use.

Dr. S. Frytak of the Mayo Clinic compared the effectiveness of THC with the standard antiemetic prochlorperzine and a placebo in treating the nausea of chemotherapy. One hundred and seventeen cancer patients were followed in this double blind study. Dr. Frytak concluded that THC showed some antiemetic activity, however, it was not superior to the standard phenothiazine antiemetic. Nevertheless, according to Dr. Frytak, THC was significantly more toxic so that such treatment was undesirable for patients in this group.

PART II.—THERAPEUTIC USES OF MARIHUANA AND THE USE OF HEROIN TO REDUCE PAIN

INTRODUCTION

The Select Committee's hearing on the therapeutic uses of marihuana sought to surface and examine the factors giving rise to the controversy. Testimony was heard from Government witnesses engaged in research and control, research specialists from the private sector engaged in research, and testimony from patients. The hearing also included testimony from Government and private witnesses on the issue to allow the use of heroin to relieve pain and suffering for the terminally ill.

In the early 1970s, there began to appear interesting anecdotal evidence from individuals who were smoking illegal marihuana to ally anxiety associated with their cancer treatments. They reported that when they smoked marihuana in association with their cancer chemotherapy, they suffered less nausea and vomiting. This led to ideas for studying the marihuana cigarette in a rigorous scientific manner for this use. In addition, delta-9 THC capsules were prepared as well as identical appearing placebos to study the efficacy of this cannabinoid in the prevention of nausea and vomiting in patients undergoing cancer chemotherapy.

For the purpose of this report, the term marihuana refers to marihuana in cigarette form (i.e. route of administration, smoking). Marihuana contains approximately 400 cannabinoids of which one is delta-9 THC. The term THC in this report will refer to synthetic capsules composed of delta-9 THC alone.

A number of government agencies are involved in the process by which a physician must go through in order to obtain THC or marihuana. Let us assume that a licensed physician has a cancer patient undergoing chemotherapy, and he feels that the patient would benefit from THC or marihuana in conjunction with chemotherapy. Since both these drugs are investigational, the physician must apply for an IND (i.e. license to use an investigation drug). He would request an application from the drug abuse staff at FDA (Food and Drug Administration), who then would send him the appropriate instructions for filing application. The physician would then submit a research protocol and accompanying forms. These forms would include documents for Institutional Review Board Clearance from associated institutions and agreement to protection of human subjects. FDA would then approve or deny the application, or request additional information or materials from the applicant.

Since both THC and marihuana are Schedule I drugs according to the Controlled Substances Act, the physician simultaneously or subsequent to filing an application for IND, would have to submit applications to DEA (Drug Enforcement Administration) for a

license to use Schedule I drugs. This application allegedly takes approximately 6 weeks to process and often requires a DEA inspector to meet with the physician to inspect the storage facility to assure that it is adequate. In addition, there is a box on the DEA regulation forms which asks whether the applicant requires order forms for the drug.

Assuming that the IND is ultimately approved, and a DEA registration number is granted, the physician then can submit an order form to the National Institute on Drug Abuse (NIDA) for the drug. NIDA is the only body which can legally manufacture THC or marihuana. It has been taking approximately 6 weeks from the time of receipt of order forms to get the drug to the physicians. When NIDA receives the order form, it forwards it to FDA, which verifies that the physician has an approved IND, and then returns it to NIDA. NIDA then submits the form to its center for distribution.

There have been plans pending which will likely be implemented by the time of this publication, to place THC only (not marihuana) in the National Cancer Institute's (NCI) Group C distribution system. This would mean that approximately 3,000 oncologists across the country would be covered by an umbrella IND held by NCI. These physicians would then not need to submit a separate application for IND.

It should be noted that in the past, FDA has encouraged individuals to submit INDs for THC capsule use as opposed to marihuana use. Often, this would manifest in the form of not granting IND for marihuana use until THC capsules were first tried. Also, IND applications could usually be more expeditiously approved for THC than for marihuana, because of FDA's preference for the use of the THC capsule.

BACKGROUND

Cancer affects at least one in four Americans. Each year there are an estimated 750,000 new cases. The last 10 years have witnessed incredible progress in the development of anticancer drugs.

Years ago, for example, choreocarcinoma was 100 percent fatal. Now, with chemotherapy, there is close to a 100-percent cure. With Hodgkins Disease and testicular cancer, cure rates have increased dramatically with chemotherapy. In all, there are at least 12 cancer types where cures can be induced by chemotherapy.

According to National Cancer Institute statistics, approximately one-half of patients treated with anticancer drugs will have nausea and vomiting, often of the most agonizing kind. In 30 to 40 percent of these individuals, the nausea and vomiting are refractory to standard anti-emetics like Compazine.

Many of the most effective anticancer agents in producing cure or significant palliation of disseminated disease (e.g. cisplatinum, adriamycin and nitrogen mustard) also induce the most severe vomiting. Patients have been known to refuse to continue effective therapy even when they are responding because of agonizing nausea and vomiting. Thus, vomiting can be a lethal side effect of chemotherapy since it can prevent the patient from receiving curative chemotherapy. Clearly, the need for effective antiemetic agents to alleviate this side effect is imperative.

In the light of the above, it is very significant that reports in recent years that THC capsules and marihuana have been effective in some patients who have failed to be relieved of nausea and vomiting by standard anti-emetic drugs have emerged. For example, Chang and his coworkers at the National Cancer Institute pointed out that if THC plasma concentration levels were greater than 10 ng./ml., the drug THC was 95 percent effective in preventing vomiting. This was true whether the drug was taken orally or by smoking.

In view of the large amounts of research and anecdotal reports on the value of these drugs, particularly THC, it has been of concern that there have been increasing reports of enormous obstacles to physicians being able to obtain these drugs for legitimate research purposes. Patients who presumably could benefit from the drugs are having such difficulty that many are purchasing marihuana illicitly on the street.

Glaucoma affects approximately 2 million persons, and is the leading cause of blindness in this country. THC or marihuana may offer hope for extended vision in some glaucoma patients.

Heroin also remains a Schedule I drug, although there is some question as to whether it should be available for medical use for pain relief in the terminally ill patient. The hearing on which this report was based dealt briefly with the heroin issue.

The principal purpose of these hearings was to examine the evidence that marihuana or THC may have legitimate medical use. In addition, the report attempts to examine whether a maze of government rules, regulations, and agencies is serving as an obstruction to legitimate research efforts in this important area.

PATIENT PANEL

The opening panel of the Select Committee on Narcotics Abuse and Control hearing on the Therapeutic Uses of Marihuana and Schedule I drugs was composed of patients who had used marihuana in the course of their treatments.

Ann Guttentag

Mrs. Ann Guttentag, a cancer patient since 1976, testified as to the agonizing nausea and vomiting she experienced during cancer chemotherapy. She reported to have lost all appetite, and her weight decreased by 25–30 pounds. Mrs. Guttentag testified:

> One hour after smoking marihuana, my appetite returned so voraciously that I was eating everything in sight . . . I regained my weight so quickly . . . once I started the marihuana.

During her first cancer chemotherapy treatment, Mrs. Guttentag reported that she "vomited straight for almost 16 hours." "Under the first treatment, I kept praying and I kept begging them to please let me die," Mrs. Guttentag testified. Concurrent with her second treatment, Mrs. Guttentag smoked marihuana, and reported "it was about 90 percent improved over the first treatment."

Convinced as to the efficacy of marihuana in her treatment (which thus far she had to obtain from the illicit market), Mrs. Guttentag and her physician proceeded to file for application to obtain the drug legally. It took 6 months to receive a drug, but it was THC in pill

form, and not marihuana cigarettes (it should be noted that FDA had been reluctant to distribute marihuana cigarettes under an IND until and unless THC capsules were first shown to be ineffective). In Mrs. Guttentag's case, she threw up the pills, and as of the day of the hearing, May 20, 1980, had still not yet received the marihuana cigarettes. In conclusion, Mrs. Guttentag requested that Congress assist in ensuring that marihuana, a drug which appears so often effective in abating the terrible side effects of cancer chemotherapy, be readily available through qualified physicians to patients who could benefit from its use.

Richard Csandl

Mr. Richard Csandl, another witness at the hearing, had been in treatment for cancer since 1978, and was aware of reports that marihuana often was effective in alleviating the illness associated with cancer chemotherapy. Mr. Csandl testified that he smoked marihuana before and after his first treatment, and did not get sick at all. For the second treatment, Csandl decided to forego the marihuana, and he reported becoming extremely ill. Since that time, he has continued to use marihuana concurrent with all his treatments. He reported that a "hit" of marihuana was effective in relieving nausea associated with his treatments. Csandl further testified:

> It, of course did not help late at night when you were sleeping. You would wake up retching, and as soon as you could stop retching long enough and take a couple of hits, it reduced the nausea immediately.

Csandl also attempted to obtain marihuana legally for his treatment, and also experienced tremendous difficulty. He testified that "with the carcinoma, where you might be dead in 4 to 6 weeks, I went for almost a whole year before I could get . . . any action with the Federal Government."

Csandl requested that marihuana be available to patients who would benefit by its use.

Robert Randall

Robert Randall testified that he suffers from the potentially blinding eye disease, glaucoma, and would be blind today had he not used marihuana over the last 6 years for the control of this disease.

Mr. Randall testified that in 1976, he became the first individual in this country to gain legal access to marihuana, as a consequence of a D.C. Superior Court ruling which determined that his use of marihuana was not criminal, but was a consequence of medical necessity. Randall stated that, at present, his private physician writes prescriptions and his pharmacy provides him with 70 prerolled marihuana cigarettes of a known potency.

Mr. Randall criticized the "gross affront" to other glaucoma and cancer patients who are threatened with loss of sight or life and are deprived of similar care, arguing that he and others have a basic right to protection of health.

Furthermore, Randall submitted written testimony that "FDA, NIDA, and NCI are 'pushing' an effort to replace natural cannabis with synthetic delta-9 THC, when all available evidence indicates delta-9 THC is medically inferior to cannabis as a therapeutic agent, but is significantly more psychoactive." Randall cited his personal experience with delta-9 THC, which he claimed proved to be medically

ineffective in the treatment of his glaucoma. In addition, he claimed that the synthetic THC produced an unpleasant sense of disorientation, unlike that with natural cannabis. Randall urged that "NIDA and FDA are . . . advocating that a mild euphoriant, natural cannabis, be replaced by synthetic THC, a major hallucinogen." Also, Randall stated that "THC is difficult to manufacture in consistent dosages, is crudely formulated according to FDA and NIDA, and has poor bioavailability." Randall argued that "bureaucratic prejudice and desire to replace cannabis with synthetic THC is rooted in drug abuse ideologies and serves the regulatory convenience of the agencies. Researchers requesting cannabis have been compelled to accept synthetic THC. Lost in this "push" toward a "synthetic solution" is a concern for the actual relief available to patients in serious need of an effective medicant. A "refined" albeit medically inferior synthetic, like THC, fits regulatory demands and bureaucratic interests. But it does not best serve the public interest or reflect medical realities."

Randall also questioned NIDA's ability and commitment to the supply of adequate cannabis to meet patient needs. He pointed out that "since 1978, 23 States have enacted laws recognizing marihuana's medical value in the treatment of glaucoma, and on easing the nausea and vomiting which often accompany cancer Chemotherapies." However, Randall clarified that only the National Institute on Drug Abuse can legally cultivate cannabis. Randall further stated:

> I think this Committee should carefully question Federal officials about the status of existing government supplies of cannabis. Last year NIDA grew 3 acres of marihuana in Mississippi and concluded that this amount would be adequate to meet the medical needs of glaucoma and cancer patients in 23 States. It is my impression that NIDA does not have enough marihuana to meet the medical needs of one State, such as Georgia or Michigan, and that supplies are so critically depleted, potency levels have fallen so low, that the agencies will use the pretext of a "supply crisis" to "push" researchers and States toward synthetic THC.

Randall further criticized Federal agencies by saying:

> In effect, I believe Federal officials from NIDA and FDA deliberately deceived more than a score of State legislatures by promising the States supplies of 'legal' marihuana which did not exist, and which the agencies have no intention of growing.

CANCER RESEARCHERS PANEL

Dr. Phillip Schein

Dr. Phillip Schein, medical oncologist at the Georgetown University School of Medicine and Chairman of the Food and Drug Administration's Advisory Committee for Oncologic Drugs, testified as to the therapeutic use of oral delta-9-tetrahydrocannabinol (THC) for the prevention of nausea and vomiting associated with cancer chemotherapy.

Dr. Schein provided an overview of research in this field. He reported that the first randomized control trial of oral THC as an antiemetic for patients receiving chemotherapeutic drugs was performed by Sallan and coworkers in Boston. The study was performed with a double-blind design, where neither the patient nor physician knew whether THC or placebo were being administered. There were 20 patients in this study, and 29 courses of therapy were evaluated, 14 with placebo and 15 with THC. There was no control of nausea and vomiting in any of the placebo courses. For THC, five patients experienced no vomiting, seven patients evidenced at least a

63-109 O - 81 - 3

50-percent reduction as compared to placebo, and in three instances there was no response. THC was found to be substantially superior to the placebo.

Chang and coworkers studied 15 patients with osteosarcoma, a malignancy of the bone. All patients were to receive methotrexate, a regimen that predictably produces nausea and vomiting. In this study, also a randomized double-blind placebo controlled protocol, each patient was given an initial dose of THC prior to therapy. If the patient vomited, he was given either a THC cigarette or a placebo cigarette as a supplement. With placebo treatment, there was a 72 percent incidence of nausea and vomiting. With THC, 8 to 15 patients had an excellent response with a greater than 80-percent reduction in number of vomiting episodes, and degrees and duration of nausea. Six of the 15 patients had a partial reduction in these symptoms. Significantly, the investigators were able to correlate the antiemetic effects of THC with plasma drug concentrations. If a plasma concentration of greater than 10 nanograms per milliliter was achieved, the incidence of nausea and vomiting was only 6 percent. This compared with an incidence of 21 percent with plasma concentrations of 5 to 10 ng./ml., and a 44-percent incidence of nausea and vomiting at plasma concentrations less than 5 ng./ml.

Lucas and Laszlo, from the Duke University Medical Center, studied 53 patients who, after receiving anticancer chemotherapy, had experienced severe nausea and vomiting which was refractory to standard antiemetic agents. Nineteen percent of patients experienced no further nausea and vomiting, and 53 percent had achieved at least a 50-percent reduction in nausea and vomiting compared to previous courses with the same cancer chemotherapy agents. These investigators concluded that their study clearly indicated that THC is an effective antiemetic agent in cancer patients receiving chemotherapy, since these same patients had achieved little if any relief from the available marketed antiemetics.

Dr. Schein then reviewed studies which compared the effectiveness of THC against the standard antiemetic in clinical practice, prochlorperazine (Compazine). Sallan and coworkers conducted a randomized double-blind trial involving 84 patients, of whom 82 had previously proved refractory to standard antiemetic therapy. Complete responses to THC was recorded in 36 of 79 courses of therapy, compared to 16 of 78 courses with Compazine. Of 25 patients who were treated with both drugs and who expressed a preference, 20 preferred THC. Results of this study demonstrated a clear superiority of THC over Compazine.

Orr and coworkers, at the Southern California Cancer Center, have compared THC and prochlorperazine (Campazine) with placebo therapy in 55 patients who have experienced severe nausea and vomiting with anticancer drug treatment. Nausea was absent in 47 percent of patients receiving THC, compared to 15 percent with prochlorperazine and only 9 percent in the placebo group. Dr. Schein reported that a study presently in progress at his research center also appears to be confirming the superiority of THC over Compazine.

Dr. Schein reported that Frytak and coworkers at the Mayo Clinic, in contrast to other studies, found that the antiemetic properties of

THC, although superior to placebo, were equal but not superior to that of the standard phenothiazine antiemetic prochlorperazine. However, it was noted that the median peak THC concentration obtained was only 4 ng./ml. (range 2.7 to 6.3). The plasma concentration achieved in this trial is below the 10 ng./ml. level which was associated with an almost complete reduction in nausea and vomiting in the Chang study.

Dr. Schein also referred to a study by Klain Neleman and coworkers, from the Center for Human Toxicology in Utrecht, the Netherlands, who performed a double-blind randomized study of THC versus placebo in 11 patients. In this study, THC therapy was found to be statistically superior to placebo and antiemetic therapy; however, the side effects and toxicities of THC were found to be so pronounced that the investigators stated that most patients preferred the treatment-related nausea and vomiting to THC (THC blood levels measured in this study were quite high, however, with a range of 25–426 ng./ml.).

Dr. Schein discussed the clinical toxicities associated with treatment with THC. In addition to the experience of a "high", the next most common side effect has been somnolence. More serious toxicities are characterized by paranoid ideation, panic and frightening hallucinations-grouped as dysphoric reactions. The overall incidence of these side effects has been quite variable across the studies. Sallan reported that 9 percent of his patients experienced dysphoric reactions. Chang and Lucas reported a 21 percent and 8 percent incidence of toxic reactions, necessitating discontinuation of therapy. In contrast, Frytak reported a 30 percent refusal to continue THC therapy because of side effects. Dr. Schein stated that there is now an attempt to carefully examine the clinical factors that may contribute to this differing degree of patient acceptance and tolerance. One probable factor is the average age of patients in each of the studies, younger patients tending to have more success with the treatment. The sensation or experience of a "high" may be entirely acceptable or desired by a young person, where the same sensation of depersonalization may be a devastating experience to some older persons. In addition, previous marihuana experience may affect the results of the studies, not only in differences in social acceptability of marihuana and expectation of treatment, but also because of differences in metabolism of this drug. In addition, Dr. Schein testified that the setting of the studies also could have differed. Finally, excessively high blood concentrations in some cases may be a contributing factor ior the increased toxicity in some studies.

In summary, Dr. Schein concluded that THC has an important salutory effect on cancer chemotherapy induced nausea and vomiting.

Dr. Schein concluded his testimony with the following statement:

The positive results of clinical trials of THC have widely published in well read, peer-reviewed medical journals as well as in the lay press. Nevertheless, THC remains a Schedule I drug ,which may be used only by approved researchers. Many oncologists find themselves in the awkward position of explaining to their patients that, while THC might be effective in controlling vomiting in their case, the material is not available from commercial sources nor is it being distributed under the auspices of the National Cancer Institute. Serious consideration must now be given to changing the schedule of this agent so it can be more widely distributed to physicians experienced in the use of antiemetics and chemotherapeutic agents. In this regard, the FDA Advisory Committee on Oncologic Drugs will be reviewing a submission by the National Cancer Institute to have THC

designated a Group C agent, whereby it can be provided to register physicians for the specific indication of chemotherapy-related nausea and vomiting. From my own perspective, I can see no justification in prohibiting physicians, licensed to prescribe narcotics such as morphine, from administering THC in an attempt to improve the quality of life of the large number of cancer victims receiving intensive forms of chemotherapy.

Dr. Steven Sallan

Dr. Steven Sallan, Assistant Professor of Harvard Medical School and Clinical Director of Pediatric Oncology at the Sidney Farber Cancer Institute and Children's Medical Center in Boston, stated in his testimony that he completely concurred with the testimony of Dr. Schein. Dr. Sallan stated that he first began doing research in patients receiving cancer chemotherapy in 1974. Patients were often perceiving their treatment as being worse than their disease, Sallan testified, and in some cases the patients refused to be treated. Anecdotal evidence began to develop in the form of reports from marihuana smokers who reported that when they were high they had less nausea and vomiting. Therefore, Sallan began to systematically study this phenomenon. Sallan reported that his study group obtained THC in pill form and identical placebos, and did their first study between 1974 and 1975. This study found that 80 percent of patients had some response to oral THC and none had any response to placebo. Over the next 4 years, Sallan testified, his study group replaced the placebo with the most commonly used oral antiemetic, Compazine. More than 80 patients were treated with THC or Compazine, neither patients nor physician knowing who was receiving which of the two drugs. Dr. Sallan reported that for half of the patients, neither treatment was effective. However, for another half, THC was an effective antiemetic. For half of that half, or a quarter of the patients, standard antiemetics like Compazine are also helpful. Therefore, Dr. Sallan testified that in his studies, for 1 in 4 patients who are receiving cancer chemotherapy, only THC was effective. No other alternative was available to them. Dr. Sallan testified as to his receiving probably thousands of telephone calls over the last 5 or 6 years from across the country asking him to supply them with THC. Sallan reported his displeasure at not being able to provide much assistance to these individuals.

Sallan further stated that his medical experience was consistent with that heard from the patient panel. Although Dr. Sallan reported that he had not studied smoked marihuana, he has had anecdotal accounts from his patients who were unable to keep any oral THC in their stomach and who subsequently went in to gain relief by smoking marihuana.

Dr. Solomon Garb

Dr. Solomon Garb, Associate Clinical Professor of Medicine at the University of Colorado Medical Center and President of the Medical Staff at the AMC Cancer Research Center and Hospital in Lakewood, Colorado, also testified as to his work with THC.

Dr. Garb testified that his research protocol has a major difference from the others in that he uses THC together with Compazine. Although Compazine has a mild antivomiting effect of its own, Garb uses it to block the undesirable cerebral effects of THC. Dr. Garb testified that in his experience, Compazine blocks most of the "highs", anxiety,

hallucinations and other side effects to be expected from large doses of THC. Garb further stated:

The concomitant use of Compazine makes it possible for me to use higher doses of THC than would otherwise be safe and thus obtain improved results. I estimate that when I can gradually increase a patient's dose of THC plus Compazine, I am able to obtain an average of approximately 80 percent prevention of nausea and vomiting. The effectiveness of THC varies from patient to patient depending on several factors including the type of chemotherapy. With several of the chemotherapeutic agents I have obtained complete or almost complete prevention of nausea and vomiting. With one, DTIC, I have not yet achieved more than 50 percent prevention.

Garb testified that there have been a number of papers by leading clinical investigators describing the clinical value of THC. One group of investigators concluded that THC was about equal to Compazine; the others found it superior. They all agree that it has antiemetic effects. Garb testified that he suspected the differences in degree comes from differences in dose schedules.

Garb made the following statement with respect to the seriousness of vomiting as a side effect of cancer chemotherapy treatment.

In some cases, severe prolonged vomiting from any cause can be fatal. I estimate that the fear of vomiting is indirectly fatal in up to 5 percent of patients with certain cancers. The chemotherapy for some cancers with a high cure rate, such as Hodgkins disease and cancer of the testes, produces extremely severe vomiting and some patients are just unable to continue. They stop treatment even though they have been told that they are losing their only chance for survival.

Garb stated that compared with other drugs, THC appears to have relatively little danger, and believed the drug to be much safer for a patient than prolonged severe nausea and vomiting.

Dr. Garb concluded his statement with the following comment about regulation.

It is not clear to me just which schedule THC and marihuana should be placed on. As I understand the law, Schedule I drugs are those that, in addition to abuse potential, have no medical value. It appears to me that there is now substantial evidence that THC does have some medical value. The question is whether the evidence for that medical value is now sufficient to remove it from Schedule I. My personal belief is that it is, but I would not be so presumptuous as to suggest that so vital a decision be made on the basis of my beliefs. I recommend that a committee of expert oncologists be asked to evaluate this issue.

Discussion

A number of significant issues were addressed at the hearing, during the question and answer period following the testimonies. In response to a question by Mr. Neal relating to differential benefits of the marihuana cigarette as contrasted to THC in pill form, Dr. Sallan stated:

There is no question in my mind that the oral route for an antiemetic, a pill, is the absolute worst route for the patient who has a lot of anticipatory nausea and vomiting. The expectation of this treatment engenders nausea and vomiting in people, the night before, and what they need is something that gets away from the stomach. A suppository is a good idea. The smoke route is in some ways ideal. Certainly when we want a drug to be absolutely sure, general anesthesia, we put it on the face, they breathe it across their lungs, it's in their bloodstream immediately. I think any drug that can be delivered that way would certainly have some use that way.

In response to a question by Mr. Neal as to whether research with marihuana cigarettes would be useful, Dr. Sallan stated:

Very much so. We know about the whole phenomenon from marihuana smokers. We listened to them. We would have pursued it with marihuana, had that been a reasonably accessible pathway. I think now we know that THC is effective for some, it should be available. We know that marihuana is effective for some. The Chang study showed that at the National Cancer Institute. It should be available. There should be more available. We should learn to put it into injectable form. We should have something by suppository route. That is good for nonsmokers and other people and children. We need more, not just a finely defined limit route of administration that might be available at this time.

Dr. Schein agreed "that giving an oral medication for the purposes of controlling nausea and vomiting does not make a great deal of sense. If the patient isn't obviously vomiting the drug up, then certainly the motility of the bowel may be disrupted in such a way so that the absorption of the drug might be quite disturbed. The pharmacology studies of oral THC have demonstrated that there is a considerable degree of variation of absorption from patient to patient. Some of this may actually relate to the effects of chemotherapy on bowel functions. So we would certainly welcome a different form of the same material, either in the form of a rectal suppository, intramuscular injections, or perhaps in the form of cigarettes. There is only a limited amount of data relating to the use of marihuana, smoked marihuana, as opposed to oral THC, and that largely came from Chang's study."

With the Chang study, no patients vomited after smoking marihuana cigarettes, if the plasma concentration was 10 nanograms per milliliter. So we may be dealing just with a dose related effect rather than a specific route, and the question is whether or not the route itself is the most effective route of administering the agent.

The following line of questioning by Congressman Neal addressed the issues of the efficacy of THC and of scheduling of THC according to the Controlled Substances Act.

Mr. NEAL. In other words, you don't have any questions about the active ingredient of marihuana that is bringing about the result? That's settled in your mind?

Dr. SCHEIN. There's little questions that delta-9 is effective. There may be other constituents of cannabis which are equally effective or more effective, but this will, of course, have to be the subject of extensive clinical investigations. This will probably have to be tested separately, or perhaps a useful study would be a random, uncontrolled trial, comparing oral THC against smoked marihuana.

Mr. NEAL. Well, just for the record, it's my understanding . . . that the assumption for a drug to be in Schedule I is that it has no medical use. And just for the record, I want to make clear that you all, the three of you, are saying that there are very definite medical uses for these substances.

Dr. SALLAN. Most definitely.

Dr. GARB. Sir, I would add there is a lot more than three of us. If you add up all the authors of the seven papers, I think you will find at least a score of us have said that.

Mr. NEAL. Well, now, would you say this about THC only, or about marihuana and THC?

Dr. GARB. I would say it about both.

Dr. SALLAN. I would say it about both, but I have much less certainty about marihuana because it doesn't have the same scientific rigor in the study at this time.

Mr. NEAL. Well, then, we need more study, and to get the study, we need a substance available for you to study, but as long as it's under Schedule I, it will not be available, because the assumption will be that there is no medical use. It's a Catch-22 situation, it seems to me.

Mr. Neal also inquired as to the difficulty involved in obtaining these drugs for research purposes.

Mr. NEAL. After your first application, how long did it take for you to get the THC?

Dr. GARB. Approximately 7 months.

Mr. NEAL. Seven months. And how long has it taken some of your colleagues?

Dr. GARB. Well, a couple of them—one of them, I know, took a year and a half, one took two years, but I think it's shorter now.

Mr. NEAL. Well, at the beginning of your testimony, you said all the Federal agencies had been so cooperative. I'd just like to know if they were so cooperative, why did it take so long?

Dr. GARB. Well, because THC and marihuana are Schedule I drugs, and there are obvious rules and regulations, and every agency has its own rules and regulations to follow, not only its own rules and regulations, they have to follow the rules and regulations of all the other agencies; and nobody can make any short-cuts, nobody can make any changes, because it's all law.

So I feel that they did everything that was reasonably possible within the law to be helpful to me, but, you know, they are a government agency. I couldn't expect them to break the law.

Mr. NEAL. So what you are saying is that whenever a drug is on Schedule I, it takes a long time to get the drug?

Dr. GARB. I think that's obvious, yes.

Mr. NEAL. If you're going to obey the law.

Dr. GARB. Yes.

Mr. NEAL. Obviously, it doesn't take a lot of people a long time to get it, marihuana, anyway.

Well, that's interesting. It seems to me very much of a Catch-22 situation.

Dr. GARB. Basically I felt that every one of the government officials whom I dealt with, dealt with me in good faith.

Mr. NEAL. The point is, is this, as I understand it: Any high school kid in America just about can go out and get marihuana in an hour, and yet it takes you, who want to do research that will help people who are experiencing severe suffering and pain, and on the verge of death, it takes you seven months to get it.

Dr. GARB. Uh-huh.

Mr. NEAL. Well, that doesn't make very much sense to me.

Communications

A number of individuals active in the oncology field have written letters to the Select Committee on Narcotics reflecting their opinions on the medical use of THC and marihuana. Dr. Larry Einhorn, one of the nation's leading cancer researchers cosigned a letter written by one of his four oncology nurses associated with his oncology program. She wrote:

Five years ago, Dr. Einhorn, when seeking THC for patients receiving chemotherapy, found his efforts futile. Several government agencies failed to respond to his preliminary research. As a result, he was limited to using commercially available antiemetics which failed to control or prevent the debilitating side effects of emesis producing chemotherapy.

Dr. Carl Ellenberger wrote the following about his experience in trying to do research in this area.

Our original application for permission to use THC on an experimental basis was sent to the Drug Enforcement Administration on January 17, 1977. We were notified by the DEA on August 18, 1977, that the research protocol was disapproved because 'the data submitted is not sufficient to permit the evaluation for studies in human volunteers'. By this time, my co-worker, Dr. Dennis Petro, had joined the FDA as a neurologic consultant. He was able to determine that our proposal had been disapproved for two reasons:

One, we did not explicitly state that we would not administer the drug to pregnant women; and two, having not read the proposal carefully, one or more individuals who made the decision for disapproval were under the impression that we proposed to treat spasticity of the colon.

Dr. John Laszlo of Duke University wrote the following:

We submit that present access to the drug by practicing oncologists is completely inadequate and that the system of distribution and licensing, as well as the schedule classification of this substance needs to be changed.

Dr. Perez-Reyes of the University of North Carolina submitted the following testimony about the question of the appropriate schedule for THC and marihuana.

It is a matter of compassion and humanity to relieve their symptoms and should not be a matter of legality. Law that placed marihuana as a Schedule I substance were enacted many years ago, out of ignorance and prejudice. To continue to uphold them in spite of widespread scientific evidence on the potential therapeutic use of marihuana and its components is absurd.

GLAUCOMA PANEL

Dr. John Merritt

The third panel of the morning addressed the therapeutic use of THC and marihuana with glaucoma patients. Glaucoma, the leading cause of preventable blindness in the United States, is characterized by increased pressures within the eye producing damage to the optic nerve.

Dr. John Merritt, ophthalmologist from the University of North Carolina testified on the results of his 3½ years studying the use of marihuana and THC in the treatment of glaucoma. Dr. Merritt feels that marihuana may be good for glaucoma, since the drug lowers intraocular pressure. However, side effects include increased heart rate, decreased blood pressure and many alterations in sensorium. Dr. Merritt stated that mental changes of depersonalization and acute panic reactions were most problematic for the elderly marihuana-naive patients. In addition, the use of marihuana high in delta-9 THC content with its known cardiovascular effects may be hazardous to elderly patients, the patient population most at risk for glaucoma. Dr. Merritt feels that THC capsules, and eyedrops should both be investigated, but also believes that studies should be performed with marihuana not high in delta-9 THC content.

Dr. Merritt stated that "there has been definitely governmental interference with the research on a bureaucratic level."

Dr. Carl Kupfer

The testimony of Dr. Carl Kupfer, Director, National Eye Institute, clarified some of the issues involved in marihuana research. Treatment for glaucoma, either with drugs or surgery, he stated, is primarily aimed at lessening intraocular pressure in an attempt to preserve vision. Marihuana is only one of many drugs known to reduce intraocular pressure. Current studies focus on whether marihuana's intraocular pressure-lowering effects last long enough to effectively impact on the disease process. Dr. Kupfer pointed out that even though a drug may lower intraocular pressure, it does not necessarily mean that it will decrease the rate of damage to visual function. Since marihuana lowers blood pressure as well as intraocular pressure, this may interfere with blood supply to the optic nerve. Therefore, even though the pressure in the eye may decrease, a patient may not be protected against losing function from the glaucoma process. Congressman McDonald even pointed out that conceivably it is possible that the lowering of blood pressure could actually result in worsening of eyesight, even though the intraocular pressure has been lessened.

Judith Quattlebaum

Testimony was presented at the hearing by Mrs. Judith Quattlebaum, President and Executive Director, National Committee on the Treatment of Intractable Pain.

Mrs. Quattlebaum argued that some cases of terminal pain cannot be treated adequately without heroin. She stated that in attempts to see that terminal cancer pain is prevented, "we have to fight a reluctant bureaucracy that frequently obscures the central issues." Mrs. Quattlebaum presented the results of a study done by Dr. Robert Twycross. In this study of 699 patients, reported in the journal Pain (1977), Dr. Twycross concluded that, while morphine is as good by mouth, heroin is superior by injections, when large doses are required.

In her testimony, Mrs. Quattlebaum claimed that Dr. Seymour Perry, Chairman of the Federal Interagency Committee on Pain and Discomfort, has implied that only a negligible minority of patients need heroin. Mrs. Quattlebaum stated that it was her Committee's intention to represent the right to heroin by this small group of patients, which she claimed consists of thousands of patients.

Mrs. Quattlebaum testified that the British have found that heroin has a faster onset of action, causes less vomiting, and is the best analgesic when injections are needed. In addition, it is more potent per unit volume than morphine, so much smaller amounts can provide more relief in less painful injections. This, stated Mrs. Quattlebaum, is crucial when emaciated patients with little flesh require frequent large doses.

Mrs. Quattlebaum stated that British doctors use heroin in some 10 percent of cancer patients and more frequently in the last 48 hours of life.

Mrs. Quattlebaum quoted Dr. William Beaver of Georgetown University Medical School who made the point that no analgesic has identical properties, and patients exhibiting allergic or idiosyncratic reactions to one narcotic may tolerate another without difficulty. This fact alone, he argues, justifies having a variety of alternative drug available.

Mrs. Quattlebaum states that Federal agencies serve to discourage research with heroin. She feels that concern about abuse in this country has overshadowed and obscured the benefit of heroin. This, states Mrs. Quattlebaum, "reflects an obsessive concern about addiction that supersedes even the agony of the dying."

Dr. Alan Mondzac

Dr. Alan Mondzac, an oncologist in Washington, D.C., and on the Board of Directors of the National Committee on the Treatment of Intractable Pain, testified that "heroin is a necessity for pain control." Dr. Mondzac testified that both Belgium and Great Britain have made heroin available to sick people. In comparing heroin and morphine, Dr. Mondzac stated that heroin does not cause the nausea which is common in patients who receive morphine. Dr. Mondzac testified that heroin "works more quickly than morphine, and is more soluble and potent than morphine, so a small volume such as 0.2 cubic

centimeters of heroin can be the equivalent of 5 to 10 cubic centimeters in volume of morphine." These properties of speed and potency were cited as elements which make heroin desirable for cancer patients.

Dr. Mondzac stated that there is little information available on heroin and its use in patients. The United States has funded two studies—one at Sloan-Kettering and one at Georgetown University. Dr. Mondzac made the following comments about these two studies:

The Sloan-Kettering study used heroin only in postoperative patients with cancer, and not for treating chronic pain. The study found no difference between heroin and morphine. Because of its structure, I think this study is meaningless and not applicable to the problem of pain control in the dying patient. The Georgetown study is too limited in scope to be of any value at present.

Mondzac again makes the argument for the use of heroin:

Morphine causes nausea, vomiting and requires the injection of large volumes of liquid to achieve adequate pain relieving doses. Large injections in themselves cause more pain and even more suffering in the already wasted body of the cancer patient, because large injections cannot be given easily and painlessly. If heroin were available for physician's use in hospitalized patients, there would be a next drug to give, and one that could be given easily and without pain, because such small quantities give so much relief. A body that is skeletally thin can easily absorb a heroin injection, but a morphine shot is terribly painful.

Discussion

During the discussion after the testimony, Mrs. Quattlebaum stated that Congressman Edward Madigan had introduced a bill to amend the Controlled Substances Act to permit heroin for the terminally ill.

Congressman Neal pointed out that one of the criteria of Schedule I drugs is that they have no medical use. However, this appeared to be in contrast to the testimony of Mrs. Quattlebaum and Dr. Mondzac, who felt that heroin does have medical use.

FEDERAL PANEL

The following section outlines the roles and orientations of each of the various Federal agencies relating to the issues of therapeutic uses of THC, marihuana and heroin. The material is based upon the testimonies of these agencies at the May 20 hearing.

National Cancer Institute (NCI)

Dr. Jack MacDonald, Associate Director for Cancer Therapy Evaluation, Division of Cancer Treatment of the National Cancer Institute testified on behalf of that organization. Dr. MacDonald stated that "THC has proved to be beneficial to some patients who have failed to be relieved of nausea and vomiting by standard antiemetic drugs." He referred to a study by Chang and his co-investigators at NCI which indicated that if THC concentration levels were greater than 10 nanograms per milliliter, the drug was 95 percent effective in preventing vomiting. This was true whether the drug was taken orally or by smoking.

Dr. MacDonald testified that the chemical data on Nabilone, a synthetic cannabinoid developed by Eli Lilly, appeared to be more promising than delta-9-THC because it appeared to relieve nausea and vomiting as effectively as THC but without some of the side effects of THC. Therefore, a decision was made to encourage development of the drug rather than delta-9-THC. However, when subsequent chronic toxicity studies of Nabilone in dogs revealed unacceptable neurologi-

cal toxicity, the National Cancer Institute submitted an Investigational New Drug Application (IND) to the Food and Drug Administration for THC.

THC was placed at that time in Group B of the distribution network making it available to investigators at cancer centers or to investigators who worked under the auspices of a National Cancer Institute drug evaluation grant or contract at another institution. Such investigators could write research protocols to study the possible benefit of THC. These protocols were reviewed by NCI staff and if approved were amended to the IND for THC. Investigators were required to have a DEA Schedule I registration and be in compliance with the appropriate DEA rules and regulations with regard to controlled substances.

Although many inquiries were made by investigators interested in studying the antiemetic effects of THC, few actually filed protocols. This small number may have resulted from a variety of reasons not the least of which are the added requirements and risks of handling and distributing Schedule I controlled substances.

MacDonald stated that representatives from Pfizer presented preclinical data relative to levonantradol. This product has entered clinical trials and appears to be promising. Representatives from Pfizer have made presentations to the Division of Cancer Treatment's Decision Network and the NCI plans to crossfile on the Pfizer levonantradol IND to expand the clinical studies of this agent through the NCI's nationwide clinical network.

Dr. MacDonald stated that THC can be a useful agent in the alleviation of nausea and vomiting induced by chemotherapy in significant numbers of patients. With this in mind, the Division of Cancer Treatment has recently proposed to the Food and Drug Administration that the drug be moved from Group B of its distribution scheme to Group C. Under Group C, a compound is considered to have documented medical efficacy for a specific indication and not be a research drug per se, although it remains investigational. Since the drug will remain a controlled substance, NCI is requesting that it be distributed to community/regional comprehensive cancer centers as well as to the medical school affiliated hospital pharmacies that would be better equipped to handle the storage and record-keeping that is involved with any controlled substance. This would amount to 500 to 600 separate pharmacies scattered around the country at these institutions.

The NCI anticipates that this change would make THC available to practicing oncologists around the country for the treatment of nausea and vomiting suffered by the patients for whom they care. Dr. MacDonald states that it is the hope of NCI that a pharmaceutical company would soon become interested in marketing this drug. However, until then, NCI feels that it will have to take responsibility for supplying this useful drug to relieve the suffering of cancer patients throughout the country.

Food and Drug Administration (FDA)

Dr. Richard Crout, Director of the Bureau of Drugs at the Food and Drug Administration, testified in behalf of that organization.

Dr. Crout stated that FDA's involvement in the handling of THC and marihuana occur in two respects:

1. Primarily FDA is charged with enforcing the requirements of the Federal Food, Drug and Cosmetic Act as to clinical investigations of all unapproved new drugs, such as THC and marihuana.

2. FDA prepares medical and scientific evaluations of drugs for the purposes of scheduling drugs under the Controlled Substances Act.

Dr. Crout testified that the only THC preparation that appears nearly ready for the new drug evaluation process is oral THC capsules for the treatment of nausea and vomiting in patients undergoing cancer chemotherapy. Studies on THC for the treatment of glaucoma are much more preliminary. FDA does not anticipate at present any submissions of new drug applications requesting approval of marihuana cigarettes. Although cigarettes are being used in a few controlled clinical trials in cancer patients, these studies are just getting under way, and meaningful scientific results are not yet available.

Dr. Crout stated that FDA is in receipt of studies indicating that orally administered THC is effective in preventing nausea and vomiting in patients undergoing cancer chemotherapy and suggest also that the drug is effective in some patients who do not respond well to other antinausea drugs. Crout specified that under the Federal Food, Drug and Cosmetic Act, THC is an investigational drug, so all studies of its therapeutic effect are required to be conducted under investigational new drug applications (IND's). A sponsor wishing to conduct research on a new drug must submit to the FDA an IND, and the FDA is required to handle that application within 30 days.

THC is not only an investigational drug, however, it is also a drug controlled in Schedule I of the Controlled Substances Act, the most strictly controlled schedule. Persons who wish to conduct research with Schedule I drugs must obtain special registration from DEA and have their investigational protocols approved by FDA. At one time, according to FDA, IND's on Schedule I substances took a long time to be approved because they were reviewed by an advisory committee that met relatively infrequently. About 2 years ago, FDA eliminated this time-consuming step, however, and in addition, established a Master File for manufacturing data and toxicity data on THC that any sponsor could use. These measures repeatedly reduce the paperwork associated with INDs on THC and result in a more expedient review process. Furthermore, FDA now gives prospective sponsors detailed guidance on submitting IND's, including examples of medical protocols, and appropriate forms for obtaining a Schedule I registration from DEA and obtaining the drug from NIDA.

According to Dr. Crout, it no longer takes 7 to 9 months to get an IND. At the time of the hearing, there were 47 active IND's on THC on file at the FDA; 37 for the treatment of nausea and vomiting, 6 for glaucoma, 3 for spasticity, and 1 for anorexia nervosa. The National Cancer Institute holds the IND under which studies supported by the Department of Health and Human Services are conducted. In addition, six States hold IND's under which investigators in those States conduct clinical trials. There have been an increasing number of applications to FDA from States.

The witness further explained that once a body of information sufficient to support the marketing of a drug has been collected under

an IND, the sponsor ordinarily submits another application, called a New Drug Application, to the FDA. This application contains the clinical and animal data on the safety and effectiveness of the drug, proposed labelling of the drug, information specifications, and so on. Its purpose is to gather the evidence together, which the FDA reviews prior to permitting a drug onto the open market. Most drugs are developed by the drug industry, and therefore the IND on the drug and the subsequent New Drug Application are usually submitted by the sponsoring drug manufacturer. No drug manufacturer has yet applied for approval to market THC, however, under a New Drug Application.

Several firms have conferred with the FDA, NIDA, NCI, and DEA about submitting an NDA, and FDA has offered all data in its files relating to chemical controls and preclinical animal studies. Clinical data developed by NCI would also be available. However, even if an application were submitted immediately, FDA could not guarantee its rapid approval. THC is not an easy substance to make and is chemically unstable, so that numerous manufacturing and quality control problems can be anticipated.

Thus, explained Crout, the distribution of THC in the near term for medical purposes would almost certainly continue only under the IND mechanism. As an interim measure, until a drug manufacturer is available and an NDA approved, the NCI has proposed that THC be made available to more cancer specialists under a standing arrangement employed by NCI for investigational cancer drugs known as the "Group C Plan." FDA has concurred with NCI that THC may be a candidate for Group C investigational status. Therefore, NCI has prepared an application for this classification which FDA received on May 12. FDA has scheduled a discussion on placing THC in the Group C cancer plan for FDA's Oncology Advisory Committee meeting to be held on June 26, 1980. (This meeting was held and that Committee recommended that THC be placed in the Group C distribution plan.)

Ordinarily, an investigational cancer drug in Group C is sent directly from NCI to a requesting physician who is a cancer specialist for the treatment of an individual patient. Because of the large number of patients who might be candidates for trials on the drug, NCI is concerned that direct shipment for individual patients may not be administratively feasible. NCI has therefore proposed that it be allowed to ship THC as an investigational drug to certain hospital pharmacies which will in turn dispense the drug to qualified cancer specialists who are registered with DEA and are included in the NCI's IND for the drug. This proposal is presently under study among the involved agencies.

National Institute on Drug Abuse (NIDA)

Dr. Marvin Snyder, Director, Division of Research, National Institute on Drug Abuse, testified on behalf of that organization.

Dr. Snyder stated that the National Institute on Drug Abuse has been supplying marihuana and THC to researchers for the past decade. These substances were being distributed to researchers in order to understand the basic biological and behavioral mode of action of marihuana and THC.

In the course of this research, NIDA developed a large body of animal toxicology data—which was transferred to FDA. To facilitate

human studies, NIDA also developed several standardized materials including marihuana cigarettes of known size and potency, THC capsules of various strengths, opthalmic preparations and some intravenous preparations.

Dr. Snyder emphasized NIDA's concern over the probable psychological effects of chronic use of marihuana in glaucoma patients. As a result of this NIDA is working with the National Eye Institute in trying to develop approved formulations for an eye-drop preparation. According to NIDA, this would elminate the psychological effects of either smoked or oral THC. NIDA is also concerned that glaucoma is a chronic disease requiring chronic medication. This reflects NIDA's expressed concern over the long term effects of marihuana use.

NIDA also expresses concern over the possibility in cancer patients that given chronic marihuana use, there might be possible adverse effects on patient's immunologic response.

According to Dr. Snyder, NIDA, in anticipation of the plan to move THC to cancer distribution Group C, in collaboration with NCI, is preparing to manufacture 500,000 capsules by July 1 of 1980. Plans call for another 500,000 to be manufactured by January 1, 1981.

In accordance with agreements reached by the Interagency Committee on New Therapies for Pain and Discomfort, NIDA will be reimbursed by NCI for the costs of producing the capsules. In view of the wide-scale distribution of THC, NIDA and NCI staff are also working on plans to transfer responsibility for large-scale production of THC to NCI. An arrangement has also been reached with the National Eye Institute, so that NIDA will be reimbursed for supplying drugs to be used in studies of the use of cannabinoids in treating glaucoma. NIDA will continue to supply the drug for its own research related to drug abuse.

Drug Enforcement Administration (DEA)

Mr. Gene Haislip, Director of the Office of Compliance and Regulatory Affairs for Drug Enforcement Administration, testified on behalf of DEA.

Mr. Haislip stated that DEA's position on the appropriate schedule for THC is quite clear. Until the FDA certifies that THC has a legitimate medical use, the drug must remain in Schedule I.

In the event that THC is approved for general marketing by the FDA and given an approved NDA, a complete review of the drug pursuant to Section 201 of the Controlled Substances Act (CSA) would have to be made in order to establish the appropriate drug schedule.

Included in this review would be a study of United States obligations under international treaties. According to DEA, as a signatory to the convention on psychotropic substances, the United States has an obligation to apply the most stringent controls on THC, even if approved for medical purposes. Under the Psychotropic Convention, THC is in Schedule I and Article 7 provides in part, that for Schedule I substances parties shall prohibit all use except for scientific and very limited medical uses by duly authorized persons in medical or scientific establishments which are directly under the control of these governments or specifically approved by them.

The provisions of CSA Schedule I limit the distribution of THC to those persons duly authorized through an approved IND and a DEA

registration for Schedule I research. In an effort to facilitate research and to ease the burden on practitioners involved in the use of THC, blanket statewide IND's and DEA registrations have been authorized which allow several practitioners to operate without individual registrations. These systems are available to any State which determines a need for THC availability and, in most cases, does not require any specific legislation at the State level. It should be noted that there are no prescription provisions for Schedule I drugs under the Psychotropic Convention.

Other treaty provisions require the "close supervision of the activities . . . of such drugs." This includes frequent and thorough inspection of manufacturers and distributors, documentation of transfers, periodic reporting of transactions involving the substance, and monitoring the uses and misuse of the substance.

In addition, DEA must "restrict the amount supplied to a duly authorized person . . ." DEA has the responsibility to limit the production of these substances to the amount necessary for medical, scientific, research and industrial needs. The mechanism by which DEA fulfills this responsibility is the quota system. If THC were removed from Schedule I, the U.S. treaty obligation would continue. The rescheduling action would require that THC be placed on a schedule that would limit its use to specific individuals, provide for the close supervision of all activities involving the drug, and provide for limited production.

According to Mr. Haislip, the U.S. Government will make available to the World Health Organization data resulting from the research of the drug's medical usefulness. If the data that the W.H.O. receives should indicate a medical usefulness, a scheduling change under the Psychotropic Convention could result, thus easing the restrictions on the use of THC.

Haislip stated that DEA is chiefly concerned over the possibility of diversion of controlled substances. DEA feels that THC can be made available to authorized oncologists, with adequate controls to prevent diversion, in its current control status. Haislip pointed out that DEA is available to assist anyone in need of help or advice on obtaining the necessary authorizations.

National Eye Institute (NEI)

Dr. Carl Kupfer, Director of the National Eye Institute, made brief additional comments on behalf of NEI as he had read comments into the record earlier in the day.

Kupfer stated that one of the National Eye Institute's (NEI) program priorities is to support the scientific evaluation of new methods of treating glaucoma. Presently, there are five funded projects in this area, at a total cost of approximately $1 million.

Kupfer stated that the main thrust of the research has been to establish the fact that marihuana and its derivatives can lower the intraocular pressure for short periods of time. The Eye Institute is presently looking toward studies which can determine whether the pressure can remain down over long periods of time, since to avoid the damage to the optic nerve, one must presumably keep the pressure down for long periods of time (see Kupfer's previous testimony).

In addition, Dr. Kupfer pointed out that there is a delicate balance between the level of the pressure in the eye, and the level of the

systemic blood pressure. The present thinking about the danger to the optic nerve is that there is some interference with the supply of blood to the optic nerve. This can be a result of increased pressure in the eye not allowing enough blood to reach the optic nerve; or, in some instances, it can be due to general (systemic) low blood pressure, in which there is insufficient blood reaching the optic nerve. Therefore, in the development of a drug for glaucoma, the effect both on intraocular pressure and on systemic pressure must be considered. The smoking of marihuana cigarettes does cause in a large number of patients a significant fall in systemic blood pressure. Studies on one antiglaucoma drug developed in another country revealed that it did produce a fall in intraocular pressure, but after many years of experience was removed from the market, because it also lowered systemic blood pressure, the danger from the glaucomic process continued, and visual function was lost.

It is therefore the position of the National Eye Institute that since the overall concern of the glaucoma patient is the prevention of eventual blindness, an assessment must be made to determine not only whether marihuana or THC lower the intraocular pressure chronically, but whether it will also prevent the ultimate loss of visual function

Because the medical use of marihuana is still under investigation, the drug's legal use in the treatment of glaucoma is limited to clinical investigations that have been approved by the FDA. In addition, the investigator must be registered with the DEA before he or she can receive the drug for research. The National Institute on Drug Abuse (NIDA), which is the primary supporter of government-sponsored marihuana research, supplies the drug to the qualified scientific investigators who carry out the studies.

Interagency Committee on Pain and Discomfort

Dr. Diane Fink from the National Cancer Institute and Chairman of the Interagency Committee on New Therapies for Pain and Discomfort testified as to the role of this Committee.

Dr. Fink stated that the Interagency Committee is composed of Federal physicians and scientists. It was created in 1977 to assess the status of research on intractable pain and the humane cure of dying patients and to develop recommendations in these two areas. The Interagency Committee has broad representation from Federal agencies involved in all aspects of the drug problem with the National Institute of Health as the lead agency.

Dr. Fink stated that a principal charge of the Interagency Committee is to develop recommendations whereby heroin, marihuana, cannabinoids and other Schedule I drugs are made available to investigators for therapeutic research purposes. The Interagency Committee has recommended to HEW and to the White House that NCI's distribution system make THC available to investigators using valid research protocols for the study of THC in nausea and vomiting of cancer patients undergoing cancer treatment. Dr. Fink reported the Committee's belief that, based on the evidence available, THC is a valuable drug for the control of nausea and vomiting in patients with cancer.

Dr. Fink pointed out that some evidence exists that the natural plant product, marihuana, may be effective as an antiemetic agent.

However, her testimony emphasized the limitations of this compound—such as the lack of uniformity on the composition of marihuana cigarettes. In addition, Fink argued that the inhalation route (smoking) is undesirable to many patients and poses its own safety problems. Also, she pointed to the insufficient chemical trial information on the true effectiveness of marihuana as compared to THC.

Fink communicated the sense that the Interagency Committee feels that the effects of marihuana in the treatment of glaucoma is unsettled and requires further research.

As part of its original mandate, the Interagency Committee was instructed to examine the potential usefulness of heroin for the management of intractable pain in cancer patients. Dr. Fink, in her testimony, emphasized that many cases of cancer pain can be managed successfully without narcotic analgesics. She referred to experts who claim that pain in cancer patients, even in dying patients, can be successfully managed by currently available medication, such as morphine and methadone. Fink further testified that a major study in England showed no advantage of heroin as compared to morphine in the management of chronic pain in dying cancer patients when the drug was given in adequate doses and by the proper schedule. In addition, the testimony on behalf of the Interagency Committee stated that the use of heroin has been largely abandoned in many of the English hospices.

However, Fink reported that the Interagency Committee, after review of available evidence did recommend that research in the United States on heroin for pain relief in dying patients be pursued. Tests were initiated to examine the therapeutic efficacy of heroin as compared to morphine. One study is at Memorial Sloan Kettering in New York and the second at Georgetown University.

DISCUSSION

THC

The issue addressed by the Select Committee is whether the Schedule I drug, THC, has shown a specific medical benefit to allow its broadened availability. In this instance, the testimony shows THC to be an effective antiemetic for cancer patients undergoing chemotherapy treatment when all other available drugs have failed. Recognizing the overwhelming abuse of marihuana, the U.S. Government concentrated on chemically fabricated THC rather than the marihuana cigarette as the antiemetic, though the marihuana cigarette is made available under very limited circumstances when the THC capsules are shown to be incapable of ingestion or otherwise ineffective. The problem arose due to the extremely limited availability of THC and the extensive bureaucratic delays in acquiring the drug which has been provided by the U.S. Government to oncologists treating cancer patients and researchers under stringent controls.

To facilitate the availability of THC to oncologists, the U.S. Government is placing THC in the National Cancer Institute's Group C nation-wide distribution system, which should not only significantly reduce the processing time required but will undoubtedly increase the number of patients that will be using the drug. We understand from the National Cancer Institute that the Group C protocol does not require the detailed reporting by oncologists to the Government noting the efficacy of the drug to particular patients, unless

63-109 O - 81 - 4

serious reactions occur. Regardless, the important result is meeting the demands of oncologists by making THC available on a timely basis, under U.S. Government production for an indefinite period. Representative Billy Evans expressed his concern over the confusion some States were experiencing as a result of the new Group C distribution of THC. Mr. Evans submitted a series of questions to NCI and gathered a clear and concise written summation of the program.*

Though pharmaceutical companies have not been responsive to undertaking the manufacturing of THC, this undertaking may well occur as THC is more widely prescribed with favorable results. Also, the issue under discussion to remove THC from Schedule I to Schedule II need not be addressed at this time since the Group C distribution satisfies the purpose—making THC available to those who need it. The controls established under the Group C distribution also satisfy the equally important issue of concern, the possibility of abuse.

The National Cancer Institute and the National Institute on Drug Abuse are to be commended for establishing a program which recognizes and meets the health needs of our citizens. It is regretful that action could not have been taken earlier to facilitate availability of THC. The National Institutes of Health and the National Cancer Institute must review their procedures to assure timely responsiveness in critical situations such as in the instant case—the administering of THC to cancer patients who cannot otherwise tolerate chemotherapy treatment.

Marihuana

There seems to be general agreement that research with marihuana for the treatment and prevention of nausea and vomiting in cancer patients undergoing chemotherapy is not as far along as that with THC. Dr. Barnett Rosenberg, Professor of Biophysics at Michigan State University, over the past 10 years, Rosenberg's laboratory has been the discoverer and a major developer of the use of platinum drugs in the treatment of cancer. Recently, the first drug, cisplatin, was approved by the FDA for the treatment of testicular and ovarian cancers in human patients. Dr. Rosenberg states in a letter to State Congressman Raymond Hood, September 25, 1970:

> It is the strong impression of many clinicians that marihuana smoking is the most successful technique yet tested to minimize the nausea and vomiting due to the use of cisplatin and other cancer treatments as well.
>
> While I strongly believe in the necessity for good research to support the use of any new drug, and whole-heartedly support the control exerted by the FDA for the protection of the people of this country, I feel that the present severe restrictions on the availability of marihuana for cancer patients has more to do with the history of the drug than with a lack of supportive medical evidence. I believe that the protocols of the FDA reflect this social stigma rather than a lack of good science.

Mr. Robert Randall, a witness at the May 20 hearing, suggested that NIDA had deliberately created a shortage of plant materials. His written testimony states, "I believe Federal officials from NIDA and FDA deliberately deceived more than a score of State legislatures by promising the States supplies of 'legal' marihuana which did not exist, and which the agencies have no intention of growing." In the testimony of the Interagency Committee on Pain and Discomfort, there is a notable emphasis on the pitfalls of marihuana, whereas the limitations problems with THC and any advantage that mari-

* See Appendix.

huana might have were not addressed. FDA encouraged researchers to submit protocols for the use of THC, although FDA claims that this was a bias only in the sense of wanting to use a purer, more quantifiable drug. It does not appear that these agencies are acting out of undue bias but merely out of genuine concern for the severe drug abuse problem they perceive, and are mandated to deal with on a daily basis. Although in theory there are some drawbacks to the use of marihuana over THC, there are theoretical advantages to inhalation such as control by the patient and ability to titrate blood level more readily.

In considering the issue of marihuana, Dr. Marvin Snyder, from the National Institute of Drug Abuse testified:

Marihuana or THC at this time is something that National Institute on Drug Abuse has been trying to do a massive public education program on. We have been, we think, relatively successful in turning around public opinion. Some of the latest surveys have shown marihuana use is changing in terms of pattern of use, especially among young people. We believe—we can't prove it, but it's a belief—that the rescheduling of marihuana—especially the cigarette; I'm not too much concerned with THC—but the perception of a rescheduling of the cigarette at this point, and what the children and adolescents would do in terms of misreading what the press has to say about that, would be detrimental to our program to impact upon marihuana use in the United States.

I have children who call on me, and parents, and say, what is wrong with marihuana? It cures cancer. And the issue of conveying that. I know even in the Committee's reports, when, keeping the distinction between THC and marihuana, when to keep among ourselves as professionals is difficult enough. To keep that distinction in the mind of a 7- or 8-year-old child or teenager is very, very difficult.

We feel that in one sense it's a very difficult argument to make. I know you haven't wanted to raise this issue, but one scenario that I can't prove, and I have argued about it myself, one can argue that in a sense making marihuana cigarettes available for cancer chemotherapy patients at this point, if that negatively impacted on prevention program, you might have an additional increase in cancer 20 or 30 years from now resulting from more people using the cigarette, which has definite carcinogenic potential.

Congressman Neal responded:

I sympathize with that point of view, except this: I have two teenage children. I have one 13 and one 15. They are in the prime age for exposure to these drugs. In fact, neighbors' kids we know use the drugs. They are widely available at their public schools where they go. And I'm very anxious to learn the best way to deal with them and this problem.

It seems to me, watching them and watching what our government has done over the years, that we have spread a good deal of misinformation. I think some of it consciously, some of it just out of probably good will and so on. And that people, and young people in particular, respond very positively to accurate information.

I really think that my own kids, 13 and 15, can understand the difference between a use of a drug for a particular illness and its recreational use.

I just have a feeling—this is just an aside, not with any germaneness really to what we're talking about—but I just have a feeling we would be much further in this game if we were to have over the years and if we were to in the future tell the American public and the young people just exactly what we know, tell them the truth, and sort of limit it to that.

We had a series of hearings here not too long ago on the health dangers of marihuana use. And what were involved in these hearings was a set of eight principles that most of the medical and almost everyone could agree to no matter what their position on the law or on the administration of the law. And those eight areas of concern send a very, I think convincing message to young people that it's not in their best interest to use marihuana or these other drugs.

It just seems to me if we could tell them that, it just doesn't seem reasonable to me we would have to sacrifice the potential for some good use of these drugs to that, it doesn't seem consistent. Not only that, but I think kids will see right through it.

Dr. Snyder later in the hearing confirmed his feeling that the placing of marihuana into Schedule II or III would be misinterpreted by the public, and expressed concern over the impact on long-term usage of marihuana.

The Department of Health and Human Services should ensure that the supply of marihuana is made available under stringent controls in such dire circumstances as related by the witness during our hearing who could not otherwise tolerate chemotherapy and THC capsules were ineffective. At the same time, the Department of Health and Human Services should vigorously continue its struggle against marihuana abuse.

Heroin

The question of whether heroin is a valuable adjunct in the relief of pain in cancer patients is still under scrutiny. The testimony of the Interagency Committee on Pain emphasizes the availability of other effective analgesics. The Interagency Committee also points out that there indeed may not be any advantage of heroin over morphine. On the other hand, groups have been critical of the Federal government being insufficiently open to research on the use of heroin for pain.

The testimony of the Federal Interagency Committee on Pain and Discomfort stated that tests were initiated to examine the therapeutic efficacy of heroin as compared to morphine. One study is at Memorial Sloan-Kettering in New York and the second at Georgetown University. Dr. Alan Mondzac, from the National Committee on Intractable Pain, made the following statement at the May 20 hearing with respect to these two studies:

> The Sloan-Kettering study used heroin only in post-operative patients with cancer, not for treating chronic pain. This study found no difference between heroin and morphine. Because of its structure, I think the study is meaningless and not applicable to the problem of pain control in the dying patient. The Georgetown study, as I know it, is too limited in its scope to be of any value at present.

Mrs. Judith Quattlebaum, who testified on behalf of the National Committee on Intractable Pain, had the following to say in reference to this issue:

> The only major research in progress, at Sloan-Kettering, is financed by, of all things, the National Institute on Drug Abuse, which is mandated to use funds for programs on drug abuse and the development of synthetic drugs to replace opium.
>
> The study has an additional difficulty. Dr. Diane Fink of NIH announced what the results should be before the study started—surely a grave burden for any federally funded research.

The fact that heroin is more soluble than morphine, so that a smaller volume of liquid is required for injections is certainly a point which might imply some utility in certain circumstances. In addition, there have been reports that heroin may produce less nausea than morphine.

In general, however, there appears to be agreement that research in the United States on the use of heroin for pain relief in dying patients be continued. The Select Committee, which has for some time been on the forefront in the effects to control heroin abuse, can well understand the temerity of Federal agencies in researching the medical uses of this drug. However, the failure to thoroughly investi-

gate the medical uses of heroin could represent disregard of a valuable analgesic for those suffering from intractable pain. Based on further study, if heroin were to be removed from Schedule I, it should be clear that there is adequate provision in the law for tight control over distribution. Morphine, for example, is a tightly controlled Schedule II drug. The Select Committee, Task Force therefore, recommends that the Food and Drug Administration make a comprehensive evaluation of the medical use potential of heroin. It is in the interest of cancer patients, physicians and the public health. In addition, the Task Force recommends the Department of Health and Human Services encourage medical research to determine the nature and extent of the medical utility of heroin.

RECOMMENDATIONS

1. The Narcotics Select Committee's Task Force endorses and supports the National Cancer Institute's proposal to move THC into its distribution system Group C provided the Drug Enforcement Administration and the Food and Drug Administration exercise guidelines for the distribution of the drug, conduct onsite inspections and there is a monitoring of records. This is an initial step in improving the distribution of THC to patients who would benefit from its use.

2. The Food and Drug Administration should continue its efforts to encourage the marketing of THC by a reputable pharmaceutical company.

3. The Food and Drug Administration and the Drug Enforcement Administration should review their procedures to facilitate the processing for oncologists to obtain drugs such as THC and marihuana for research purposes.

4. The Department of Health and Human Services should encourage qualified researchers to investigate thoroughly the potential medical uses of both marihuana and heroin.

5. The Department of Health and Human Services should thoroughly explore mechanisms for the development of drugs that show a strong public benefit, but for which no drug company has an interest.

6. Decisions to remove drugs from Schedule I should be based upon extensive research clearly establishing a medical benefit to meet the broad public health needs, and should not be unduly inhibited by abuse potential.

APPENDIX

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20205

NATIONAL CANCER INSTITUTE

February 10, 1981

Honorable Billy L. Evans
Congress of the United States
House of Representatives
Washington, D.C. 20516

Dear Sir:

The answers to your recent written inquiry regarding marijuana and Delta-9-tetrahydrocannabinol (THC) are:

Question 1. Please define Class C distribution and the difference in the distribution of marijuana as opposed to THC pills.

Answer: Group C drugs are drugs demonstrating efficacy within a tumor type in more than one study, which alter the pattern of care of the disease in question, and are safely administered by properly trained physicians without requiring specialized supportive care facilities. They are provided to properly registered investigators who are skilled in the treatment of cancer patients. The drugs are sent directly to the investigators or to their agent.

THC is a group C investigational drug. It was placed in the group C category on October 8, 1980, (attachment 1).* But because THC is also a Schedule I substance in addition to being a Group C drug, a tighter control on the distribution was required. Consequently, a distribution system which was acceptable to the Drug Enforcement Agency (DEA) and FDA was devised and is detailed in attachment 2.

Patients may obtain THC by prescription from qualified cancer specialists who are registered with the NCI. The prescription can be filled only at an approved hospital pharmacy. At present there are in excess of 1000 physicians and 500 pharmacies participating nationwide.

*Attachment 1 is not included in this submission.

Marijuana is not a Group C drug. Properly designed research which will establish whether it is effective and meets the criteria for Group C Classification is ongoing, and should provide answers within the year. Currently, marijuana cigarettes are distributed for research purposes to investigators who have approved clinical studies registered with the NCI, or who hold their own Investigational New Drug notice (IND).

Question 2. Please differentiate between synthetically produced drugs and marijuana cigarettes.

Answer: Marijuana and THC are not the same. Marijuana is a colloquial term, of Mexican origin, for a particular variety of hemp plant known as Cannabis Sativa. THC is the active psychosomimetic agent responsible for the physiological activity of smoked marijuana. This chemical can be made in the laboratory (a synthetically produced drug) and is the one used in the NCI program.

Question 3. Explain which hospitals will receive THC under this new form of distribution.

Answer: Basically, hospital pharmacies which provide both in and outpatient facilities and can meet DEA requirements of Schedule I substances, may participate. Currently there are about 500 pharmacies registered with NCI (attachment 3).

Question 4. Please describe the federal law under which these two drugs are placed.

Answer: 21CFR, Part 1300 to end, Paragraph 1308.11.

Question 5. Explain the distribution of the I-V system.

Answer: At present there is no intravenous (I.V.) form of THC.

Question 6. Please note that confiscated state marijuana cannot be used.

Answer: This decision resides with the DEA. However, NCI does not use any confiscated marijuana.

Question 7. Please describe the only purpose for enacting state legislation.

Answer: We suggest, in regard to research and treatment with marijuana and related products for cancer patients, that new state legislation is most needed in those states in which state law is more restrictive than federal law. Relaxation of such state law will facilitate programs which seek to make these substances available for cancer patients.

Sincerely yours,

Daniel F. Hoth, Jr., M.D.
Acting Chief
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment

David Abraham, Ph.D.
Health Scientist Administrator
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment

Enclosures

ATTACHMENT #2

Mechanism of Drug Distribution for

Delta-9-Tetrahydrocannabinol

TABLE OF CONTENTS

1. Background

2. Hospital Eligibility

3. Hospital Application and Registration with NCI

4. Hospital Pharmacy Registration with DEA

5. Physician Registration

6. Review of Physician FDA-1573 Application

7. Drug Procurement by Registered Hospital Pharmacies

8. NCI Criteria for Distribution Regulation

9. Drug Supply Shortage

10. National Cancer Institute Storage and Distribution Facility Operations

11. Guideline for Pharmacy Dispensing of Delta-9-THC Capsules

12. Guidelines for the Prescribing of Delta-9-THC

13. Obtaining Delta-9-THC for an In-patient at a Non-Registered Hospital

14. Hospital Pharmacy Regulatory Requirements

15. Dispensing Fee

16. Chemistry

17. Pharmaceutical Data

18. Sources for Further Information

Guide to Abbreviations

Appendix

1. BACKGROUND

With the existence of a wide variety of chemotherapeutic agents, the treatment of many neoplasmas has improved markedly. However, one particular toxic manifestation of chemotherapeutic agents, gastrointestinal toxicity, has received little attention. Even though many patients are given standard antinauseants prior to the administration of a chemotherapy agent, nausea and vomiting still occur. This uncontrollable nausea and vomiting can be violent and long-lasting.

Anecdotal accounts from patients have suggested that smoking marijuana, prior to receiving intravenous antitumor drugs, results in a decreased incidence of nausea and vomiting. A number of investigators over the past several years have initiated formal studies testing the efficacy of oral delta-9-tetrahydrocannabinol (delta-9-THC) in chemotherapy-induced nausea and vomiting. Overall, the results have indicated that delta-9-THC is effective as an antiemetic agent, especially in patients who have been failures on standard antiemetics.

The National Cancer Institute (NCI) has initiated a national delta-9-THC distribution program by applying to the Food and Drug Administration (FDA) for its classification as a Group C investigational agent.

Delta-9-THC is a Schedule I Investigational Drug and therefore requires the strictest adherence to Drug Enforcement Agency (DEA) security and safety regulations. The purpose of this document is to describe the mechanisms of control and distribution which are mandatory for delta-9-THC.

2. HOSPITAL ELIGIBILITY

2.1 To be considered eligible, an institution must be one of the following:

2.11 An NCI recognized Cancer Center (P-30 grant supported)

2.12 An NCI designated New Drug Study Group

2.13 A member of the Council of Teaching Hospitals

2.2 The Division of Cancer Treatment (DCT) of the NCI may select additional hospital pharmacies in inadequately represented geographic areas as required.

2.21 Additional institutions must meet the following minimal criteria:

2.211 Employ a full-time hospital pharmacist

2.212 Be accredited by the Joint Commission on the Accreditation of Hospitals (JCAH).

2.213 Provide both in-patient and out-patient pharmacy services

3. HOSPITAL APPLICATION AND REGISTRATION WITH NCI

3.1 Application for Registration

3.11 Hospitals meeting the eligibility criteria in Sect. 2.1 and wishing to participate should send a letter to the Drug Regulatory Affairs Section (DRAS) expressing willingness of both hospital pharmacy and administration to participate. This letter should include:

3.111 Names and signatures of both a hospital administrator and the director of pharmacy services.

3.112 Hospital name and address

3.113 Hospital pharmacy's DEA registration number and date of expiration.

3.114 Name and State license registration number of the pharmacist responsible for the program.

3.115 If a dispensing fee for services rendered is to be charged (see Sect. 15) a statement verifying that the charge is based on a service cost only basis must be stated in the letter to NCI.

3.12 Institutions not meeting the requirements listed in Sect. 2.1 that wish to apply should:

3.121 Write to DRAS as noted in Sect. 3.1.

3.122 Additionally provide

3.1221 Documentation of JCAH accreditation

3.1222 Description of In-patient and Out-patient pharmacy services

3.2 Application Review and Approval

3.21 Hospital applicants eligible under Sect. 2.1 will be considered registered upon receipt of letter by NCI and pending DEA Schedule I registration (see Sect. 4).

3.22 Hospital applicants categorized by Sect. 2.2, who send the necessary information (Sect. 3.12) will be reviewed by DRAS.

3.221 DRAS will inform applicant of its decision.

3.3 Upon application review and approval by NCI, an information packet will be mailed to the pharmacy. The contents of this packet are as follows:

3.31 Group C Guidelines for the Use of Delta-9-THC, with

3.311 Form FDA 1573, for physician registration

3.312 Informed Consent Forms

3.32 DEA schedule modification applications (see Sect. 4.3).

3.33 A supply of Clinical Drug Request Forms (NIH-986)

HOSPITAL PHARMACY REGISTRATION WITH DEA

4.1 The NCI information packet contains the material necessary to modify the pharmacies schedule registration (DEA form 225). This modification places them in the Schedule I researcher category.

4.2 The DEA has waived the customary fee.

4.3 DEA registration material includes: (See appendix for sample copies)

4.31 Instruction sheet

4.32 Sample DEA Form 225

4.33 DEA Form 225

4.34 A preaddressed return envelope to DEA

4.4 Eligible hospitals should fill out DEA Form 225 as noted, and return to the DEA.

4.5 The DEA central office will contact a DEA inspector closest to the hospital. The inspector will evaluate the pharmacy and report back to the DEA registration section. Schedule I registration will then be processed by the DEA's registration section.

4.6 DEA will notify both the hospital and NCI that schedule registration has been approved and the hospital pharmacy's registration with NCI can then be considered activated.

4.7 Preprinted DEA-222 order forms prepared by the DEA will be received by the hospital pharmacy following activation.

5. PHYSICIAN REGISTRATION

5.1 Criteria for physician eligibility:

To be eligible to prescribe delta-9-THC a physician must meet the following criteria:

5.11 Have experience in cancer chemotherapy. The Basis Of This Experience Must Be Noted on Form FDA-1573.

5.12 Have a current DEA registration number and list this registration number on Form FDA-1573*. Physicians need not have Schedule I registration.

* This does not apply to U.S. Military Personnel (CSA reg. 1301.25)

5.13 Agree to abide by the Guidelines for Use of Delta-9-THC. All adverse drug reactions are to be reported immediately to the Drug Regulatory Affairs Section of NCI.

5.14 Be registered with a participating pharmacy on Form FDA-1573.

5.2 Procedures for registration:

5.21 Physicians wishing to prescribe delta-9-THC may become eligible by contacting a participating hospital pharmacy to obtain a FDA-1573 form. The Drug Regulatory Affairs Section of the Investigational Drug Branch (IDB) can supply the name of the closest participating hospital pharmacy.

5.22 Once completed, Form FDA-1573 is to be delivered to the hospital pharmacy to which the physician intends to refer patients for delta-9-THC.

5.23 The pharmacy will retain a copy of Form FDA-1573 for their files and send the original to the Drug Regulatory Affairs Section.

5.24 Drug Regulatory Affairs Section will review the submitted FDA-1573, determine if the applicant is qualified and will inform the pharmacy of the decision.

5.25 The pharmacy will then notify the physician of his eligibility status.

6. REVIEW OF PHYSICIAN FORM FDA-1573 APPLICATION:

6.1 By Pharmacy:

6.11 If a registered hospital pharmacy feels a physician has failed to adhere to established standards of medical practice in prescribing of controlled substances, NCI should be notified in writing. Information rendered will be strictly confidential.

6.2 By NCI:

6.21 If NCI rejects a physician's Form FDA-1573, NCI will contact the physician stating the basis for rejection.

6.22 A physician may resubmit his application to NCI along with a written statement of rebuttal. This document will be reviewed by NCI for final decision.

7. DRUG PROCUREMENT BY REGISTERED HOSPITAL PHARMACIES

7.1 Procedure for Ordering THC From NCI

7.11 Once registration has been activated, (DEA registration and NCI approval received) the hospital pharmacy may order delta-9-THC from NCI by completing DEA Form 222 and NIH Clinical Drug Request Form (NIH-986).

7.12 The DEA Form 222 is pre-printed and sent directly, by DEA, to the pharmacy. Clinical Drug Request Form (NIH-986) has already been sent, by NCI, in the original registration packet.

7.13 Both completed forms are to be sent to the Drug Regulatory Affairs Section of the Investigational Drug Branch, NCI.

7.14 NO telephone orders for delta-9-THC will be accepted.

7.2 NCI Drug Order Procedure

7.21 The quantity requested is reviewed and shipment authorized by the Drug Regulatory Affairs Section.

7.22 Drug Regulatory Affairs Section will forward the endorsed DEA Form 222 and verified NIH-986 to the Pharmaceutical Resources Branch of NCI for shipment of drug to the hospital pharmacy and also for purpose of inventory adjustment.

7.23 Delta-9-THC will be shipped in accordance with all applicable rules and regulations.

7.24 NIH Form 986 is for internal use by the various departments of NCI for maintenance of inventory and control.

7.25 DEA Form 222 and NIH-986 serve as legal documents certifying all delta-9-THC orders and shipments.

63-109 O - 81 - 5

8. NCI CRITERIA FOR DISTRIBUTION REGULATION

8.1 Procedure for Drug Order Verification:

8.11 The Drug Regulatory Affairs Section of IDB will review and authorize all shipments of delta-9-THC.

8.12 Items which will be reviewed are:

8.121 DEA schedule registration number of hospital pharmacy

8.122 Frequency of distribution

8.123 Quantity previously ordered

8.124 Quantity presently ordered

8.2 Allocations of Delta-9-THC are based on the following criteria:

8.21 Number of physicians registered with that hospital pharmacy

8.22 Number of Research Orders for Medication (See Sect. 11.2) received by pharmacy

8.23 Amount of drug currently in pharmacy's inventory

8.24 Amount of drug available in general NCI inventory

8.3 Estimates of drug needs can be made on the basis of previous patient history with other antiemetics.

9. DRUG SUPPLY SHORTAGE

9.1 Supply shortage - Hospital

9.11 Distribution between dispenser-registrants is permitted under DEA regulation 1307.11.

9.12 Registrant receiving the delta-9-THC furnishes the supplier registrant (another pharmacy) with an executed order form (DEA 222) in conformance with regulation 1305.

9.2 NCI inventory shortage

9.21 If a situation of inadequate drug supply arises, NCI policy would dictate distribution to patients with demonstrated benefit from delta-9-THC. Patients who have not yet had a trial with delta-9-THC would receive second priority.

10. NATIONAL CANCER INSTITUTE STORAGE AND DISTRIBUTION FACILITY OPERATIONS

10.1 The NCI Contractor, acting as the central distribution and storage facility for delta-9-THC, will register with the DEA as a Schedule I distributor.

10.2 The distributor assumes responsibility for maintenance of records and inventories.

10.3 As is required of all distributors of Schedule I substances, reports will be filed with the DEA (21 CFR 1304.41) and security requirements (21 CRF 1301.7 through 1301.74) will be maintained.

11. GUIDELINE FOR PHARMACY DISPENSING OF DELTA-9-THC CAPSULES

11.1 The pharmacy will dispense delta-9-THC upon presentation of a "Research Order for Medication" signed by a physician who:

11.11 Has a current DEA registration.

11.12 Is registered with the pharmacy by filing a Form FDA-1573

11.13 Affirms that the patient consent form has been signed by the patient

11.14 Limits the use of the drug to the indication outlined in the guidelines.

11.15 Will report adverse drug reactions immediately to the Investigational Drug Branch of the National Cancer Institute.

11.2 Procedure for filling a research order for medication:

11.21 The following items of information are on a valid research order:

11.211 All common prescription information, as required by law, must be included.

11.212 A standard prescription blank may be used, but confirmation of informed patient consent must be incorporated on the order, above the physician's

signature. The phrase, "I affirm that informed patient consent has been obtained", is sufficient.

11.213 Name of hospital at which the physician is registered to prescribe delta-9-THC .

11.22 If any of the above items are missing, the Research Order is to be considered INVALID and is NOT to be filled.

12. GUIDELINES FOR THE PRESCRIBING OF DELTA-9-THC

12.1 A physician meeting the criteria set forth in Section 5 may write a "Research Order for Medication" for delta-9-THC.

12.2 Writing a "Research Order for Medication"

12.21 The following information, in addition to normal prescribing information, is mandatory for these "orders" to be considered valid.

12.211 Confirmation of obtained patient consent should be incorporated above the physicians signature. The phrase "I affirm that informed patient consent has been obtained" will be sufficient.

12.212 Name of hospital at which the physician is registered

12.22 The completed "Research Order for Medication" is then taken to a participating hospital pharmacy where, upon verification, it is filled.

12.3 Limitations:

12.31 Delta-9-THC is a Schedule I drug and as such, falls under DEA regulations (DEA 1306.01 through 1306.06) concerning general issuance of prescriptions for controlled drugs.

12.32 Research Orders for delta-9-THC are NOT refillable.

12.33 A maximum of one bottle (of any given strength) may be dispensed upon a single research order.

13. OBTAINING DELTA-9-THC FOR AN IN-PATIENT AT A NON-REGISTERED HOSPITAL

13.1 Registered physicians may prescribe delta-9-THC for a patient in this circumstance.

13.2 A relative or member of that hospital's staff may be authorized to obtain the drug from a participating pharmacy.

13.3 The non-registered hospital may provide authorization to allow a patients delta-9-THC medication to be brought into the hospital.

13.4 Delta-9-THC may be obtained for patients on an INDIVIDUAL BASIS and only one bottle per patient may be obtained.

13.5 The non-registered hospital's pharmacy is not to store quantities of delta-9-THC under any circumstances. This is a direct violation of DEA regulations!

13.6 Delta-9-THC for a single patients use will be stored in the locked narcotic cabinet at the patient's nursing station.

14. HOSPITAL PHARMACY REGULATORY REQUIREMENTS

14.1 Security

14.11 The minimum security required under 21 CFR 1301.75 is that the delta-9-THC be stored in a securely locked, substantially constructed cabinet.

14.12 It is anticipated that most of the hospital pharmacies will already have facilities which provide more stringent security than the minimum required.

14.2 Recordkeeping and Reporting Requirements (1304.41):

14.21 Inventories:

14.211 An initial inventory and a biennial inventory is required by DEA regulations for the delta-9-THC obtained.

14.22 Records of Receipt of the Delta-9-THC:

14.221 The properly completed DEA order form (DEA form 222) used to order the drug through the National Cancer Institute, will be the primary record of receipt of the delta-9-THC.

14.222 A copy of NIH-986 will also be considered legal receipt of delivery.

14.23 Registered Physicians List:

14.231 Pharmacies will keep on file their copy of the physicians Form FDA-1573 form as reference to determine which physicians are registered to prescribe delta-9-THC.

14.232 Most physicians will write research orders in the same geographical area. Therefore, if a patient goes to a registered pharmacy other than the one at which their physician is registered, it is possible (because the name of the hospital at which the physician is registered is on the Research Order for Medication (See Sect. 12)) to call the other pharmacy and certify registration.

14.24 Dispensing Records:

14.241 The "Research Order for Medication" will be the primary record for the dispensing of delta-9-THC by the hospital pharmacy.

14.242 As a Schedule I Controlled Substance, orders for delta-9-THC must be filed separately from all other business records (DEA regulation 1304).

14.25 Administration Records:

14.251 Delta-9-THC dispensed under a "Research Order for Medication" for an in-patient will normally be sent to a Nursing Station for administration to that patient.

14.252 Complete and accurate records of administration must be kept of that administration.

14.253 Any unused medication should be returned to the dispensing hospital pharmacy for proper disposal.

14.254 The completed administration records should be returned to the hospital pharmacy for filing.

14.26 Disposal of Delta-9-THC:

14.261 By Pharmacy:

14.2611 Disposal of delta-9-THC shall be carried out under the procedures set up by the DEA Regional Office in which the hospital pharmacy is located.

14.262 By Patient:

14.2621 Patients are to return unused delta-9-THC to the dispensing hospital pharmacy for proper disposal.

14.27 Reports Required of the Hospital Pharmacy:

14.271 The hospital pharmacy is not required to make reports to the DEA other than reports of loss or theft of the delta-9-THC.

14.272 A quarterly report to NCI is required. It should contain the following information:

14.2721 Amount of delta-9-THC present in inventory at time of report.

14.2722 The number of patients that have received delta-9-THC in the reporting interval.

14.2723 The number of research orders filled during the reporting interval.

14.2724 Record of drug returns and quantity disposed.

14.273 In order to evaluate drug safety and efficacy, some hospitals, on a voluntary basis, will be invited to participate in an in-depth survey of the current program.

15. DISPENSING FEE:

15.1 Hospital pharmacies may charge a dispensing fee for services rendered.

15.2 Hospitals must verify to NCI, in writing, that patients are charged on a cost only basis.

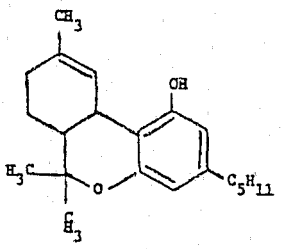
15.3 Pharmacies MAY NOT charge for the drug itself.

16. CHEMISTRY:

16.1 Delta-9-THC is the principal psychoactive substance isolated from Cannabis sativa L.

16.2 It has the empirical formula $C_{21}H_{30}O_2$ with the molecular weight of 314.45.

16.3 It has the following structural formula:



17. PHARMACEUTICAL DATA:

17.1 Delta-9-THC is supplied in 2.5 and 5 mg. soft gelatin, amber, capsules.

17.2 Delta-9-THC is chemically synthesized and formulated in sesame oil and encapsulated.

17.3 The capsules are packaged in amber bottles of 25 each.

17.4 Delta-9-THC capsules should be stored in a cool place, (8°-15°C). Room temperature storage (15°C to 30°C) for as long as 3 months has not resulted in measurable degradation. This period may be extended upon completion of shelf-life studies.

18. SOURCES FOR FURTHER INFORMATION

18.1 For information relating to registration to participate in this study, contact Investigational Drug Branch, Landow Building, Room 4C-17, Bethesda, Maryland 20205.

18.2 For information relating to placing orders or the status of orders, contact the Drug Regulatory Affairs Section, Landow Building, Room 4C-19 Bethesda, Maryland 20205.

18.3 For information relating to the nature of the drug product, contact the Pharmaceutical Resources Branch, Blair Building, 8300 Colesville Road, Room 532, Silver Spring, Maryland 20910.

GUIDE TO ABBREVIATIONS

1. Delta-9-THC = Delta-9-Tetrahydrocannabinol
2. NCI = National Cancer Institute
3. DCT = Division of Cancer Treatment
4. JCAH = Joint Commission on the Accreditation of Hospitals
5. FDA = Food and Drug Administration
6. DEA = Drug Enforcement Agency
7. NIH = National Institutes of Health
8. IDB = Investigational Drug Branch
9. DRAS = Drug Regulatory Affairs Section
10. CSA = Controlled Substances Act
11. PRB = Pharmaceutical Resources Branch

[The following excerpts are from the "Controlled Substances Act" and DEA regulations concerning Narcotics and Dangerous Drugs]

§ 1301.25 Exemption of certain military and other personnel.

(a) The requirement of registration is waived for any official of the U.S. Army, Navy, Marine Corps, Air Force, Coast Guard, Public Health Service, or Bureau of Prisons who is authorized to prescribe, dispense, or administer, but not to procure or purchase, controlled substances in the course of his official duties. Such officials shall follow procedures set forth in Part 1306 of this chapter regarding prescriptions, but shall state the branch of service or agency (e.g., "U.S. Army" or "Public Health Service") and the service identification number of the issuing official in lieu of the registration number required on prescription forms. The service identification number for a Public Health Service employee is his Social Security identification number.

(b) If any official exempted by this section also engages as a private individual in any activity or group of activities for which registration is required, such official shall obtain a registration for such private activities.

[36 FR 7778, Apr. 24, 1971, as amended at 36 FR 18729, Sept. 21, 1971; 38 FR 756, Jan. 4, 1973. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1301.26 Exemption of law enforcement officials.

(a) The requirement of registration is waived for the following persons in the circumstances described in this section:

(1) Any officer or employee of the Administration, any officer of the U.S. Customs Service, any officer or employee of the United States Food and Drug Administration, and any other Federal officer who is lawfully engaged in the enforcement of any Federal law relating to controlled substances, drugs or customs, and is duly authorized to possess controlled substances in the course of his official duties; and

(2) Any officer or employee of any State, or any political subdivision or agency thereof, who is engaged in the enforcement of any State or local law relating to controlled substances and is duly authorized to possess controlled substances in the course of his official duties.

(b) Any official exempted by this section may, when acting in the course of his official duties, possess any controlled substance and distribute any such substance to any other official who is also exempted by this section and acting in the course of his official duties.

(c) Any official exempted by this section may procure any controlled substance in the course of an inspection, in accordance with § 1316.03(d), or in the course of any criminal investigation involving the person from whom the substance was procured.

(d) In order to enable law enforcement agency laboratories to obtain and transfer controlled substances for use as standards in chemical analysis, such laboratories must obtain annually a registration to conduct chemical analysis. Such laboratories shall be exempted from payment of a fee for registration. Laboratory personnel, when acting in the scope of their official duties, are deemed to be officials exempted by this section and within the activity described in section 515(d) of the Act (21 U.S.C. 885(d)). For purposes of this paragraph, laboratory activities shall not include field or other preliminary chemical tests by officials exempted by this section.

(e) Laboratories of the Administration shall obtain annually a registration to conduct chemical analysis in accordance with paragraph (d) of this section. In addition to the activities authorized under a registration to conduct chemical analysis pursuant to § 1301.22(b) (4), laboratories of the Administration shall be authorized to manufacture or import controlled substances for any lawful purpose, to distribute or export such substances to any person, and to import and export such substances in emergencies without regard to the requirements of Part 1312 of this chapter if a report concerning the importation or exportation is made to the Distribution Audit Branch of the Administration within 30 days of such importation or exportation.

SECURITY REQUIREMENTS

§ 1301.71 Security requirements generally.

(a) All applicants and registrants shall provide effective controls and procedures to guard against theft and diversion of controlled substances. In order to determine whether a registrant has provided effective controls against diversion, the Administrator shall use the security requirements set forth in §§ 1301.72-1301.76 as standards for the physical security controls and operating procedures necessary to prevent diversion. Materials and construction which will provide a structural equivalent to the physical security controls set forth in §§ 1301.72,

1301.73 and 1301.75 may be used in lieu of the materials and construction described in those sections.

(b) Substantial compliance with the standards set forth in §§ 1301.72-1301.76 may be deemed sufficient by the Administrator after evaluation of the overall security system and needs of the applicant or registrant. In evaluating the overall security system of a registrant or applicant, the Administrator may consider any of the following factors as he may deem relevant to the need for strict compliance with security requirements:

(1) The type of activity conducted (e.g., processing of bulk chemicals, preparing dosage forms, packaging, labeling, cooperative buying, etc.);

(2) The type and form of controlled substances handled (e.g., bulk liquids or dosage units, usable powders or nonusable powders);

(3) The quantity of controlled substances handled;

(4) The location of the premises and the relationship such location bears on security needs;

(5) The type of building construction comprising the facility and the general characteristics of the building or buildings;

(6) The type of vault, safe, and secure enclosures or other storage system (e.g., automatic storage and retrieval system) used;

(7) The type of closures on vaults, safes, and secure enclosures;

(8) The adequacy of key control systems and/or combination lock control systems;

(9) The adequacy of electric detection and alarm systems, if any including use of supervised transmittal lines and standby power sources;

(10) The extent of unsupervised public access to the facility, including the presence and characteristics of perimeter fencing, if any;

(11) The adequacy of supervision over employees having access to manufacturing and storage areas;

(12) The procedures for handling business guests, visitors, maintenance personnel, and nonemployee service personnel;

(13) The availability of local police protection or of the registrant's or applicant's security personnel, and;

(14) The adequacy of the registrant's or applicant's system for monitoring the receipt, manufacture, distribution, and disposition of controlled substances in its operations.

(c) When physical security controls become inadequate as a result of a controlled substance being transferred to a different schedule, or as a result of a noncontrolled substance being listed on any schedule, or as a result of a significant increase in the quantity of controlled substances in the possession of the registrant during normal business operations, the physical security controls shall be expanded and extended accordingly. A registrant may adjust physical security controls within the requirements set forth in §§ 1301.72-1301.76 when the need for such controls decreases as a result of a controlled substance being transferred to a different schedule, or a result of a controlled substance being removed from control, or as a result of a significant decrease in the quantity of controlled substances in the possession of the registrant during normal business operations.

(d) Any registrant or applicant desiring to determine whether a proposed security system substantially complies with, or is the structural equivalent of, the requirements set forth in §§ 1301.72-1301.76 may submit any plans, blueprints, sketches or other materials regarding the proposed security system either to the Regional Administrator in the region in which the system will be used, or to the Compliance Investigations Division, Drug Enforcement Administration, Department of Justice, Washington, D.C. 20537.

(e) Physical security controls of locations registered under the Harrison Narcotic Act or the Narcotics Manufacturing Act of 1960 on April 30, 1971, shall be deemed to comply substantially with the standards set forth in §§ 1301.72, 1301.73 and 1301.75. Any new facilities or work or storage areas constructed or utilized for controlled substances, which facilities or work or storage areas have not been previously approved by the Administration, shall not necessarily be deemed to comply substantially with the standards set forth in §§ 1301.72, 1301.73 and

63-109 O - 81 - 6

1301.75, notwithstanding that such facilities or work or storage areas have physical security controls similar to those previously approved by the Administration.

[38 FR 18729, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1301.72 Physical security controls for non-practitioners; narcotic treatment programs and compounders for narcotic treatment programs; storage areas.

(a) *Schedules I and II.* Raw materials, bulk materials awaiting further processing, and finished products which are controlled substances listed in Schedule I or II shall be stored in one of the following secure storage areas:

(1) Where small quantities permit, a safe or steel cabinet;

(i) Which safe or steel cabinet shall have the following specifications or the equivalent: 30 man-minutes against surreptitious entry, 10 man-minutes against forced entry, 20 man-hours against lock manipulation, and 20 man-hours against radiological techniques;

(ii) Which safe or steel cabinet, if it weighs less than 750 pounds, is bolted or cemented to the floor or wall in such a way that it cannot be readily removed; and

(iii) Which safe or steel cabinet, if necessary, depending upon the quantities and type of controlled substances stored, is equipped with an alarm system which, upon attempted unauthorized entry, shall transmit a signal directly to a central protection company or a local or State police agency which has a legal duty to respond, or a 24-hour control station operated by the registrant, or such other protection as the Administrator may approve.

(2) A vault constructed before, or under construction on, September 1, 1971, which is of substantial construction with a steel door, combination or key lock, and an alarm system; or

(3) A vault constructed after September 1, 1971:

(i) The walls, floors, and ceilings of which vault are constructed of at least 8 inches of reinforced concrete or other substantial masonry, reinforced vertically and horizontally with ½-inch steel rods tied 6 inches on center, or the structural equivalent to such reinforced walls, floors, and ceilings;

(ii) The door and frame unit of which vault shall conform to the following specifications or the equivalent: 30 man-minutes against surreptitious entry, 10 man-minutes against forced entry, 20 man-hours against lock manipulation, and 20 man-hours against radiological techniques;

(iii) Which vault, if operations require it to remain open for frequent access, is equipped with a "day-gate" which is self-closing and self-locking, or the equivalent, for use during the hours of operation in which the vault door is open;

(iv) The walls or perimeter of which vault are equipped with an alarm, which upon unauthorized entry shall transmit a signal directly to a central station protection company, or a local or State police agency which has a legal duty to respond, or a 24-hour control station operated by the registrant, or such other protection as the Administrator may approve, and, if necessary, holdup buttons at strategic points of entry to the perimeter area of the vault;

(v) The door of which vault is equipped with contact switches; and

(vi) Which vault has one of the following: complete electrical lacing of the walls, floor and ceilings; sensitive ultrasonic equipment within the vault; a sensitive sound accumulator system; or such other device designed to detect illegal entry as may be approved by the Administration.

(b) *Schedules III, IV and V.* Raw materials, bulk materials awaiting further processing, and finished products which are controlled substances listed in Schedules III, IV and V shall be stored in the following secure storage areas:

(1) A safe or steel cabinet as described in paragraph (a)(1) of this section;

(2) A vault as described in paragraph (a)(2) or (3) of this section equipped with an alarm system as described in paragraph (b)(4)(v) of this section;

(3) A building used for storage of Schedules III through V controlled substances with perimeter security which limits access during working

hours and provides security after working hours and meets the following specifications:

(i) Has an electronic alarm system as described in paragraph (b)(4)(v) of this section,

(ii) Is equipped with self-closing, self-locking doors constructed of substantial material commensurate with the type of building construction, provided, however, a door which is kept closed and locked at all times when not in use and when in use is kept under direct observation of a responsible employee or agent of the registrant is permitted in lieu of a self-closing, self-locking door. Doors may be sliding or hinged. Regarding hinged doors, where hinges are mounted on the outside, such hinges shall be sealed, welded or otherwise constructed to inhibit removal. Locking devices for such doors shall be either of the multiple-position combination or key lock type and:

(a) In the case of key locks, shall require key control which limits access to a limited number of employees, or;

(b) In the case of combination locks, the combination shall be limited to a minimum number of employees and can be changed upon termination of employment of an employee having knowledge of the combination;

(4) A cage, located within a building on the premises, meeting the following specifications:

(i) Having walls constructed of not less than No. 10 gauge steel fabric mounted on steel posts, which posts are:

(a) At least one inch in diameter;

(b) Set in concrete or installed with lay bolts that are pinned or brazed; and

(c) Which are placed no more than ten feet apart with horizontal one and one-half inch reinforcements every sixty inches;

(ii) Having a mesh construction with openings of not more than two and one-half inches across the square,

(iii) Having a ceiling constructed of the same material, or in the alternative, a cage shall be erected which reaches and is securely attached to the structural ceiling of the building. A lighter gauge mesh may be used for the ceilings of large enclosed areas if walls are at least 14 feet in height,

(iv) Is equipped with a door constructed of No. 10 gauge steel fabric on a metal door frame in a metal door flange, and in all other respects conforms to all the requirements of 21 CFR 1301.72(b)(3)(ii), and

(v) Is equipped with an alarm system which upon unauthorized entry shall transmit a signal directly to a central station protection agency or a local or state police agency, each having a legal duty to respond, or to a 24-hour control station operated by the registrant, or to such other source of protection as the Administrator may approve;

(5) An enclosure of masonry or other material, approved in writing by the Administrator as providing security comparable to a cage;

(6) A building or enclosure within a building which has been inspected and approved by DEA or its predecessor agency, BNDD, and continues to provide adequate security against the diversion of Schedule III through V controlled substances, of which fact written acknowledgment has been made by the Regional Director of DEA for the Region in which such building or enclosure is situated;

(7) Such other secure storage areas as may be approved by the Administrator after considering the factors listed in § 1301.71(b); (1) through (14);

(8)(i) Schedule III through V controlled substances may be stored with Schedules I and II controlled substances under security measures provided by 21 CFR 1301.72(a);

(ii) Non-controlled drugs, substances and other materials may be stored with Schedule III through V controlled substances in any of the secure storage areas required by 21 CFR 1301.72(b), provided that permission for such storage of non-controlled items is obtained in advance, in writing, from the Regional Director of DEA for the Region in which such storage area is situated. Any such permission tendered must be upon the Regional Director's written determination that such non-segregated storage does not diminish security effectiveness for Schedules III through V controlled substances.

(c) *Multiple storage areas.* Where several types or classes of controlled substances are handled separately by the registrant or applicant for different purposes (e.g., returned goods, or goods in process), the controlled substances may be stored separately, provided that each storage area complies with the requirements set forth in this section.

(d) *Accessibility to storage areas.* The controlled substances storage areas shall be accessible only to an absolute minimum number of specifically authorized employees. When it is necessary for employee maintenance personnel, nonemployee maintenance personnel, business guests, or visitors to be present in or pass through controlled substances storage areas, the registrant shall provide for adequate observation of the area by an employee specifically authorized in writing.

[36 FR 18730, Sept. 21, 1971, as amended at 37 FR 15919, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 37984, Oct. 25, 1974; 41 FR 16460, Apr. 19, 1976; 41 FR 17382, Apr. 26, 1976]

§ 1301.73 Physical security controls for non-practitioners; compounders for narcotic treatment programs; manufacturing and compounding areas.

All manufacturing activities (including processing, packaging and labeling) involving controlled substances listed in any schedule and all activities of compounders shall be conducted in accordance with the following:

(a) All in-process substances shall be returned to the controlled substances storage area at the termination of the process. If the process is not terminated at the end of a workday (except where a continuous process or other normal manufacturing operation should not be interrupted), the processing area or tanks, vessels, bins or bulk containers containing such substances shall be securely locked, with adequate security for the area or building. If such security requires an alarm, such alarm, upon unauthorized entry, shall transmit a signal directly to a central station protection company, or local or state police agency which has a legal duty to respond, or a 24-hour control station operated by the registrant.

(b) Manufacturing activities with controlled substances shall be conducted in an area or areas of clearly defined limited access which is under surveillance by an employee or employees designated in writing as responsible for the area. "Limited access" may be provided, in the absence of physical dividers such as walls or partitions, by traffic control lines or restricted space designation. The employee designated as responsible for the area may be engaged in the particular manufacturing operation being conducted: *Provided,* That he is able to provide continuous surveillance of the area in order that unauthorized persons may not enter or leave the area without his knowledge.

(c) During the production of controlled substances, the manufacturing areas shall be accessible to only those employees required for efficient operation. When it is necessary for employee maintenance personnel, nonemployee maintenance personnel, business guests, or visitors to be present in or pass through manufacturing areas during production of controlled substances, the registrant shall provide for adequate observation of the area by an employee specifically authorized in writing.

[36 FR 18731, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973 and amended at 39 FR 37984, Oct. 25, 1974]

§ 1301.74 Other security controls for non-practitioners; narcotic treatment programs and compounders for narcotic treatment programs.

(a) Before distributing a controlled substance to any person who the registrant does not know to be registered to possess the controlled substance, the registrant shall make a good faith inquiry either with the Administration or with the appropriate State controlled substances registration agency, if any, to determine that the person is registered to possess the controlled substance.

(b) The registrant shall design and operate a system to disclose to the registrant suspicious orders of controlled substances. The registrant shall inform the Regional Office of the Administration in his region of suspicious orders when discovered by the regis-

trant. Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.

(c) The registrant shall notify the Regional Office of the Administration in his region of any theft of significant loss of any controlled substances upon discovery of such theft or loss. The supplier shall be responsible for reporting in-transit losses of controlled substances by the common or contract carrier selected pursuant to § 1301.74(e), upon discovery of such theft or loss. The registrant shall also complete DEA Form 106 regarding such theft or loss. Thefts must be reported whether or not the controlled substances are subsequently recovered and/or the responsible parties are identified and action taken against them.

(d) The registrant shall not distribute any controlled substance listed in Schedules II through V as a complimentary sample to any potential or current customer (1) without the prior written request of the customer, (2) to be used only for satisfying the legitimate medical needs of patients of the customer, and (3) only in reasonable quantities. Such request must contain the name, address, and registration number of the customer and the name and quantity of the specific controlled substance desired. The request shall be preserved by the registrant with other records of distribution of controlled substances. In addition, the requirements of Part 1305 of the chapter shall be complied with for any distribution of a controlled substance listed in Schedule II. For purposes of this paragraph, the term 'customer' includes a person to whom a complimentary sample of a substance is given in order to encourage the prescribing or recommending of the substance by the person.

(e) When shipping controlled substances, a registrant is responsible for selecting common or contract carriers which provide adequate security to guard against in-transit losses. When storing controlled substances in a public warehouse, a registrant is responsible for selecting a warehouseman which will provide adequate security to guard against storage losses; wherever possible, the registrant shall store controlled substances in a public warehouse which complies with the requirements set forth in § 1301.72. In addition, the registrant shall employ precautions (e.g., assuring that shipping containers do not indicate that contents are controlled substances) to guard against storage or in-transit losses.

(f) When distributing controlled substances through agents (e.g., detailmen), a registrant is responsible for providing and requiring adequate security to guard against theft and diversion while the substances are being stored or handled by the agent or agents.

(g) Before the initial distribution of etorphine hydrochloride and/or diprenorphine to any person, the registrant must verify that the person is authorized to handle the substances(s) by contacting the Drug Enforcement Administration.

(h) The acceptance of delivery of narcotic substances by a narcotic treatment program shall be made only by a licensed practitioner employed at the facility or other authorized individuals designated in writing. At the time of delivery, the licensed practitioner or other authorized individual designated in writing (excluding persons currently or previously dependent on narcotic drugs), shall sign for the narcotics and place his specific title (if any) on any invoice. Copies of these signed invoices shall be kept by the distributor.

(i) Narcotics dispensed or administered at a narcotic treatment program will be dispensed or administered directly to the patient by either (1) the licensed practitioner, (2) a registered nurse under the direction of the licensed practitioner, (3) a licensed practical nurse under the direction of the licensed practitioner, or (4) a pharmacist under the direction of the licensed practitioner.

(j) Persons enrolled in a narcotic treatment program will be required to wait in an area physically separated from the narcotic storage and dispensing area. This requirement will be enforced by the program physician and employees.

(k) All narcotic treatment programs must comply with standards established by the Secretary of Health, Education, and Welfare (after consultation with the Administration) respecting the quantities of narcotic drugs which may be provided to persons enrolled in a narcotic treatment program for unsupervised use.

(l) DEA may exercise discretion regarding the degree of security required in narcotic treatment programs based on such factors as the location of a program, the number of patients enrolled in a program and the number of physicians, staff members and security guards. Similarly, such factors will be taken into consideration when evaluating existing security or requiring new security at a narcotic treatment program.

[36 FR 7778, Apr. 24, 1971; 36 FR 13386, July 21, 1971, as amended at 36 FR 18731, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 17838, May 21, 1974; 39 FR 26022, July 16, 1974; 39 FR 37984, Oct. 25, 1974]

§ 1301.75 Physical security controls for practitioners.

(a) Controlled substances listed in Schedule I shall be stored in a securely locked, substantially constructed cabinet.

(b) Controlled substances listed in Schedules II, III, IV, and V shall be stored in a securely locked, substantially constructed cabinet. However, pharmacies and institutional practitioners (as defined in § 1304.02(e) of this chapter) may disperse such substances throughout the stock of noncontrolled substances in such a manner as to obstruct the theft or diversion of the controlled substances.

(c) This section shall also apply to nonpractitioners authorized to conduct research or chemical analysis under another registration.

(d) Etorphine hydrochloride and diprenorphine shall be stored in a safe or steel cabinet equivalent to a U.S. Government Class V security container.

[39 FR 3674, Jan. 29, 1974, as amended at 39 FR 17838, May 21, 1974]

§ 1301.76 Other security controls for practitioners.

(a) The registrant shall not employ as an agent or employee who has access to controlled substances any person who has had an application for registration denied, or has had his registration revoked, at any time.

(b) The registrant shall notify the Regional Office of the Administration in his region of the theft or significant loss of any controlled substances upon discovery of such loss or theft. The registrant shall also complete DEA (or BND) Form 106 regarding such loss or theft.

(c) Whenever the registrant distributes a controlled substance (without being registered as a distributor, as permitted in § 1301.22(b) and/or §§ 1307.11–1307.14), he shall comply with the requirements imposed on nonpractitioners in § 1301.74 (a), (b), and (e).

[36 FR 7778, Apr. 24, 1971, as amended at 36 FR 18731, Sept. 21, 1971; 37 FR 15919, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1304.04 Maintenance of records and inventories.

(a) Every inventory and other record required to be kept under the Part shall be kept by the registrant and be available, for at least 2 years from the date of such inventory or record, for inspecting and copying by authorized employees of the Administration, except that financial and shipping records (such as invoices and packing slips but not executed order forms subject to § 1305.13 of this chapter) may be kept at a central location, rather than at the registered location, if the registrant obtains from the Administration approval of his central recordkeeping system and a permit to keep central records. The central recordkeeping system of any person whose system was approved by the Administration prior to May 1, 1971, shall continue to be approved under this paragraph if such person satisfies the Administration by July 1, 1971, of such approval and applies for a permit to keep central records. The permit to keep central records shall be issued by the Administration to a registrant upon application if the Administration approves his central recordkeeping system and shall be subject to the following conditions:

(1) The permit shall specify the nature of the records to be kept centrally and the exact location where the records will be kept;

(2) The registrant agrees to deliver all or any part of such records to the registered location within 48 hours of receipt of a written request from the Administration for such records and, if the Administration chooses to do so in lieu of requiring delivery of such records to the registered location, to

allow authorized employees of the Administration to inspect such records at the central location upon request by such employees without a warrant of any kind; and

(3) The failure of the registrant to perform his agreements under the permit shall revoke without further action by the Administration such permit and all other such permits held by the registrant under other registrations. In the event of a revocation of other permits under this subparagraph, the registrant shall, within 30 days after such revocation, comply with the requirements of this section that all records be kept at the registered location.

(b) Each registered manufacturer, distributor, importer, narcotic treatment program and compounder for narcotic treatment program shall maintain inventories and records of controlled substances as follows:

(1) Inventories and records of controlled substances listed in Schedules I and II shall be maintained separately from all of the records of the registrant; and

(2) Inventories and records of controlled substances listed in Schedules III, IV, and V shall be maintained either separately from all other records of the registrant or in such form that the information required is readily retrievable from the ordinary business records of the registrant.

(c) Each registered individual practitioner required to keep records and institutional practitioner shall maintain inventories and records of controlled substances in the manner prescribed in paragraph (b) of this section.

(d) Each registered pharmacy shall maintain the inventories and records of controlled substances as follows:

(1) Inventories and records of all controlled substances listed in Schedules I and II shall be maintained separately from all other records of the pharmacy, and prescriptions for such substances shall be maintained in a separate prescription file; and

(2) Inventories and records of controlled substances listed in Schedules III, IV, and V shall be maintained either separately from all other records of the pharmacy or in such form that the information required is readily retrievable from ordinary business records of the pharmacy, and prescriptions for such substances shall be maintained either in separate prescription file for controlled substances listed in Schedules III, IV, and V only or in such form that they are readily retrievable from the other prescription records of the pharmacy. Prescriptions will be deemed readily retrievable if, at the time they are initially filed, the face of the prescription is stamped in red ink in the lower right corner with the letter "C" no less than 1-inch high and filed either in the prescription file for controlled substances listed in Schedules I and II or in the usual consecutively numbered prescription file for non-controlled substances.

[36 FR 7790, Apr. 24, 1971, as amended at 36 FR 13386, July 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 37935, Oct. 25, 1974]

§ 1304.41 Reports from distributors.

Each person who is registered to distribute controlled substances shall report as follows:

(a) *Substances covered.* Reports shall include data on each controlled substance listed in Schedules I and II and on each narcotic controlled substance listed in Schedule III (but not on any material, compound, mixture or preparation containing a quantity of a substance having a stimulant effect on the central nervous system, which material, compound, mixture or preparation is listed in Schedule III or on any narcotic controlled substance listed in Schedule V). Data shall be presented in such a manner as to identify the particular form, strength, and trade name, if any, of the product containing the controlled substance for which the report is being made. For this purpose, persons filing reports shall utilize the National Drug Code Number assigned to the product under the National Drug Code System of the Food and Drug Administration.

(b) *Transactions reported.* Reports shall provide data on each acquisition to inventory (identifying whether it is, e.g., by purchase or transfer, return from a customer, or supply by the Federal Government) and each reduction from inventory (identifying whether it is, e.g., by sale or transfer, sampling, theft, destruction, or seizure by Government agencies). These reports shall be filed every month not later than the 15th day of the month succeeding the month for which it is submitted: except that a registrant may be given permission to file more frequently or less frequently (but not less than quarterly), depending on the number of transactions being reported each time by that registrant.

(c) *Inventories reported.* Reports shall provide data on the stocks of each reported controlled substance on hand as of the close of business on December 31 of each year. These reports shall be filed no later than January 15 of the following year.

(d) *Exceptions.* A registered institutional practitioner which distributes exclusively to (for dispensing by) agents, employees, or affiliated institutional practitioners of the registrant, may be exempted from filing reports under this section by applying to the Distribution Audit Branch of the Administration.

[37 FR 28714, Dec. 29, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 38 FR 34998, Dec. 21, 1973]

§ 1304.42 Reports from manufacturers importing poppy straw or concentrate of poppy straw.

(a) Every manufacturer importing poppy straw or concentrate of poppy straw shall submit in addition to Form 333, Form DEA 247(c) accounting for the importation and for all manufacturing operations performed between importation and the production in bulk of finished marketable products, standardized in accordance with the U.S. Pharmacopeia, National Formulary, or other recognized medical standards. Subsequent manufacture from such products, including bottling or packaging operations, shall be accounted for in the returns on DEA Form 333 (§ 1304.38) and its supplements. DEA Form 247(c) shall be submitted quarterly to the Regulatory Investigations Section, Drug Enforcement Administration, Department of Justice, Washington, D.C. 20537, on or before the 15th day of the month immediately following the period for which it is submitted.

(b) The report of manufacture from poppy straw or concentrate of poppy straw shall consist of summaries with supporting detail sheets accounting for original manufacture from poppy straw to concentrate, and from concentrate of poppy straw, production from morphine for further manufacture and also accounting for all stocks of poppy straw, concentrate of poppy straw, morphine for further manufacture and other crude alkaloids.

(c) The detail sheets (DEA 247(c)) supporting the summary of manufacture from poppy straw or concentrate of poppy straw shall show separately the amount of poppy straw or concentrate imported, the poppy straw used for production of concentrate, the concentrate used for extraction of alkaloids, subsequent manufacture from those alkaloids and the inventory of poppy straw and concentrate of poppy straw at the close of the reporting period.

(d) Upon importation of poppy straw or concentrate of poppy straw, samples will be selected and assays made by the importing manufacturer in a manner and according to a method previously approved by DEA. Where final assay data is not determined at the time of rendering report, the report shall be made on the basis of the best data available, subject to adjustment, and the necessary adjusting entries shall be made on the next report.

(e) Upon withdrawal of poppy straw or concentrate of poppy straw from Customs custody, the importing manufacturer shall assign to each lot or container an identification number by which the poppy straw or concentrate will be associated with the lot assay and identified in reports.

(f) Where factory procedure is such that partial withdrawals of poppy straw or concentrate are made from individual containers, there shall be attached to each container a stock record card on which shall be kept a complete record of all withdrawals therefrom.

(g) Concentrate of poppy straw and derivatives produced for exclusive use in further manufacturing purposes shall be reported produced when they come into existence in that form in which they are to be so used. Alkaloids or derivatives produced exclusively for distribution shall be reported as produced when manufacture has actually been completed and the finished marketable product ready for packaging and distribution. Such products shall be regarded as ready for packaging and distribution as soon as all processing other than mere packaging has been completed. Products manufactured partly for distribution and partly for use in further manufacture will be reported produced as soon as manufacture is complete and they are ready either for use in further manufacture or for packaging for distribution.

(h) Subject to § 1303.24(c) of this chapter, no accumulations of morphine or other narcotic controlled substances in their pure or near-pure states shall be permitted to remain inactively in process for an unreasonable time in light of efficient industrial practices. All such products nearing completion of their respective processes and approaching a condition of purity shall be carefully protected, promptly completed, and immediately transferred to finished stocks, and reported as produced.

(i) In making conversions of concentrate of poppy straw alkaloids and their salts to anhydrous morphine the quantity of the particular alkaloid or salt in avoirdupois ounces shall be multiplied by a conversion factor arrived at by ascertaining the ratio, carried to the fourth decimal place, between the respective molecular weight of such alkaloid or salt and the molecular weight of anhydrous morphine (285.16), such weights being computed to the third decimal place from the chemical formulae of the substances and the atomic weights of elements, as adopted by the International Committee on Chemical Elements and published in the latest edition of the U.S. Pharmacopoeia.

[40 FR 6779, Feb. 14, 1975, as amended at 40 FR 42866, Sept. 17, 1975]

PART 1305—ORDER FORMS

Sec.

1305.01 Scope of Part 1305.
1305.02 Definitions.
1305.03 Distributions requiring order forms.
1305.04 Persons entitled to obtain and execute order forms.
1305.05 Procedure for obtaining order forms.
1305.06 Procedure for executing order forms.
1305.07 Power of attorney.
1305.08 Persons entitled to fill order forms.
1305.09 Procedure for filling order forms.
1305.10 Procedure for endorsing order forms.
1305.11 Unaccepted and defective order forms.
1305.12 Lost and stolen order forms.
1305.13 Preservation of order forms.
1305.14 Return of unused order forms.
1305.15 Cancellation and voiding of order forms.
1305.16 Special procedure for filling certain order forms.

AUTHORITY: Secs. 301, 308, 501(b), 84 Stat. 1253, 1259, 1260, 1271; 21 U.S.C. 821, 828, 871(b).

SOURCE: 36 FR 7796, Apr. 24, 1971, unless otherwise noted. Redesignated at 38 FR 26609, Sept. 24, 1973.

NOMENCLATURE CHANGES: 38 FR 26609, Sept. 24, 1973.

§ 1305.01 Scope of Part 1305.

Procedures governing the issuance, use, and preservation of order forms pursuant to section 1308 of the Act (21 U.S.C. 828) are set forth generally by that section and specifically by the sections of this part.

§ 1305.02 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) The term "Act" means the Controlled Substances Act (84 Stat. 1242; 21 U.S.C. 801) and/or the Controlled Substances Import and Export Act (84 Stat. 1285; 21 U.S.C. 951).

(b) The term "purchaser" means any registered person entitled to obtain and execute order forms pursuant to § 1305.04 and § 1305.06.

(c) The term "supplier" means any registered person entitled to fill order forms pursuant to § 1305.08.

(d) Any term not defined in this section shall have the definition set forth in section 102 of the Act (21 U.S.C. 802) and §§ 1301.02 and 1302.02 of this chapter.

§ 1305.03 Distributions requiring order forms.

An order form (DEA (or BND) Form 222c) is required for each distribution of a controlled substance listed in Schedule I or II, except for the following:

(a) The exportation of such substances from the United States in conformity with the Act;

(b) The delivery of such substances to or by a common or contract carrier for carriage in the lawful and usual course of its business, or to or by a warehouseman for storage in the lawful and usual course of its business (but excluding such carriage or storage by the owner of the substance in connection with the distribution to a third person);

(c) The procurement of a sample of such substances by an exempt law enforcement official pursuant to § 1316.04 (d) of this chapter, provided that the receipt required by that section is used and is preserved in the manner prescribed in this part for order forms;

(d) The procurement of such substances by a civil defense or disaster relief organization, pursuant to § 1301.27 of this chapter, provided that

the Civil Defense Emergency Order Form required by that section is used and is preserved with other records of the registrant; and

(e) The purchase of such substances by the master of a vessel pursuant to § 1301.28 of this chapter: *Provided*, That the special order form provided by the U.S. Public Health Service as required by that section is used and preserved in the manner prescribed on this order form.

(f) The delivery of such substances to a registered analytical laboratory, or its agent approved by DEA, from an anonymous source for the analysis of the drug sample, provided the laboratory has obtained a written waiver of the order form requirement from the Regional Director of the Region in which the laboratory is located, which waiver may be granted upon agreement of the laboratory to conduct its activities in accordance with Administration guidelines.

[36 FR 7796, Apr. 24, 1971, as amended at 37 FR 15920, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 15031, Apr. 30, 1974]

§ 1305.04 Persons entitled to obtain and execute order forms.

(a) Order forms may be obtained only by persons who are registered under section 303 of the Act (21 U.S.C. 823) to handle controlled substances listed in Schedules I and II, and by persons who are registered under section 1008 of the Act (21 U.S.C. 958) to export such substances. Persons not registered to handle controlled substances listed in Schedule I or II and persons registered only to import controlled substances listed in any schedule are not entitled to obtain order forms.

(b) An order form may be executed only on behalf of the registrant named thereon and only if his registration as to the substances being purchased has not expired or been revoked or suspended.

§ 1305.05 Procedure for obtaining order forms.

(a) Order forms are issued in books of six forms, each form containing an original, duplicate and triplicate copy (respectively, Copy 1, Copy 2, and Copy 3). A limit of three books of forms will be furnished on any requisition, unless additional books are specifically requested and a reasonable need for such additional books is shown.

(b) Any person applying for a registration which would entitle him to obtain order forms may requisition such forms by so indicating on the application form; order forms will be supplied upon the registration of the applicant. Any person holding a registration entitling him to obtain order forms may requisition such forms for the first time on DEA (or BND) Form 222d, which may be obtained from the Registration Branch of the Administration. Any person already holding order forms may requisition additional forms only on DEA (or BND) Form 222b, which is contained in each book of order forms. All requisitions shall be submitted to the Registration Branch, Drug Enforcement Administration, Department of Justice, Post Office Box 28083, Central Station, Washington, D.C. 20005.

(c) Each requisition shall show the name, address, and registration number of the registrant and the number of books of order forms desired. Each requisition shall be signed and dated by the same person who signed the most recent application for registration or for reregistration, or by any person authorized to obtain and execute order forms by a power of attorney pursuant to § 1305.07.

(d) Order forms will be serially numbered and issued with the name, address and registration number of the registrant, the authorized activity and schedules of the registrant. This information cannot be altered or changed by the registrant; any errors must be corrected by the Registration Branch of the Administration by returning the forms with notification of the error.

[36 FR 7796, Apr. 24, 1971, as amended at 36 FR 18732, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1305.06 Procedure for executing order forms.

(a) Order forms shall be prepared and executed by the purchaser simultaneously in triplicate by means of in-

terleaved carbon sheets which are part of the DEA (or BND) Form 222c. Order forms shall be prepared by use of a typewriter, pen, or indelible pencil.

(b) Only one item shall be entered on each numbered line. There are five lines on each order form. If one order form is not sufficient to include all items in an order, additional forms shall be used. Order forms for etorphine hydrochloride and diprenorphine shall contain only these substances. The total number of items ordered shall be noted on that form in the space provided.

(c) An item shall consist of one or more commercial or bulk containers of the same finished or bulk form and quantity of the same substance; a separate item shall be made for each commercial or bulk container of different finished or bulk form, quantity or substance. For each item the form shall show the name of the article ordered, the finished or bulk form of the article (e.g., 10-milligram tablet, 10-milligram concentration per fluid ounce or milliliter, or U.S.P.), the number of units or volume in each commercial or bulk container (e.g., 100-tablet bottle or 3-milliliter vial) or the quantity or volume of each bulk container (e.g., 10 kilograms), the number of commercial or bulk containers ordered, and the name and quantity per unit of the controlled substance or substances contained in the article if not in pure form. The catalogue number of the article may be included at the discretion of the purchaser.

(d) The name and address of the supplier from whom the controlled substances are being ordered shall be entered on the form. Only one supplier may be listed on any one form.

(e) Each order form shall be signed and dated by a person authorized to sign a requisition for order forms on behalf of the purchaser pursuant to § 1305.05(c). The name of the purchaser, if different from the individual signing the order form, shall also be inserted in the signature space. Unexecuted order forms may be kept and may be executed at a location other than the registered location printed on the form, provided that all unexecuted forms are delivered promptly to the registered location upon an inspection of such location by any officer authorized to make inspections, or to enforce, any Federal, State, or local law regarding controlled substances.

[36 FR 7796, Apr. 24, 1971, as amended at 36 FR 13386, July 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 17838, May 21, 1974]

§ 1305.07 Power of attorney.

Any purchaser may authorize one or more individuals, whether or not located at the registered location of the purchaser, to obtain and execute order forms on his behalf by executing a power of attorney for each such individual. The power of attorney shall be signed by the same person who signed (or was authorized to sign, pursuant to § 1301.32(f) of this chapter or § 1311.32(f) of this chapter) the most recent application for registration or reregistration and by the individual being authorized to obtain and execute order forms. The power of attorney shall be filed with the executed order forms of the purchaser, and shall be retained for the same period as any order form bearing the signature of the attorney. The power of attorney shall be available for inspection together with other order form records. Any power of attorney may be revoked at any time by executing a notice of revocation, signed by the person who signed (or was authorized to sign) the power of attorney or by a successor, whoever signed the most recent application for registration or reregistration, and filing it with the power of attorney being revoked. The form for the power of attorney and notice of revocation shall be similar to the following:

POWER OF ATTORNEY FOR DEA ORDER FORMS

_____ (Name of registrant)
_____ (Address of registrant)
_____ (DEA registration number)

I, _____ (name of person granting power), the undersigned, who is authorized to sign the current application for registration of the above-named registrant under the Controlled Substances Act or Controlled Substances Import and Export Act, have made, constituted, and appointed, and by these presents, do make, constitute, and appoint _____ (name of attorney-in-

fact), my true and lawful attorney for me in my name, place, and stead, to execute applications for books of official order forms and to sign such order forms in requisition for Schedule I and II controlled substances, in accordance with section 308 of the Controlled Substances Act (21 U.S.C. 828) and Part 305 of Title 21 of the Code of Federal Regulations. I hereby ratify and confirm all that said attorney shall lawfully do or cause to be done by virtue hereof.

(Signature of person granting power)

I, ———— (name of attorney-in-fact), hereby affirm that I am the person named herein as attorney-in-fact and that the signature affixed hereto is my signature.

(Signature of attorney-in-fact)

Witnesses:

1. ————.
2. ————.

Signed and dated on the —— day of ————, 19——, at ————.

NOTICE OF REVOCATION

The foregoing power of attorney is hereby revoked by the undersigned, who is authorized to sign the current application for registration of the above-named registrant under the Controlled Substances Act of the Controlled Substances Import and Export Act. Written notice of this revocation has been given to the attorney-in-fact ———— this same day.

(Signature of person revoking power)

Witnesses:

1. ————.
2. ————.

Signed and dated on the —— day of ————, 19——, at ————.

[37 FR 15921, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973]

CONTROLLED SUBSTANCES LISTED IN SCHEDULE II

Sec.

1306.11 Requirement of prescription.
1306.12 Refilling prescriptions.
1306.13 Partial filling of prescriptions.
1306.14 Labeling of substances.
1306.15 Filing of prescriptions.

CONTROLLED SUBSTANCES LISTED IN SCHEDULES III AND IV

1306.21 Requirement of prescription.
1306.22 Refilling of prescriptions.
1306.23 Partial filling of prescriptions.
1306.24 Labeling of substances.
1306.25 Filing prescriptions.

CONTROLLED SUBSTANCES LISTED IN SCHEDULES V

1306.31 Requirement of prescription.
1306.32 Dispensing without prescription.

AUTHORITY: Secs. 301, 309, 501(b), 84 Stat. 1253, 1260, 1271; 21 U.S.C. 821, 829, 871(b).

SOURCE: 36 FR 7799, Apr. 24, 1971; 36 FR 13386, July 21, 1971, unless otherwise noted. Redesignated at 38 FR 26609, Sept. 24, 1973.

NOMENCLATURE CHANGES: 38 FR 26609, Sept. 24, 1973.

PART 1306—PRESCRIPTIONS

GENERAL INFORMATION

Sec.

1306.01 Scope of Part 1306.
1306.02 Definitions.
1306.03 Persons entitled to issue prescriptions.
1306.04 Purpose of issue of prescription.
1306.05 Manner of issuance of prescriptions.
1306.06 Persons entitled to fill prescriptions.
1306.07 Administering or dispensing of narcotic drugs.

§ 1306.01 Scope of Part 1306.

Rules governing the issuance, filling and filing of prescriptions pursuant to section 309 of the Act (21 U.S.C. 829) are set forth generally in that section and specifically by the sections of this part.

§ 1306.02 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) The term "Act" means the Controlled Substances Act (84 Stat. 1242; 21 U.S.C. 801).

(b) The term "individual practitioner" means a physician, dentist, veterinarian, or other individual licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which he practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacist, a pharmacy, or an institutional practitioner.

(c) The term "institutional practitioner" means a hospital or other person (other than an individual) licensed, registered, or otherwise per

mitted, by the United States or the jurisdiction in which it practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacy.

(d) The term "pharmacist" means any pharmacist licensed by a State to dispense controlled substances, and shall include any other person (e.g., a pharmacist intern) authorized by a State to dispense controlled substances under the supervision of a pharmacist licensed by such State.

(e) The term "prescription" means an order for medication which is dispensed to or for an ultimate user but does not include an order for medication which is dispensed for immediate administration to the ultimate used. (e.g., an order to dispense a drug to a bed patient for immediate administration in a hospital is not a prescription.)

(f) The terms "register" and "registered" refer to registration required and permitted by section 303 of the Act (21 U.S.C. 823).

(g) Any term not defined in this section shall have the definition set forth in section 102 of the Act (21 U.S.C. 802) or § 1301.02 of this chapter.

[36 FR 7799, Apr. 24, 1971, as amended at 36 FR 18732, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1306.03 Persons entitled to issue prescriptions.

(a) A prescription for a controlled substance may be issued only by an individual practitioner who is:

(1) authorized to prescribe controlled substances by the jurisdiction in which he is licensed to practice his profession and

(2) either registered or exempted from registration pursuant to §§ 1301.24(c) and 1301.25 of this chapter.

(b) A prescription issued by an individual practitioner may be communicated to a pharmacist by an employee or agent of the individual practitioner.

[36 FR 7799, Apr. 24, 1971, as amended at 36 FR 18732, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1306.04 Purpose of issue of prescription.

(a) A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (21 U.S.C. 829) and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.

(b) A prescription may not be issued in order for an individual practitioner to obtain controlled substances for supplying the individual practitioner for the purpose of general dispensing to patients.

(c) A prescription may not be issued for the dispensing of narcotic drugs listed in any schedule for "detoxification treatment" or "maintenance treatment" as defined in Section 102 of the Act (21 U.S.C. 802).

[36 FR 7799, Apr. 24, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 37986, Oct. 25, 1974]

§ 1306.05 Manner of issuance of prescriptions.

(a) All prescriptions for controlled substances shall be dated as of, and signed on, the day when issued and shall bear the full name and address of the patient, and the name, address, and registration number of the practitioner. A practitioner may sign a prescription in the same manner as he would sign a check or legal document (e.g., J. H. Smith or John H. Smith). Where an oral order is not permitted, prescriptions shall be written with ink or indelible pencil or typewriter and shall be manually signed by the practitioner. The prescriptions may be prepared by a secretary or agent for the signature of a practitioner, but the prescribing practitioner is responsible in case the prescription does not conform in all essential respects to the

law and regulations. A corresponding liability rests upon the pharmacist who fills a prescription not prepared in the form prescribed by these regulations.

(b) An intern, resident, or foreign-trained physician, or physician on the staff of a Veterans Administration facility, exempted from registration under § 1301.24(c) shall include on all prescriptions issued by him the registration number of the hospital or other institution and the special internal code number assigned to him by the hospital or other institution as provided in § 1301.24 (c), in lieu of the registration number of the practitioner required by this section. Each written prescription shall have the name of the physician stamped, typed, or handprinted on it, as well as the signature of the physician.

(c) An official exempted from registration under § 1301.25 shall include on all prescriptions issued by him his branch of service or agency (e.g., "U.S. Army" or "Public Health Service") and his service identification number, in lieu of the registration number of the practitioner required by this section. The service identification number for a Public Health Service employee is his Social Security identification number. Each prescription shall have the name of the officer stamped, typed, or handprinted on it, as well as the signature of the officer.

[36 FR 7799, Apr. 24, 1971, as amended at 36 FR 18733, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1306.06 Persons entitled to fill prescriptions.

A prescription for controlled substances may only be filled by a pharmacist acting in the usual course of his professional practice and either registered individually or employed in a registered pharmacy or registered institutional practitioner.

§ 1306.07 Administering or dispensing of narcotic drugs.

(a) The administering or dispensing directly (but not prescribing) of narcotic drugs listed in any schedule to a narcotic drug dependent person for "detoxification treatment" or "maintenance treatment" as defined in section 102 of the Act (21 U.S.C. 802) shall be deemed to be within the meaning of the term "in the course of his professional practice or research" in section 308(e) and section 102(20) of the Act (21 U.S.C. 828 (e)): *Provided*, That the practitioner is separately registered with the Attorney General as required by section 303(g) of the Act (21 U.S.C. 823(g)) and then thereafter complies with the regulatory standards imposed relative to treatment qualification, security, records and unsupervised use of drugs pursuant to such Act.

(b) Nothing in this section shall prohibit a physician who is not specifically registered to conduct a narcotic treatment program from administering (but not prescribing) narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms when necessary while arrangements are being made for referral for treatment. Not more than one day's medication may be administered to the person or for the person's use at one time. Such emergency treatment may be carried out for not more than three days and may not be renewed or extended.

(c) This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts.

[39 FR 37986, Oct. 25, 1974]

63-109 O - 81 - 7

1316 of this chapter by filing a written request stating the reasons for such exception. Requests shall be filed with the Administrator, Drug Enforcement Administration, Department of Justice, Washington, D.C. 20537. The Administrator may grant an exception in his discretion, but in no case shall he be required to grant an exception to any person which is not otherwise required by law or the regulations cited in this section.

SPECIAL EXCEPTIONS FOR MANUFACTURE AND DISTRIBUTION OF CONTROLLED SUBSTANCES

§ 1307.11 Distribution by dispenser to another practitioner.

(a) A practitioner who is registered to dispense a controlled substance may distribute (without being registered to distribute) a quantity of such substance to another practitioner for the purpose of general dispensing by the practitioner to his or its patients: Provided, That:

(1) The practitioner to whom the controlled substance is to be distributed is registered under the Act to dispense that controlled substance;

(2) The distribution is recorded by the distributing practitioner in accordance with § 1304.24(e) of this chapter and by the receiving practitioner in accordance with § 1304.24(c) of this chapter;

(3) If the substance is listed in Schedule I or II, an order form is used as required in Part 1305 of this chapter;

(4) The total number of dosage units of all controlled substances distributed by the practitioner pursuant to this section during the 12-month period in which the practitioner is registered to dispense does not exceed 5 percent of the total number of dosage units of all controlled substances distributed and dispensed by the practitioner during the 12-month period.

(b) If, at any time during the 12-month period during which the practitioner is registered to dispense, the practitioner has reason to believe that the total number of dosage units of all controlled substances which will be distributed by him pursuant to this section will exceed 5 percent of the

§ 1307.02 Application of State law and other Federal law.

Nothing in Parts 1301-1308, 1311, 1312, or 1316 of this chapter shall be construed as authorizing or permitting any person to do any act which such person is not authorized or permitted to do under other Federal laws or obligations under international treaties, conventions or protocols, or under the law of the State in which he desires to do such act nor shall compliance with such Parts be construed as compliance with other Federal or State laws unless expressly provided in such other laws.

§ 1307.03 Exceptions to regulations.

Any person may apply for an exception to the application of any provision of Parts 1301-1308, 1311, 1312, or

total number of dosage units of all controlled substances distributed and dispensed by him during the 12-month period, the practitioner shall obtain a registration to distribute controlled substances.

[36 FR 18733, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1307.12 Manufacture and distribution of narcotic solutions and compounds by a pharmacist.

As an incident to a distribution under § 1307.11, a pharmacist may manufacture (without being registered to manufacture) an aqueous or oleaginous solution or solid dosage form containing a narcotic controlled substance in a proportion not exceeding 20 percent of the complete solution, compound, or mixture.

[36 FR 18733, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1301.25 Exemption of certain military and other personnel.

(a) The requirement of registration is waived for any official of the U.S. Army, Navy, Marine Corps, Air Force, Coast Guard, Public Health Service, or Bureau of Prisons who is authorized to prescribe, dispense, or administer, but not to procure or purchase, controlled substances in the course of his official duties. Such officials shall follow procedures set forth in Part 1306 of this chapter regarding prescriptions, but shall state the branch of service or agency (e.g., "U.S. Army" or "Public Health Service") and the service identification number of the issuing official in lieu of the registration number required on prescription forms. The service identification number for a Public Health Service employee is his Social Security identification number.

(b) If any official exempted by this section also engages as a private individual in any activity or group of activities for which registration is required, such official shall obtain a registration for such private activities.

[36 FR 7778, Apr. 24, 1971, as amended at 36 FR 18739, Sept. 21, 1971; 38 FR 756, Jan. 4, 1973. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1301.26 Exemption of law enforcement officials.

(a) The requirement of registration is waived for the following persons in the circumstances described in this section:

(1) Any officer or employee of the Administration, any officer of the U.S. Customs Service, any officer or employee of the United States Food and Drug Administration, and any other Federal officer who is lawfully engaged in the enforcement of any Federal law relating to controlled substances, drugs or customs, and is duly authorized to possess controlled substances in the course of his official duties; and

(2) Any officer or employee of any State, or any political subdivision or agency thereof, who is engaged in the enforcement of any State or local law relating to controlled substances and is duly authorized to possess controlled substances in the course of his official duties.

(b) Any official exempted by this section may, when acting in the course of his official duties, possess any controlled substance and distribute any such substance to any other official who is also exempted by this section and acting in the course of his official duties.

(c) Any official exempted by this section may procure any controlled substance in the course of an inspection, in accordance with § 1316.03(d), or in the course of any criminal investigation involving the person from whom the substance was procured.

(d) In order to enable law enforcement agency laboratories to obtain and transfer controlled substances for use as standards in chemical analysis, such laboratories must obtain annually a registration to conduct chemical analysis. Such laboratories shall be exempted from payment of a fee for registration. Laboratory personnel, when acting in the scope of their official duties, are deemed to be officials exempted by this section and within the activity described in section 515(d) of the Act (21 U.S.C. 885(d)). For purposes of this paragraph, laboratory activities shall not include field or other preliminary chemical tests by officials exempted by this section.

(e) Laboratories of the Administration shall obtain annually a registration to conduct chemical analysis in accordance with paragraph (d) of this section. In addition to the activities authorized under a registration to conduct chemical analysis pursuant to § 1301.22(b)(4), laboratories of the Administration shall be authorized to manufacture or import controlled substances for any lawful purpose, to distribute or export such substances to any person, and to import and export such substances in emergencies without regard to the requirements of Part 1312 of this chapter if a report concerning the importation or exportation is made to the Distribution Audit Branch of the Administration within 30 days of such importation or exportation.

SECURITY REQUIREMENTS

§ 1301.71 Security requirements generally.

(a) All applicants and registrants shall provide effective controls and procedures to guard against theft and diversion of controlled substances. In order to determine whether a registrant has provided effective controls against diversion, the Administrator shall use the security requirements set forth in §§ 1301.72–1301.76 as standards for the physical security controls and operating procedures necessary to prevent diversion. Materials and construction which will provide a structural equivalent to the physical security controls set forth in §§ 1301.72,

1301.73 and 1301.75 may be used in lieu of the materials and construction described in those sections.

(b) Substantial compliance with the standards set forth in §§ 1301.72-1301.76 may be deemed sufficient by the Administrator after evaluation of the overall security system and needs of the applicant or registrant. In evaluating the overall security system of a registrant or applicant, the Administrator may consider any of the following factors as he may deem relevant to the need for strict compliance with security requirements:

(1) The type of activity conducted (e.g., processing of bulk chemicals, preparing dosage forms, packaging, labeling, cooperative buying, etc.);

(2) The type and form of controlled substances handled (e.g., bulk liquids or dosage units, usable powders or nonusable powders);

(3) The quantity of controlled substances handled;

(4) The location of the premises and the relationship such location bears on security needs;

(5) The type of building construction comprising the facility and the general characteristics of the building or buildings;

(6) The type of vault, safe, and secure enclosures or other storage system (e.g., automatic storage and retrieval system) used;

(7) The type of closures on vaults, safes, and secure enclosures;

(8) The adequacy of key control systems and/or combination lock control systems;

(9) The adequacy of electric detection and alarm systems, if any including use of supervised transmittal lines and standby power sources;

(10) The extent of unsupervised public access to the facility, including the presence and characteristics of perimeter fencing, if any;

(11) The adequacy of supervision over employees having access to manufacturing and storage areas;

(12) The procedures for handling business guests, visitors, maintenance personnel, and nonemployee service personnel;

(13) The availability of local police protection or of the registrant's or applicant's security personnel, and;

(14) The adequacy of the registrant's or applicant's system for monitoring the receipt, manufacture, distribution, and disposition of controlled substances in its operations.

(c) When physical security controls become inadequate as a result of a controlled substance being transferred to a different schedule, or as a result of a noncontrolled substance being listed on any schedule, or as a result of a significant increase in the quantity of controlled substances in the possession of the registrant during normal business operations, the physical security controls shall be expanded and extended accordingly. A registrant may adjust physical security controls within the requirements set forth in §§ 1301.72-1301.76 when the need for such controls decreases as a result of a controlled substance being transferred to a different schedule, or a result of a controlled substance being removed from control, or as a result of a significant decrease in the quantity of controlled substances in the possession of the registrant during normal business operations.

(d) Any registrant or applicant desiring to determine whether a proposed security system substantially complies with, or is the structural equivalent of, the requirements set forth in §§ 1301.72-1301.76 may submit any plans, blueprints, sketches or other materials regarding the proposed security system either to the Regional Administrator in the region in which the system will be used, or to the Compliance Investigations Division, Drug Enforcement Administration, Department of Justice, Washington, D.C. 20537.

(e) Physical security controls of locations registered under the Harrison Narcotic Act or the Narcotics Manufacturing Act of 1960 on April 30, 1971, shall be deemed to comply substantially with the standards set forth in §§ 1301.72, 1301.73 and 1301.75. Any new facilities or work or storage areas constructed or utilized for controlled substances, which facilities or work or storage areas have not been previously approved by the Administration, shall not necessarily be deemed to comply substantially with the standards set forth in §§ 1301.72, 1301.73 and

1301.75, notwithstanding that such facilities or work or storage areas have physical security controls similar to those previously approved by the Administration.

[36 FR 18729, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1301.72 Physical security controls for non-practitioners; narcotic treatment programs and compounders for narcotic treatment programs; storage areas.

(a) *Schedules I and II.* Raw materials, bulk materials awaiting further processing, and finished products which are controlled substances listed in Schedule I or II shall be stored in one of the following secure storage areas:

(1) Where small quantities permit, a safe or steel cabinet;

(i) Which safe or steel cabinet shall have the following specifications or the equivalent: 30 man-minutes against surreptitious entry, 10 man-minutes against forced entry, 20 man-hours against lock manipulation, and 20 man-hours against radiological techniques;

(ii) Which safe or steel cabinet, if it weighs less than 750 pounds, is bolted or cemented to the floor or wall in such a way that it cannot be readily removed; and

(iii) Which safe or steel cabinet, if necessary, depending upon the quantities and type of controlled substances stored, is equipped with an alarm system which, upon attempted unauthorized entry, shall transmit a signal directly to a central protection company or a local or State police agency which has a legal duty to respond, or a 24-hour control station operated by the registrant, or such other protection as the Administrator may approve.

(2) A vault constructed before, or under construction on, September 1, 1971, which is of substantial construction with a steel door, combination or key lock, and an alarm system; or

(3) A vault constructed after September 1, 1971:

(i) The walls, floors, and ceilings of which vault are constructed of at least 8 inches of reinforced concrete or other substantial masonry, reinforced vertically and horizontally with ½-inch steel rods tied 6 inches on center, or the structural equivalent to such reinforced walls, floors, and ceilings;

(ii) The door and frame unit of which vault shall conform to the following specifications or the equivalent: 30 man-minutes against surreptitious entry, 10 man-minutes against forced entry, 20 man-hours against lock manipulation, and 20 man-hours against radiological techniques;

(iii) Which vault, if operations require it to remain open for frequent access, is equipped with a "day-gate" which is self-closing and self-locking, or the equivalent, for use during the hours of operation in which the vault door is open;

(iv) The walls or perimeter of which vault are equipped with an alarm, which upon unauthorized entry shall transmit a signal directly to a central station protection company, or a local or State police agency which has a legal duty to respond, or a 24-hour control station operated by the registrant, or such other protection as the Administrator may approve, and, if necessary, holdup buttons at strategic points of entry to the perimeter area of the vault;

(v) The door of which vault is equipped with contact switches; and

(vi) Which vault has one of the following: complete electrical lacing of the walls, floor and ceilings; sensitive ultrasonic equipment within the vault; a sensitive sound accumulator system; or such other device designed to detect illegal entry as may be approved by the Administration.

(b) *Schedules III, IV and V.* Raw materials, bulk materials awaiting further processing, and finished products which are controlled substances listed in Schedules III, IV and V shall be stored in the following secure storage areas:

(1) A safe or steel cabinet as described in paragraph (a)(1) of this section;

(2) A vault as described in paragraph (a)(2) or (3) of this section equipped with an alarm system as described in paragraph (b)(4)(v) of this section;

(3) A building used for storage of Schedules III through V controlled substances with perimeter security which limits access during working

hours and provides security after working hours and meets the following specifications:

(i) Has an electronic alarm system as described in paragraph (b)(4)(v) of this section,

(ii) Is equipped with self-closing, self-locking doors constructed of substantial material commensurate with the type of building construction, provided, however, a door which is kept closed and locked at all times when not in use and when in use is kept under direct observation of a responsible employee or agent of the registrant is permitted in lieu of a self-closing, self-locking door. Doors may be sliding or hinged. Regarding hinged doors, where hinges are mounted on the outside, such hinges shall be sealed, welded or otherwise constructed to inhibit removal. Locking devices for such doors shall be either of the multiple-position combination or key lock type and:

(*a*) In the case of key locks, shall require key control which limits access to a limited number of employees, or;

(*b*) In the case of combination locks, the combination shall be limited to a minimum number of employees and can be changed upon termination of employment of an employee having knowledge of the combination;

(4) A cage, located within a building on the premises, meeting the following specifications:

(i) Having walls constructed of not less than No. 10 gauge steel fabric mounted on steel posts, which posts are:

(*a*) At least one inch in diameter;

(*b*) Set in concrete or installed with lay bolts that are pinned or brazed; and

(*c*) Which are placed no more than ten feet apart with horizontal one and one-half inch reinforcements every sixty inches;

(ii) Having a mesh construction with openings of not more than two and one-half inches across the square,

(iii) Having a ceiling constructed of the same material, or in the alternative, a cage shall be erected which reaches and is securely attached to the structural ceiling of the building. A lighter gauge mesh may be used for the ceilings of large enclosed areas if walls are at least 14 feet in height,

(iv) Is equipped with a door constructed of No. 10 gauge steel fabric on a metal door frame in a metal door flange, and in all other respects conforms to all the requirements of 21 CFR 1301.72(b)(3)(ii), and

(v) Is equipped with an alarm system which upon unauthorized entry shall transmit a signal directly to a central station protection agency or a local or state police agency, each having a legal duty to respond, or to a 24-hour control station operated by the registrant, or to such other source of protection as the Administrator may approve;

(5) An enclosure of masonry or other material, approved in writing by the Administrator as providing security comparable to a cage;

(6) A building or enclosure within a building which has been inspected and approved by DEA or its predecessor agency, BNDD, and continues to provide adequate security against the diversion of Schedule III through V controlled substances, of which fact written acknowledgment has been made by the Regional Director of DEA for the Region in which such building or enclosure is situated;

(7) Such other secure storage areas as may be approved by the Administrator after considering the factors listed in § 1301.71(b); (1) through (14);

(8)(i) Schedule III through V controlled substances may be stored with Schedules I and II controlled substances under security measures provided by 21 CFR 1301.72(a);

(ii) Non-controlled drugs, substances and other materials may be stored with Schedule III through V controlled substances in any of the secure storage areas required by 21 CFR 1301.72(b), provided that permission for such storage of non-controlled items is obtained in advance, in writing, from the Regional Director of DEA for the Region in which such storage area is situated. Any such permission tendered must be upon the Regional Director's written determination that such non-segregated storage does not diminish security effectiveness for Schedules III through V controlled substances.

(c) *Multiple storage areas.* Where several types or classes of controlled substances are handled separately by the registrant or applicant for different purposes (e.g., returned goods, or goods in process), the controlled substances may be stored separately, provided that each storage area complies with the requirements set forth in this section.

(d) *Accessibility to storage areas.* The controlled substances storage areas shall be accessible only to an absolute minimum number of specifically authorized employees. When it is necessary for employee maintenance personnel, nonemployee maintenance personnel, business guests, or visitors to be present in or pass through controlled substances storage areas, the registrant shall provide for adequate observation of the area by an employee specifically authorized in writing.

[36 FR 18730, Sept. 21, 1971, as amended at 37 FR 15919, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 37984, Oct. 25, 1974; 41 FR 16460, Apr. 19, 1976; 41 FR 17382, Apr. 26, 1976]

§ 1301.73 Physical security controls for non-practitioners; compounders for narcotic treatment programs; manufacturing and compounding areas.

All manufacturing activities (including processing, packaging and labeling) involving controlled substances listed in any schedule and all activities of compounders shall be conducted in accordance with the following:

(a) All in-process substances shall be returned to the controlled substances storage area at the termination of the process. If the process is not terminated at the end of a workday (except where a continuous process or other normal manufacturing operation should not be interrupted), the processing area or tanks, vessels, bins or bulk containers containing such substances shall be securely locked, with adequate security for the area or building. If such security requires an alarm, such alarm, upon unauthorized entry, shall transmit a signal directly to a central station protection company, or local or state police agency which has a legal duty to respond, or a 24-hour control station operated by the registrant.

(b) Manufacturing activities with controlled substances shall be conducted in an area or areas of clearly defined limited access which is under surveillance by an employee or employees designated in writing as responsible for the area. "Limited access" may be provided, in the absence of physical dividers such as walls or partitions, by traffic control lines or restricted space designation. The employee designated as responsible for the area may be engaged in the particular manufacturing operation being conducted: *Provided,* That he is able to provide continuous surveillance of the area in order that unauthorized persons may not enter or leave the area without his knowledge.

(c) During the production of controlled substances, the manufacturing areas shall be accessible to only those employees required for efficient operation. When it is necessary for employee maintenance personnel, nonemployee maintenance personnel, business guests, or visitors to be present in or pass through manufacturing areas during production of controlled substances, the registrant shall provide for adequate observation of the area by an employee specifically authorized in writing.

[36 FR 18731, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973 and amended at 39 FR 37984, Oct. 25, 1974]

§ 1301.74 Other security controls for non-practitioners; narcotic treatment programs and compounders for narcotic treatment programs.

(a) Before distributing a controlled substance to any person who the registrant does not know to be registered to possess the controlled substance, the registrant shall make a good faith inquiry either with the Administration or with the appropriate State controlled substances registration agency, if any, to determine that the person is registered to possess the controlled substance.

(b) The registrant shall design and operate a system to disclose to the registrant suspicious orders of controlled substances. The registrant shall inform the Regional Office of the Administration in his region of suspicious orders when discovered by the regis-

trant. Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.

(c) The registrant shall notify the Regional Office of the Administration in his region of any theft of significant loss of any controlled substances upon discovery of such theft or loss. The supplier shall be responsible for reporting in-transit losses of controlled substances by the common or contract carrier selected pursuant to § 1301.74(e), upon discovery of such theft or loss. The registrant shall also complete DEA Form 106 regarding such theft or loss. Thefts must be reported whether or not the controlled substances are subsequently recovered and/or the responsible parties are identified and action taken against them.

(d) The registrant shall not distribute any controlled substance listed in Schedules II through V as a complimentary sample to any potential or current customer (1) without the prior written request of the customer, (2) to be used only for satisfying the legitimate medical needs of patients of the customer, and (3) only in reasonable quantities. Such request must contain the name, address, and registration number of the customer and the name and quantity of the specific controlled substance desired. The request shall be preserved by the registrant with other records of distribution of controlled substances. In addition, the requirements of Part 1305 of the chapter shall be complied with for any distribution of a controlled substance listed in Schedule II. For purposes of this paragraph, the term 'customer' includes a person to whom a complimentary sample of a substance is given in order to encourage the prescribing or recommending of the substance by the person.

(e) When shipping controlled substances, a registrant is responsible for selecting common or contract carriers which provide adequate security to guard against in-transit losses. When storing controlled substances in a public warehouse, a registrant is responsible for selecting a warehouseman which will provide adequate security to guard against storage losses; wherever possible, the registrant shall store controlled substances in a public warehouse which complies with the requirements set forth in § 1301.72. In addition, the registrant shall employ precautions (e.g., assuring that shipping containers do not indicate that contents are controlled substances) to guard against storage or in-transit losses.

(f) When distributing controlled substances through agents (e.g., detailmen), a registrant is responsible for providing and requiring adequate security to guard against theft and diversion while the substances are being stored or handled by the agent or agents.

(g) Before the initial distribution of etorphine hydrochloride and/or diprenorphine to any person, the registrant must verify that the person is authorized to handle the substances(s) by contacting the Drug Enforcement Administration.

(h) The acceptance of delivery of narcotic substances by a narcotic treatment program shall be made only by a licensed practitioner employed at the facility or other authorized individuals designated in writing. At the time of delivery, the licensed practitioner or other authorized individual designated in writing (excluding persons currently or previously dependent on narcotic drugs), shall sign for the narcotics and place his specific title (if any) on any invoice. Copies of these signed invoices shall be kept by the distributor.

(i) Narcotics dispensed or administered at a narcotic treatment program will be dispensed or administered directly to the patient by either (1) the licensed practitioner, (2) a registered nurse under the direction of the licensed practitioner, (3) a licensed practical nurse under the direction of the licensed practitioner, or (4) a pharmacist under the direction of the licensed practitioner.

(j) Persons enrolled in a narcotic treatment program will be required to wait in an area physically separated from the narcotic storage and dispensing area. This requirement will be enforced by the program physician and employees.

(k) All narcotic treatment programs must comply with standards established by the Secretary of Health, Education, and Welfare (after consultation with the Administration) respecting the quantities of narcotic drugs which may be provided to persons enrolled in a narcotic treatment program for unsupervised use.

(l) DEA may exercise discretion regarding the degree of security required in narcotic treatment programs based on such factors as the location of a program, the number of patients enrolled in a program and the number of physicians, staff members and security guards. Similarly, such factors will be taken into consideration when evaluating existing security or requiring new security at a narcotic treatment program.

[36 FR 7778, Apr. 24, 1971; 36 FR 13386, July 21, 1971, as amended at 36 FR 18731, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 17838, May 21, 1974; 39 FR 26022, July 16, 1974; 39 FR 37984, Oct. 25, 1974]

§ 1301.75 Physical security controls for practitioners.

(a) Controlled substances listed in Schedule I shall be stored in a securely locked, substantially constructed cabinet.

(b) Controlled substances listed in Schedules II, III, IV, and V shall be stored in a securely locked, substantially constructed cabinet. However, pharmacies and institutional practitioners (as defined in § 1304.02(e) of this chapter) may disperse such substances throughout the stock of noncontrolled substances in such a manner as to obstruct the theft or diversion of the controlled substances.

(c) This section shall also apply to nonpractitioners authorized to conduct research or chemical analysis under another registration.

(d) Etorphine hydrochloride and diprenorphine shall be stored in a safe or steel cabinet equivalent to a U.S. Government Class V security container.

[39 FR 3674, Jan. 29, 1974, as amended at 39 FR 17838, May 21, 1974]

§ 1301.76 Other security controls for practitioners.

(a) The registrant shall not employ as an agent or employee who has access to controlled substances any person who has had an application for registration denied, or has had his registration revoked, at any time.

(b) The registrant shall notify the Regional Office of the Administration in his region of the theft or significant loss of any controlled substances upon discovery of such loss or theft. The registrant shall also complete DEA (or BND) Form 106 regarding such loss or theft.

(c) Whenever the registrant distributes a controlled substance (without being registered as a distributor, as permitted in § 1301.22(b) and/or §§ 1307.11–1307.14), he shall comply with the requirements imposed on nonpractitioners in § 1301.74 (a), (b), and (e).

[36 FR 7778, Apr. 24, 1971, as amended at 36 FR 18731, Sept. 21, 1971; 37 FR 15919, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1304.04 Maintenance of records and inventories.

(a) Every inventory and other record required to be kept under the Part shall be kept by the registrant and be available, for at least 2 years from the date of such inventory or record, for inspecting and copying by authorized employees of the Administration, except that financial and shipping records (such as invoices and packing slips but not executed order forms subject to § 1305.13 of this chapter) may be kept at a central location, rather than at the registered location, if the registrant obtains from the Administration approval of his central recordkeeping system and a permit to keep central records. The central recordkeeping system of any person whose system was approved by the Administration prior to May 1, 1971, shall continue to be approved under this paragraph if such person satisfies the Administration by July 1, 1971, of such approval and applies for a permit to keep central records. The permit to keep central records shall be issued by the Administration to a registrant upon application if the Administration approves his central recordkeeping system and shall be subject to the following conditions:

(1) The permit shall specify the nature of the records to be kept centrally and the exact location where the records will be kept;

(2) The registrant agrees to deliver all or any part of such records to the registered location within 48 hours of receipt of a written request from the Administration for such records and, if the Administration chooses to do so in lieu of requiring delivery of such records to the registered location, to

allow authorized employees of the Administration to inspect such records at the central location upon request by such employees without a warrant of any kind; and

(3) The failure of the registrant to perform his agreements under the permit shall revoke without further action by the Administration such permit and all other such permits held by the registrant under other registrations. In the event of a revocation of other permits under this subparagraph, the registrant shall, within 30 days after such revocation, comply with the requirements of this section that all records be kept at the registered location.

(b) Each registered manufacturer, distributor, importer, narcotic treatment program and compounder for narcotic treatment program shall maintain inventories and records of controlled substances as follows:

(1) Inventories and records of controlled substances listed in Schedules I and II shall be maintained separately from all of the records of the registrant; and

(2) Inventories and records of controlled substances listed in Schedules III, IV, and V shall be maintained either separately from all other records of the registrant or in such form that the information required is readily retrievable from the ordinary business records of the registrant.

(c) Each registered individual practitioner required to keep records and institutional practitioner shall maintain inventories and records of controlled substances in the manner prescribed in paragraph (b) of this section.

(d) Each registered pharmacy shall maintain the inventories and records of controlled substances as follows:

(1) Inventories and records of all controlled substances listed in Schedules I and II shall be maintained separately from all other records of the pharmacy, and prescriptions for such substances shall be maintained in a separate prescription file; and

(2) Inventories and records of controlled substances listed in Schedules III, IV, and V shall be maintained either separately from all other records of the pharmacy or in such form that the information required is readily retrievable from ordinary business records of the pharmacy, and prescriptions for such substances shall be maintained either in separate prescription file for controlled substances listed in Schedules III, IV, and V only or in such form that they are readily retrievable from the other prescription records of the pharmacy. Prescriptions will be deemed readily retrievable if, at the time they are initially filed, the face of the prescription is stamped in red ink in the lower right corner with the letter "C" no less than 1-inch high and filed either in the prescription file for controlled substances listed in Schedules I and II or in the usual consecutively numbered prescription file for non-controlled substances.

[36 FR 7790, Apr. 24, 1971, as amended at 36 FR 13386, July 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 37985, Oct. 25, 1974]

§ 1304.41 Reports from distributors.

Each person who is registered to distribute controlled substances shall report as follows:

(a) *Substances covered.* Reports shall include data on each controlled substance listed in Schedules I and II and on each narcotic controlled substance listed in Schedule III (but not on any material, compound, mixture or preparation containing a quantity of a substance having a stimulant effect on the central nervous system, which material, compound, mixture or preparation is listed in Schedule III or on any narcotic controlled substance listed in Schedule V). Data shall be presented in such a manner as to identify the particular form, strength, and trade name, if any, of the product containing the controlled substance for which the report is being made. For this purpose, persons filing reports shall utilize the National Drug Code Number assigned to the product under the National Drug Code System of the Food and Drug Administration.

(b) *Transactions reported.* Reports shall provide data on each acquisition to inventory (identifying whether it is, e.g., by purchase or transfer, return from a customer, or supply by the Federal Government) and each reduction from inventory (identifying whether it is, e.g., by sale or transfer, sampling, theft, destruction, or seizure by Government agencies). These reports shall be filed every month not later than the 15th day of the month succeeding the month for which it is submitted: except that a registrant may be given permission to file more frequently or less frequently (but not less than quarterly), depending on the number of transactions being reported each time by that registrant.

(c) *Inventories reported.* Reports shall provide data on the stocks of each reported controlled substance on hand as of the close of business on December 31 of each year. These reports shall be filed no later than January 15 of the following year.

(d) *Exceptions.* A registered institutional practitioner which distributes exclusively to (for dispensing by) agents, employees, or affiliated institutional practitioners of the registrant may be exempted from filing reports under this section by applying to the Distribution Audit Branch of the Administration.

[37 FR 28714, Dec. 29, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 38 FR 34998, Dec. 21, 1973]

§ 1304.42 Reports from manufacturers importing poppy straw or concentrate of poppy straw.

(a) Every manufacturer importing poppy straw or concentrate of poppy straw shall submit in addition to Form 333, Form DEA 247(c) accounting for the importation and for all manufacturing operations performed between importation and the production in bulk of finished marketable products, standardized in accordance with the U.S. Pharmacopeia, National Formulary, or other recognized medical standards. Subsequent manufacture from such products, including bottling or packaging operations, shall be accounted for in the returns on DEA Form 333 (§ 1304.38) and its supplements. DEA Form 247(c) shall be submitted quarterly to the Regulatory Investigations Section, Drug Enforcement Administration, Department of Justice, Washington, D.C. 20537, on or before the 15th day of the month immediately following the period for which it is submitted.

(b) The report of manufacture from poppy straw or concentrate of poppy straw shall consist of summaries with supporting detail sheets accounting for original manufacture from poppy straw to concentrate, and from concentrate of poppy straw, production from morphine for further manufacture and also accounting for all stocks of poppy straw, concentrate of poppy straw, morphine for further manufacture and other crude alkaloids.

(c) The detail sheets (DEA 247(c)) supporting the summary of manufacture from poppy straw or concentrate of poppy straw shall show separately the amount of poppy straw or concentrate imported, the poppy straw used for production of concentrate, the concentrate used for extraction of alkaloids, subsequent manufacture from those alkaloids and the inventory of poppy straw and concentrate of poppy straw at the close of the reporting period.

(d) Upon importation of poppy straw or concentrate of poppy straw, samples will be selected and assays made by the importing manufacturer in a manner and according to a method previously approved by DEA. Where final assay data is not determined at the time of rendering report, the report shall be made on the basis of the best data available, subject to adjustment, and the necessary adjusting entries shall be made on the next report.

(e) Upon withdrawal of poppy straw or concentrate of poppy straw from Customs custody, the importing manufacturer shall assign to each lot or container an identification number by which the poppy straw or concentrate will be associated with the lot assay and identified in reports.

(f) Where factory procedure is such that partial withdrawals of poppy straw or concentrate are made from individual containers, there shall be attached to each container a stock record card on which shall be kept a complete record of all withdrawals therefrom.

(g) Concentrate of poppy straw and derivatives produced for exclusive use in further manufacturing purposes shall be reported produced when they come into existence in that form in which they are to be so used. Alkaloids or derivatives produced exclusively for distribution shall be reported as produced when manufacture has actually been completed and the finished marketable product ready for packaging and distribution. Such products shall be regarded as ready for packaging and distribution as soon as all processing other than mere packaging has been completed. Products manufactured partly for distribution and partly for use in further manufacture will be reported produced as soon as manufacture is complete and they are ready either for use in further manufacture or for packaging for distribution.

(h) Subject to § 1303.24(c) of this chapter, no accumulations of morphine or other narcotic controlled substances in their pure or near-pure states shall be permitted to remain inactively in process for an unreasonable time in light of efficient industrial practices. All such products nearing completion of their respective processes and approaching a condition of purity shall be carefully protected, promptly completed, and immediately transferred to finished stocks, and reported as produced.

(i) In making conversions of concentrate of poppy straw alkaloids and their salts to anhydrous morphine the quantity of the particular alkaloid or salt in avoirdupois ounces shall be multiplied by a conversion factor arrived at by ascertaining the ratio, carried to the fourth decimal place, between the respective molecular weight of such alkaloid or salt and the molecular weight of anhydrous morphine (285.16), such weights being computed to the third decimal place from the chemical formulae of the substances and the atomic weights of elements, as adopted by the International Committee on Chemical Elements and published in the latest edition of the U.S. Pharmacopoeia.

[40 FR 6779, Feb. 14, 1975, as amended at 40 FR 42866, Sept. 17, 1975]

PART 1305—ORDER FORMS

Sec.
1305.01 Scope of Part 1305.
1305.02 Definitions.
1305.03 Distributions requiring order forms.
1305.04 Persons entitled to obtain and execute order forms.
1305.05 Procedure for obtaining order forms.
1305.06 Procedure for executing order forms.
1305.07 Power of attorney.
1305.08 Persons entitled to fill order forms.
1305.09 Procedure for filling order forms.
1305.10 Procedure for endorsing order forms.
1305.11 Unaccepted and defective order forms.
1305.12 Lost and stolen order forms.
1305.13 Preservation of order forms.
1305.14 Return of unused order forms.
1305.15 Cancellation and voiding of order forms.
1305.16 Special procedure for filling certain order forms.

AUTHORITY: Secs. 301, 308, 501(b), 84 Stat. 1253, 1259, 1260, 1271; 21 U.S.C. 821, 828, 871(b).

SOURCE: 36 FR 7796, Apr. 24, 1971, unless otherwise noted. Redesignated at 38 FR 26609, Sept. 24, 1973.

NOMENCLATURE CHANGES: 38 FR 26609, Sept. 24, 1973.

§ 1305.01 Scope of Part 1305.

Procedures governing the issuance, use, and preservation of order forms pursuant to section 1308 of the Act (21 U.S.C. 828) are set forth generally by that section and specifically by the sections of this part.

§ 1305.02 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) The term "Act" means the Controlled Substances Act (84 Stat. 1242; 21 U.S.C. 801) and/or the Controlled Substances Import and Export Act (84 Stat. 1285; 21 U.S.C. 951).

(b) The term "purchaser" means any registered person entitled to obtain and execute order forms pursuant to § 1305.04 and § 1305.06.

(c) The term "supplier" means any registered person entitled to fill order forms pursuant to § 1305.08.

(d) Any term not defined in this section shall have the definition set forth in section 102 of the Act (21 U.S.C. 802) and §§ 1301.02 and 1302.02 of this chapter.

§ 1305.03 Distributions requiring order forms.

An order form (DEA (or BND) Form 222c) is required for each distribution of a controlled substance listed in Schedule I or II, except for the following:

(a) The exportation of such substances from the United States in conformity with the Act;

(b) The delivery of such substances to or by a common or contract carrier for carriage in the lawful and usual course of its business, or to or by a warehouseman for storage in the lawful and usual course of its business (but excluding such carriage or storage by the owner of the substance in connection with the distribution to a third person);

(c) The procurement of a sample of such substances by an exempt law enforcement official pursuant to § 1316.04 (d) of this chapter, provided that the receipt required by that section is used and is preserved in the manner prescribed in this part for order forms;

(d) The procurement of such substances by a civil defense or disaster relief organization, pursuant to § 1301.27 of this chapter, provided that

the Civil Defense Emergency Order Form required by that section is used and is preserved with other records of the registrant; and

(e) The purchase of such substances by the master of a vessel pursuant to § 1301.28 of this chapter: *Provided*, That the special order form provided by the U.S. Public Health Service as required by that section is used and preserved in the manner prescribed on this order form.

(f) The delivery of such substances to a registered analytical laboratory, or its agent approved by DEA, from an anonymous source for the analysis of the drug sample, provided the laboratory has obtained a written waiver of the order form requirement from the Regional Director of the Region in which the laboratory is located, which waiver may be granted upon agreement of the laboratory to conduct its activities in accordance with Administration guidelines.

[36 FR 7796, Apr. 24, 1971, as amended at 37 FR 15920, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 15031, Apr. 30, 1974]

§ 1305.04 Persons entitled to obtain and execute order forms.

(a) Order forms may be obtained only by persons who are registered under section 303 of the Act (21 U.S.C. 823) to handle controlled substances listed in Schedules I and II, and by persons who are registered under section 1008 of the Act (21 U.S.C. 958) to export such substances. Persons not registered to handle controlled substances listed in Schedule I or II and persons registered only to import controlled substances listed in any schedule are not entitled to obtain order forms.

(b) An order form may be executed only on behalf of the registrant named thereon and only if his registration as to the substances being purchased has not expired or been revoked or suspended.

§ 1305.05 Procedure for obtaining order forms.

(a) Order forms are issued in books of six forms, each form containing an original, duplicate and triplicate copy (respectively, Copy 1, Copy 2, and Copy 3). A limit of three books of forms will be furnished on any requisition, unless additional books are specifically requested and a reasonable need for such additional books is shown.

(b) Any person applying for a registration which would entitle him to obtain order forms may requisition such forms by so indicating on the application form; order forms will be supplied upon the registration of the applicant. Any person holding a registration entitling him to obtain order forms may requisition such forms for the first time on DEA (or BND) Form 222d, which may be obtained from the Registration Branch of the Administration. Any person already holding order forms may requisition additional forms only on DEA (or BND) Form 222b, which is contained in each book of order forms. All requisitions shall be submitted to the Registration Branch, Drug Enforcement Administration, Department of Justice, Post Office Box 28083, Central Station, Washington, D.C. 20005.

(c) Each requisition shall show the name, address, and registration number of the registrant and the number of books of order forms desired. Each requisition shall be signed and dated by the same person who signed the most recent application for registration or for reregistration, or by any person authorized to obtain and execute order forms by a power of attorney pursuant to § 1305.07.

(d) Order forms will be serially numbered and issued with the name, address and registration number of the registrant, the authorized activity and schedules of the registrant. This information cannot be altered or changed by the registrant; any errors must be corrected by the Registration Branch of the Administration by returning the forms with notification of the error.

[36 FR 7796, Apr. 24, 1971, as amended at 36 FR 18732, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1305.06 Procedure for executing order forms.

(a) Order forms shall be prepared and executed by the purchaser simultaneously in triplicate by means of in-

63-109 O - 81 - 8

terleaved carbon sheets which are part of the DEA (or BND) Form 222c. Order forms shall be prepared by use of a typewriter, pen, or indelible pencil.

(b) Only one item shall be entered on each numbered line. There are five lines on each order form. If one order form is not sufficient to include all items in an order, additional forms shall be used. Order forms for etorphine hydrochloride and diprenorphine shall contain only these substances. The total number of items ordered shall be noted on that form in the space provided.

(c) An item shall consist of one or more commercial or bulk containers of the same finished or bulk form and quantity of the same substance; a separate item shall be made for each commercial or bulk container of different finished or bulk form, quantity or substance. For each item the form shall show the name of the article ordered, the finished or bulk form of the article (e.g., 10-milligram tablet, 10-milligram concentration per fluid ounce or milliliter, or U.S.P.), the number of units or volume in each commercial or bulk container (e.g., 100-tablet bottle or 3-milliliter vial) or the quantity or volume of each bulk container (e.g., 10 kilograms), the number of commercial or bulk containers ordered, and the name and quantity per unit of the controlled substance or substances contained in the article if not in pure form. The catalogue number of the article may be included at the discretion of the purchaser.

(d) The name and address of the supplier from whom the controlled substances are being ordered shall be entered on the form. Only one supplier may be listed on any one form.

(e) Each order form shall be signed and dated by a person authorized to sign a requisition for order forms on behalf of the purchaser pursuant to § 1303.05(c). The name of the purchaser, if different from the individual signing the order form, shall also be inserted in the signature space. Unexecuted order forms may be kept and may be executed at a location other than the registered location printed on the form, provided that all unexecuted forms are delivered promptly to the registered location upon an inspection of such location by any officer authorized to make inspections, or to enforce, any Federal, State, or local law regarding controlled substances.

[36 FR 7796, Apr. 24, 1971, as amended at 36 FR 13386, July 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 17838, May 21, 1974]

§ 1305.07 Power of attorney.

Any purchaser may authorize one or more individuals, whether or not located at the registered location of the purchaser, to obtain and execute order forms on his behalf by executing a power of attorney for each such individual. The power of attorney shall be signed by the same person who signed (or was authorized to sign, pursuant to § 1301.32(f) of this chapter or § 1311.32(f) of this chapter) the most recent application for registration or reregistration and by the individual being authorized to obtain and execute order forms. The power of attorney shall be filed with the executed order forms of the purchaser, and shall be retained for the same period as any order form bearing the signature of the attorney. The power of attorney shall be available for inspection together with other order form records. Any power of attorney may be revoked at any time by executing a notice of revocation, signed by the person who signed (or was authorized to sign) the power of attorney or by a successor, whoever signed the most recent application for registration or reregistration, and filing it with the power of attorney being revoked. The form for the power of attorney and notice of revocation shall be similar to the following:

POWER OF ATTORNEY FOR DEA ORDER FORMS

_____ (Name of registrant)
_____ (Address of registrant)
_____ (DEA registration number)

I, _____ (name of person granting power), the undersigned, who is authorized to sign the current application for registration of the above-named registrant under the Controlled Substances Act or Controlled Substances Import and Export Act, have made, constituted, and appointed, and by these presents, do make, constitute, and appoint _____ (name of attorney-in-

fact), my true and lawful attorney for me in my name, place, and stead, to execute applications for books of official order forms and to sign such order forms in requisition for Schedule I and II controlled substances, in accordance with section 308 of the Controlled Substances Act (21 U.S.C. 828) and Part 305 of Title 21 of the Code of Federal Regulations. I hereby ratify and confirm all that said attorney shall lawfully do or cause to be done by virtue hereof.

(Signature of person granting power)

I, ———— (name of attorney-in-fact), hereby affirm that I am the person named herein as attorney-in-fact and that the signature affixed hereto is my signature.

(Signature of attorney-in-fact)

Witnesses:

1. ————.
2. ————.

Signed and dated on the —— day of ————, 19——, at ————.

NOTICE OF REVOCATION

The foregoing power of attorney is hereby revoked by the undersigned, who is authorized to sign the current application for registration of the above-named registrant under the Controlled Substances Act of the Controlled Substances Import and Export Act. Written notice of this revocation has been given to the attorney-in-fact ———— this same day.

(Signature of person revoking power)

Witnesses:

1. ————.
2. ————.

Signed and dated on the —— day of ————, 19——, at ————.

[37 FR 15921, Aug. 8, 1972. Redesignated at 38 FR 26609, Sept. 24, 1973]

CONTROLLED SUBSTANCES LISTED IN SCHEDULE II

Sec.

1306.11 Requirement of prescription.
1306.12 Refilling prescriptions.
1306.13 Partial filling of prescriptions.
1306.14 Labeling of substances.
1306.15 Filing of prescriptions.

CONTROLLED SUBSTANCES LISTED IN SCHEDULES III AND IV

1306.21 Requirement of prescription.
1306.22 Refilling of prescriptions.
1306.23 Partial filling of prescriptions.
1306.24 Labeling of substances.
1306.25 Filing prescriptions.

CONTROLLED SUBSTANCES LISTED IN SCHEDULES V

1306.31 Requirement of prescription.
1306.32 Dispensing without prescription.

AUTHORITY: Secs. 301, 309, 501(b), 84 Stat. 1253, 1260, 1271; 21 U.S.C. 821, 829, 871(b).

SOURCE: 36 FR 7799, Apr. 24, 1971; 36 FR 13386, July 21, 1971, unless otherwise noted. Redesignated at 38 FR 26609, Sept. 24, 1973.

NOMENCLATURE CHANGES: 38 FR 26609, Sept. 24, 1973.

PART 1306—PRESCRIPTIONS

GENERAL INFORMATION

Sec.

1306.01 Scope of Part 1306.
1306.02 Definitions.
1306.03 Persons entitled to issue prescriptions.
1306.04 Purpose of issue of prescription.
1306.05 Manner of issuance of prescriptions.
1306.06 Persons entitled to fill prescriptions.
1306.07 Administering or dispensing of narcotic drugs.

GENERAL INFORMATION

§ 1306.01 Scope of Part 1306.

Rules governing the issuance, filling and filing of prescriptions pursuant to section 309 of the Act (21 U.S.C. 829) are set forth generally in that section and specifically by the sections of this part.

§ 1306.02 Definitions.

As used in this part, the following terms shall have the meanings specified:

(a) The term "Act" means the Controlled Substances Act (84 Stat. 1242; 21 U.S.C. 801).

(b) The term "individual practitioner" means a physician, dentist, veterinarian, or other individual licensed, registered, or otherwise permitted, by the United States or the jurisdiction in which he practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacist, a pharmacy, or an institutional practitioner.

(c) The term "institutional practitioner" means a hospital or other person (other than an individual) licensed, registered, or otherwise per

mitted, by the United States or the jurisdiction in which it practices, to dispense a controlled substance in the course of professional practice, but does not include a pharmacy.

(d) The term "pharmacist" means any pharmacist licensed by a State to dispense controlled substances, and shall include any other person (e.g., a pharmacist intern) authorized by a State to dispense controlled substances under the supervision of a pharmacist licensed by such State.

(e) The term "prescription" means an order for medication which is dispensed to or for an ultimate user but does not include an order for medication which is dispensed for immediate administration to the ultimate used. (e.g., an order to dispense a drug to a bed patient for immediate administration in a hospital is not a prescription.)

(f) The terms "register" and "registered" refer to registration required and permitted by section 303 of the Act (21 U.S.C. 823).

(g) Any term not defined in this section shall have the definition set forth in section 102 of the Act (21 U.S.C. 802) or § 1301.02 of this chapter.

[36 FR 7799, Apr. 24, 1971, as amended at 36 FR 18732, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1306.03 Persons entitled to issue prescriptions.

(a) A prescription for a controlled substance may be issued only by an individual practitioner who is:

(1) authorized to prescribe controlled substances by the jurisdiction in which he is licensed to practice his profession and

(2) either registered or exempted from registration pursuant to §§ 1301.24(c) and 1301.25 of this chapter.

(b) A prescription issued by an individual practitioner may be communicated to a pharmacist by an employee or agent of the individual practitioner.

[36 FR 7799, Apr. 24, 1971, as amended at 36 FR 18732, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1306.04 Purpose of issue of prescription.

(a) A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (21 U.S.C. 829) and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.

(b) A prescription may not be issued in order for an individual practitioner to obtain controlled substances for supplying the individual practitioner for the purpose of general dispensing to patients.

(c) A prescription may not be issued for the dispensing of narcotic drugs listed in any schedule for "detoxification treatment" or "maintenance treatment" as defined in Section 102 of the Act (21 U.S.C. 802).

[36 FR 7799, Apr. 24, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973, and amended at 39 FR 37986, Oct. 25, 1974]

§ 1306.05 Manner of issuance of prescriptions.

(a) All prescriptions for controlled substances shall be dated as of, and signed on, the day when issued and shall bear the full name and address of the patient, and the name, address, and registration number of the practitioner. A practitioner may sign a prescription in the same manner as he would sign a check or legal document (e.g., J. H. Smith or John H. Smith). Where an oral order is not permitted, prescriptions shall be written with ink or indelible pencil or typewriter and shall be manually signed by the practitioner. The prescriptions may be prepared by a secretary or agent for the signature of a practitioner, but the prescribing practitioner is responsible in case the prescription does not conform in all essential respects to the

law and regulations. A corresponding liability rests upon the pharmacist who fills a prescription not prepared in the form prescribed by these regulations.

(b) An intern, resident, or foreign-trained physician, or physician on the staff of a Veterans Administration facility, exempted from registration under § 1301.24(c) shall include on all prescriptions issued by him the registration number of the hospital or other institution and the special internal code number assigned to him by the hospital or other institution as provided in § 1301.24 (c), in lieu of the registration number of the practitioner required by this section. Each written prescription shall have the name of the physician stamped, typed, or handprinted on it, as well as the signature of the physician.

(c) An official exempted from registration under § 1301.25 shall include on all prescriptions issued by him his branch of service or agency (e.g., "U.S. Army" or "Public Health Service") and his service identification number, in lieu of the registration number of the practitioner required by this section. The service identification number for a Public Health Service employee is his Social Security identification number. Each prescription shall have the name of the officer stamped, typed, or handprinted on it, as well as the signature of the officer.

[36 FR 7799, Apr. 24, 1971, as amended at 36 FR 18733, Sept. 21, 1971. Redesignated at 38 FR 26609, Sept. 24, 1973]

§ 1306.06 Persons entitled to fill prescriptions.

A prescription for controlled substances may only be filled by a pharmacist acting in the usual course of his professional practice and either registered individually or employed in a registered pharmacy or registered institutional practitioner.

§ 1306.07 Administering or dispensing of narcotic drugs.

(a) The administering or dispensing directly (but not prescribing) of narcotic drugs listed in any schedule to a narcotic drug dependent person for "detoxification treatment" or "maintenance treatment" as defined in section 102 of the Act (21 U.S.C. 802) shall be deemed to be within the meaning of the term "in the course of his professional practice or research" in section 308(e) and section 102(20) of the Act (21 U.S.C. 828 (e)): *Provided*, That the practitioner is separately registered with the Attorney General as required by section 303(g) of the Act (21 U.S.C. 823(g)) and then thereafter complies with the regulatory standards imposed relative to treatment qualification, security, records and unsupervised use of drugs pursuant to such Act.

(b) Nothing in this section shall prohibit a physician who is not specifically registered to conduct a narcotic treatment program from administering (but not prescribing) narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms when necessary while arrangements are being made for referral for treatment. Not more than one day's medication may be administered to the person or for the person's use at one time. Such emergency treatment may be carried out for not more than three days and may not be renewed or extended.

(c) This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts.

[39 FR 37986, Oct. 25, 1974]

1316 of this chapter by filing a written request stating the reasons for such exception. Requests shall be filed with the Administrator, Drug Enforcement Administration, Department of Justice, Washington, D.C. 20537. The Administrator may grant an exception in his discretion, but in no case shall he be required to grant an exception to any person which is not otherwise required by law or the regulations cited in this section.

SPECIAL EXCEPTIONS FOR MANUFACTURE AND DISTRIBUTION OF CONTROLLED SUBSTANCES

§ 1307.11 Distribution by dispenser to another practitioner.

(a) A practitioner who is registered to dispense a controlled substance may distribute (without being registered to distribute) a quantity of such substance to another practitioner for the purpose of general dispensing by the practitioner to his or its patients: Provided, That:

(1) The practitioner to whom the controlled substance is to be distributed is registered under the Act to dispense that controlled substance;

(2) The distribution is recorded by the distributing practitioner in accordance with § 1304.24(e) of this chapter and by the receiving practitioner in accordance with § 1304.24(c) of this chapter;

(3) If the substance is listed in Schedule I or II, an order form is used as required in Part 1305 of this chapter;

(4) The total number of dosage units of all controlled substances distributed by the practitioner pursuant to this section during the 12-month period in which the practitioner is registered to dispense does not exceed 5 percent of the total number of dosage units of all controlled substances distributed and dispensed by the practitioner during the 12-month period.

(b) If, at any time during the 12-month period during which the practitioner is registered to dispense, the practitioner has reason to believe that the total number of dosage units of all controlled substances which will be distributed by him pursuant to this section will exceed 5 percent of the

§ 1307.02 Application of State law and other Federal law.

Nothing in Parts 1301-1308, 1311, 1312, or 1316 of this chapter shall be construed as authorizing or permitting any person to do any act which such person is not authorized or permitted to do under other Federal laws or obligations under international treaties, conventions or protocols, or under the law of the State in which he desires to do such act nor shall compliance with such Parts be construed as compliance with other Federal or State laws unless expressly provided in such other laws.

§ 1307.03 Exceptions to regulations.

Any person may apply for an exception to the application of any provision of Parts 1301-1308, 1311, 1312, or

ATTACHMENT #3

HOSPITAL PHARMACIES REGISTERED WITH NCI FOR THC
DISTRIBUTION AS OF FEBRUARY 6, 1981 = 510

STATE	CITY	INSTITUTION
ALABAMA	Birmingham	Baptist Medical Center Montclair (N)
		Baptist Medical Center Princeton (N)
		University of Alabama
		Russell Ambulatory Ctr.
		V. A. Hospital
		Brookwood Medical Ctr. (N)
	Huntsville	Huntsville Hospital (N)
	Mobile	U. of S. Alabama
	Montgomery	Baptist Medical Center (N)
		Jackson Hospital & Clinic (N)
ALASKA	------	---------
ARIZONA	Phoenix	Good Samaritan Hospital
		Phoenix General Hospital (N)
		St. Joseph's
	Tucson	Tucson Medical Center
		U. of Arizona
		V.A. Hospital
ARKANSAS	Fort Smith	Sparks Regional Med. College (N)
	Jonesboro	St. Bernards Regional Cancer Ctr. (N)
	Little Rock	Baptist Medical College
		Doctor's Hospital (N)
		St. Vincent Infirmary (N)
		U. of Arkansas

STATE	CITY	INSTITUTION
CALIFORNIA	Anaheim	Anaheim Memorial Hosp. (N)
	Fresno	VA Medical Center (N)
	L.A.	Cedars-Sinai Medical Center Hosp. of the Good Samaritan U. of California U. of Southern Cal. V.A. Hospital
	Loma Linda	V.A. Hospital
	Long Beach	Memorial V.A. Hospital
	Martinez	V.A. Hospital
	Orange	U. of Cal at Irvine
	Palo Alto	V.A. Hospital
	Panorama City	Kaiser Foundation Hosps. (N)
	Pasadena	Huntington Memorial
	San Fran.	Kaiser Foundation U.S.Public Health Service Hospital (N) VA Medical Center (N)
	San Diego	Mercy V.A. Hospital
	San Jose	Santa Clara Valley Medical Center (N)
	Sepulveda	V.A. Hospital
	Stanford	Stanford Med. Center
	Torrance	L.A. County-Harbor (UCLA)
	Walnut Creek	John Muir

STATE	CITY	INSTITUTION
COLORADO	Colorado Springs	Penrose Hospital (N)
	Denver	Porter Memorial (N) Presbyterian Denver Hospital Rose Medical Center (N) Saint Luke's Hospital Saint Joseph Hospital (N) U. of Colo. Health Sci. Ctr.
	Fort Collins	Poudre Valley Hospital
	Grand Junction	St. Mary's Hospital (N)
CONNECTICUT	Bridgeport	Bridgeport Hospital St. Vincent's
	Danbury	Danbury Hospital (N)
	Farmington	John Dempsey Hospital
	Hartford	Hartford Hospital Mt. Sinai St. Francis
	Middletown	Middlesex Mem. Hosp. (N)
	New Britain	New Britain Gen. Hosp.
	New Haven	The Hosp. of St. Raphael Yale-New Haven Hospital
	Newington	V.A. Hospital
	Norwalk	Norwalk Hospital (N)
	Stamford	Stamford Hospital St. Joseph Hospital (N)
	Waterbury	Waterbury Hospital

STATE	CITY	INSTITUTION
DELAWARE	Wilmington	Wilmington Med. Ctr.
DISTRICT OF COLUMBIA	Washington, D.C.	Georgetown U. George Washington U. Howard University Walter Reed Army Med. Ctr. Washington Hospital Ctr.
FLORIDA	Gainesville	U. of Florida, Shands
	Miami	Jackson Mem. Hosp. South Miami
	Miami Beach	Mt. Sinai Med. Ctr.
	New Port Richey	Community Hospital of New Port Richey (N)
	Orlando	Florida Hospital (N)
	Pensacola	Baptist Hospital (N) W. Florida Hospital (N)
	Pompano Beach	North Broward Hospital (N)
	Port Charlotte	St. Joseph Hospital (N)
	Punta Gorda	Medical Center (N)
	Tallahassee	Tallahassee Memorial Regional Medical Ctr. (N)
	Tamarac	University Community Hospital (N)
GEORGIA	Atlanta	Henrietta Eggleston Hosp.
	Augusta	Medical College of Georgia University Hospital (N) V.A. Hospital
	Gainesville	NE Georgia Med. Ctr. (N)
HAWAII	Honolulu	U. of Hawaii at Manoa
IDAHO	Boise	St. Luke's Hospital (N)

STATE	CITY	INSTITUTION
ILLINOIS	Berwyn	MacNeal Memorial Hospital (N)
	Blue Island	St. Francis Hosp. (N)
	Chicago	Childrens Memorial Hospital Columbus.Cuneo.Cabrini Medical Center (N) Illinois Masonic Med. Ctr. Michael Reese Hospital Mt. Sinai Rush Presbyterian-St. Luke St. Mary of Nazareth (N) Swedish Covenant Hospital (N) University of Illinois Hosp.
	De Kalb	Kishwaukee Community Hospital (N)
	Evanston	Evanston Hospital St. Francis Hospital
	Granite City	Saint Elizabeth Hosp. (N)
	Harvey	Ingalls Memorial Hosp. (N)
	Hines	V.A. Hospital
	Hinsdale	Hinsdale Sanitarium & Hosp. (N)
	Lake Forest	Lake Forest Hospital (N)
	Mattoon	Sarah Bush Lincoln Health Center (N)
	Olympia Fields	Olympia Fields Osteopathic Medical Center (N)
	Park Ridge	Lutheran Gen Hosp
	Peoria	St. Francis Hosp. Med. Ctr.
	Rockford	Swedish American (N)
	Rock Island	Franciscan Hospital (N)
	Scott Air Force Base	USAF Medical Center (N)
	Streator	St. Mary's Hospital

STATE	CITY	INSTITUTION
INDIANA	Beech Grove	St. Francis Hospital
	Evansville	St. Mary's Hospital (N)
	Fort Wayne	Parkview Hospital
	Indianapolis	Indiana U. Hospital Methodist Hospital St. Vincent (N)
	Muncie	Ball Memorial
	South Bend	St. Joseph's Hospital (N)
IOWA	Des Moines	Des Moines Gen. Ort. Hosp.(N) Iowa Methodist Med. Ctr. Mercy Hospital Medical Ctr.(N)
	Iowa City	University of Iowa VA Hospital
	Mason City	St. Joseph Mercy Hosp. (N)
KANSAS	Garden City	St. Catherine Hosp. (N)
	Kansas City	U. of Kansas
	Wichita	St. Francis Hospital (N) St. Joseph Med. Ctr (N) Wesley

STATE	CITY	INSTITUTION
KENTUCKY	Covington	St. Elizabeth's Medical Ctr.
	Edgewood	St. Elizabeth's Medical Ctr.
	Fort Thomas	St. Luke's Hospital (H)
	Lexington	University of Kentucky St. Joseph's Hospital (H)
	Louisville	Highland Baptist Hospital Jewish Hospital Norton Children's Hospital

STATE	CITY	INSTITUTION
LOUISIANA	Lafayette	Lafayette Charity Hosp. (N)
	New Orleans	Ochner Foundation Touro Infirmary Tulane University V.A. Hospital
	Shreveport	V.A. Hospital
MAINE	Augusta	Kennebec Valley Med. Ctr. (N)
	Bangor	Eastern Maine Med. Ctr. (N)
	Norway	Stephens Mem. Hosp. (N)
	Presque Isle	ARG MHA. R. Gold Mem. Hosp. (N)
	Waterville	Mid-Maine Med. Ctr. (N)
MARYLAND	Baltimore	Baltimore City Hospital Franklin Square Hosp. (N) Greater Baltimore Med. Ctr. (N) Johns Hopkins Hospital Maryland General Hospital Mercy Hospital, Inc. (N) Sinai Hospital The Good Samaritan Hospital (N) Union Memorial Hosp.
	Bethesda	National Naval Med Ctr. NIH Clinical Center Suburban Hosp. Assoc. (N)
	Cumberland	Sacred Heart Hospital
	Frederick	Frederick Mem. Hosp. Inc. (N)

STATE	CITY	INSTITUTION
MASSACHUSETTS	Boston	Beth Israel
		Boston Hosp. for Women
		Falmouth Hospital (N)
		Faulkner Hospital
		Mass. General Hospital
		N.E. Deaconess
		N.E. Medical Center
		Sidney Farber Cancer Ctr.
		The Children's Hosp. Med. Ctr.
		V.A. Hospital
	Brockton	Cardinal Cushing General Hosp. (N)
	Lowell	St. John's Hospital (N)
	Melrose	Melrose-Wakefield Hosp. Association (N)
	Methune	Bon Secours
	New Bedford	Saint Luke's Hosp. (N)
	Newton Lower Falls	Newton-Wellesley Hosp. (N)
	Norfolk	Pondville Hospital (N)
	Salem	Salem Hospital
	Springfield	Baystate Hospital
	Worcester City	Memorial Hospital
		St. Vincent's
		University of Mass. Med. Ctr.
		Worcester City Hospital

STATE	CITY	INSTITUTION
MICHIGAN	Ann Arbor	St. Joseph Mercy Hospital
	Bay City	Bay Medical Center (N)
	Dearborn	Oakwood Hospital
	Detroit	Children's Hospital Sinai Hospital Harper-Grace-Harper Harper-Grace-Grace
	Flint	Hurley Medical Center
	Grand Rapids	Butterworth Hospital
	Kalamazoo	Bronson Methodist Hosp.
	Lansing	Edward W. Sparrow Hosp.
	Pontiac	St. Joseph's Mercy Hospital
	Royal Oak	William Beaumont Hospital
	Saginaw	St. Mary's Hospital (N)
	Westland	Wayne County General Hosp.

STATE	CITY	INSTITUTION
MINNESOTA	Fridley	Unity Hospital (N)
	Minneapolis	Abbott Northwestern Hosp.(N) St. Mary's Hospital (N) University of Minnesota V.A. Hospital
	St. Cloud	St. Cloud Hospital (N)
	St. Louis Park	Methodist Hospital
	St. Paul	St. John's Hospital (N) St. Paul-Ramsey Med. Ctr. United Hospitals (N)
	Rochester	Rochester Methodist
MISSISSIPPI	Greenville	Delta Medical Center (N)
	Hattiesburg	Forrest General
	Jackson	U. of Miss. Med. Ctr
	Tupelo	North Mississippi Med. Ctr. (N)
MISSOURI	Bridgeton	De Paul Community Health Center (N)
	Columbia	Boone County University of Missouri
	Joplin	Saint John's Med. Ctr. (N)
	Kansas City	Menorah Medical Center (N) Research Medical Ctr. (N) VA Medical Center
	Keesler AFB	USAF Med. Ctr. (N)
	Kirkwood	Saint Joseph Hospital
	Saint Louis	Barnes Hospital Incarnate Word Hospital (N) St. Louis Children's Hospital St. Louis Univ. Med. Ct. St. Mary's Health Ctr. The Jewish Hospital of Saint Louis V.A. Hospital

STATE	CITY	INSTITUTION
MONTANA	Missoula	Missoula Community Hospital (N) Saint Patrick Hospital (N)
NEBRASKA	Omaha	St. Joseph Hospital U. of Nebraska

STATE	CITY	INSTITUTION
NEVADA	Las Vegas	Southern Nevada Mem. Hosp. (N)
NEW HAMPSHIRE	Concord	Concord Hospital (N)
	Hanover	Mary Hitchcock
	Manchester	Catholic Med. Ctr. (N) Elliot Hospital (N)
NEW JERSEY	Atlantic City	Atlantic City Med. Ctr. (N)
	Camden	Cooper Med. Ctr. (N)
	Elizabeth	Elizabeth Gen. Hosp. (N)
	Englewood	Englewood Hosp. Association (N)
	Flemington	Hunterdon Medical Center (N)
	Hackensack	Hackensack Hospital
	Livingston	St. Barnabus Hospital
	Long Branch	Monmouth Med. Ctr.
	Morristown	Morristown Mem. Hosp.
	Newark	College of Med. & Dentistry Newark Beth Israel Med. Ctr. St. Michael's Med. Ctr.
	New Brunswick	College of Med. & Dent. Middlesex Hospital St. Peter's Med. Ctr.
	Pomona	Atlantic City Med. Ctr.
	Princeton	Medical Center at Princeton (N)
	Summit	Overlook Hospital
NEW MEXICO	Albuquerque	Cancer R & T Univ. of New Mexico

STATE	CITY	INSTITUTION
NEW YORK	Albany	Albany Medical Ctr. St. Peter's Hospital V.A. Hospital
	Bay Shore	Southside Hospital (N)
	Binghamton	Our Lady of Lourdes Mem. Hosp.(N)
	Bronx	Albert Einstein Medical Ctr. Misericordia Hospital Med. Ctr. Montefiore Hospital & Med. Ctr. V.A. Bronx
	Brooklyn	Brookdale Hospital Brooklyn Hospital Jewish Hospital State U. of New York Methodist
	Buffalo	Buffalo General Hospital (N) Deaconess Hospital Roswell Park Memorial Institute V.A. Hospital
	Cooperstown	Mary Imogene Bassett
	Elmira	St. Joseph's Hospital (N.
	Flushing	Booth Memorial
	Hudson	Columbia Memorial Hospital (N)
	Jamaica	Catholic Medical Center
	Johnson City	Charles S. Wilson Memorial Hosp.
	Long Island	Long Island College Hospital
	Manhasset	North Shore Hospital, Cornell U.
	Mineola	Nassau Hospital
	New Hyde Park	Long Island Jewish Hillside Medical Ctr.

STATE	CITY	INSTITUTION
NEW YORK	New York City	Beth Israel
		Cabrini Med. Ctr.
		Lennox Hill Hosp.
		Mercy Hospital
		Mt. Sinai Medical Ctr.
		N.Y. Univ. Med. Center
		Presbyterian Hospital Columbia
		St. Lukes-Roosevelt Hosp. 428 W. 59th Street
		St. Lukes-Roosevelt Hosp. Center (at Amsterdam Ave.)
		St. Vincent Hosp. & Med. Ctr.
		The New York Hosp.
	North Tarrytown	Phelps Memorial
	Nyack	Nyack
	Patchogue	Brookhaven Memorial
	Plainview	Central General Hospital
	Poughkeepsie	Saint Francis Hosp.
	Rochester	Genessee Hospital
		Highland Hospital
		Rochester General Hospital
		University of Rochester
	Rockville Ctr.	Mercy Hospital
	Schenectady	Ellis Hospital
		St. Clare's Hospital
	Staten Island	St. Vincent's of Richmond
		Staten Island Hospital (N)
	Syracuse	SUNY
		V.A. Hospital
	Troy	Samaritan Hospital
	Valhalla	Westchester County Med. Ctr.

STATE	CITY	INSTITUTION
NORTH CAROLINA	Chapel Hill	N.C. Memorial
	Charlotte	Memorial
	Durham	Duke U. Medical Center Durham County General Hosp. (N) VA Medical Center
	Greensboro	Moses H. Cone Mem. Hosp. Wesley Long Hospital (N)
	Greenville	Pitt Co. Mem. Hosp. (N)
	Raleigh	Wake County Hosp. System, Inc.
	Salisbury	Rowan Memorial Hospital, Inc. (N)
	Shelby	Cleveland Mem. Hosp. (N)
	Tarboro	Edgecombe General Hosp., Inc. (N)
	Wilmington	New Hanover Mem. Hospital
	Winston-Salem	N.C. Baptist
NORTH DAKOTA	Fargo	St. Luke's Hospital (N)

STATE	CITY	INSTITUTION
OHIO	Akron	Akron City Hospital
		Akron General
		St. Thomas Hospital & Med. Ctr.
	Canton	Timkin Mercy Medical Ctr.
	Cincinnati	Bethesda Hospital & Deaconess Association (N)
		Children's Hospital
		Christ Hospital
		Good Samaritan
		Jewish Hospital of Cincinnati (N)
		U. of Cinn. Med. Center
		V.A. Hospital
	Cleveland	Cleveland Clinic
		Cuyahoga Cty. Hospital (Cleveland Metro. General)
		Huron Road Hospital
		Mt. Sinai Hospital
		St. Luke's Hospital
		University Hospital
		V.A. Hospital
	Columbus	Ohio State University
		Grant Hospital (N)
	Dayton	Good Samaritan
		Miami Valley
		St. Elizabeth's Hospital (N)
	Dover	Union Hospital
	Kettering	Kettering Hospital
	Steubenville	Ohio Valley Hospital
	Toledo	Medical College of Ohio
		The Toledo Hospital (N)
	Youngstown	St. Elizabeth's Hosp. & Med.Ctr.(N)
OKLAHOMA	Enid	Memorial Baptist Hosp. (N)
	Oklahoma City	Baptist Med. Ctr. of Oklahoma
		Mercy Health Center (N)
		Presbyterian Hospital (N)
		Saint Anthony (N)
	Tulsa	Hillcrest (N)
		St. Francis

STATE	CITY	INSTITUTION
OREGON	Portland	Emanuel Hospital
		Good Samaritan Hospital & Medical Center (N)
		V.A. Hospital

STATE	CITY	INSTITUTION
PENNSYLVANIA	Allentown	Allentown/Sacred Heart Hosp.
	Bristol	Delaware Valley Medical Center (N)
	Bryn Mawr	Bryn Mawr Hospital
	Danville	Geisinger Med. Ctr.
	Erie	Hamot Medical Center St. Vincent Health Ctr. (N)
	Franklin	Franklin Hosp. (N)
	Harrisburg	Harrisburg Hospital
	Hershey	Milton Hershey-Penn State
	Johnstown	Conemaugh Valley
	Philadelphia	Albert Einstein American Oncologic Episcopal Hospital Lankenau Hospital Med. College of Pa. & Hospital Mercy Catholic of S.E. Penn Presbyterian U. of Penn. Temple University Thomas Jefferson The Children's Hosp. of Philadelphia University of Pennsylvania
	Pittsburgh	Allegheny General Hospital Children's Hospital of Pitt. Eye & Ear Hospital of Pitt. Magee-Women's Hospital Mercy Hospital Montefiore Hospital Presbyterian Univ. Hospital St.Francis General Hospital Western Penn. Hosp.
	Scranton	Mercy Hospital (N)
	Sellersville	Grand View Hospital (N)
	Sewickley	Sewickley Valley Hospital (N)
	State College	Centre Community Hosp. (N)
	Wilkes Barre	Mercy Hospital
	Williamsport	Divine Providence Hosp. (N) Williamsport Hospital (N)
	York	York Hospital

STATE	CITY	INSTITUTION
RHODE ISLAND	Pawtucket	Memorial Hospital
	Providence	The Miriam Hospital Rhode Island Hosp. Roger Williams General
	Westerly	The Westerly Hospital (N)
SOUTH CAROLINA	Charleston	Med. Univ. of S. Carolina
	Columbia	Richland Memorial Hosp. (N)
	Greenville	Greenville Hosp. Ctr.
	Greenwood	Self Memorial Hosp.
	Spartanburg	Spartanburg General Hosp. (N)
SOUTH DAKOTA	Rapid City	Rapid City Regional Hospital
	Sioux Falls	Royal C. Johnson V.A. Mem. Hosp.
TENNESSEE	Chattanooga	Erlanger Medical Center
	Knoxville	East Tennessee Baptist (N) University of Tennessee Memorial (N)
	Memphis	Baptist Memorial City of Memphis Hospital Methodist Hospital (N) St. Francis Hospital St. Judes Childrens Hospital U. of Tenn. Cancer Clinic U. of Tenn. Medical Center V.A. Hospital
	Nashville	Meharry Med. College/Hubbard St. Thomas Vanderbilt University

STATE	CITY	INSTITUTION
TEXAS	Austin	City of Austin Brackenridge Hospital
		Holy Cross Hospital (N)
	Carthage	Panola Gen. Hospital (N)
	Dallas	Baylor U. Med. Ctr. (N)
		Medical City Hospital
		Methodist Hospital of Dallas
		Parkland Memorial Hospital
		Presbyterian Hosp. of Dallas
		St. Paul Hospital
	El Paso	Highland Park Hosp. (N)
		Southwest Hospital (N)
	Fort Worth	St. Joseph Hospital (N)
	Galveston	U. of Texas
	Houston	Hermann Hospital
		Methodist Hospital (N)
		Park Plaza Hospital (N)
		Rosewood Gen. Hosp. (N)
		U. of Texas Sys., M.D. Anderson
	Lubbock	Health Science Center
	Nacogdoches	Memorial Hospital (N)
	San Antonio	Bexar County Hospital District
		Robert B. Green Memorial Hosp.
	Temple	Scott & White Mem. Hosp.
	Waco	Hillcrest Baptist

STATE	CITY	INSTITUTION
UTAH	Salt Lake City	L.D.S. Hospital U. of Utah V.A. Hospital
VERMONT	Burlington	Med. Ctr. of Vermont
VIRGINIA	Charlottesville	U. of Virginia
	Falls Church	Fairfax Hospital
	Leesburg	Loudoun Mem. Hospital
	Norfolk	Children's Hosp. of the King's Daughters (N) Norfolk General Hospital
	Richmond	Med. College of Virginia
	Roanoke	Roanoke Memorial Hospital (N)
	Salem	VA Medical Center
WASHINGTON	Seattle	Virginia Mason Hospital U.S.P.H.S. Hospital V.A. Hospital
	Vancouver	Southwest Wash. Hosp. (N)
	Yakima	St. Elizabeth Hospital Yakima Valley Mem. Hosp. (N)
WEST VIRGINIA	Charleston	Charleston Area Med. Ctr.
	Huntington	St. Mary's
	Morgantown	W. Va. University

STATE	CITY	INSTITUTION
WISCONSIN	Eau Claire	Luther Hospital (N)
	Green Bay	St. Vincent's Hospital (N)
	La Crosse	La Crosse Lutheran Hosp. (N)
	Madison	Madison General Hospital University of Wisconsin Hospital & Clinics V.A. Hospital
	Marshallfield	Saint Joseph's Hosp. (N)
	Milwaukee	Milwaukee Children's Hospital (N) Milwaukee County Hospital Mt. Sinai Medical Center St. Luke's Hospital St. Mary's Hospital
	Monroe	St. Clare Hosp. (N)
	Neenah	Theda Clark Regional Med. Ctr. (N)
WYOMING	-------	----------

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