DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Mr. Francis M. Mullen, Jr.
Acting Administrator
Drug Enforcement Administration
1405 Eye St., N.W.
Washington, DC 20537

AUG 16 1982

Dear Mr. Mullen:

Pursuant to section 201(b) of the Controlled Substances Act (CSA), 21 U.S.C. 811(b), this letter is notification of the Department of Health and Human Services (DHHS) recommendation for the continued control of tetrahydrocannabinol (THC) in Schedule I of the CSA. However, if a new drug application for THC is approved by the Food and Drug Administration, DHHS recommends that THC be rescheduled to Schedule II. Both of these recommendations, and FDA's consideration of the eight factors and scheduling criteria listed in sections 201(c) and 202(b) of the CSA are discussed in attachment A. I concur with these two recommendations.

In making the scientific and medical findings and evaluation of THC, DHHS took into account new evidence concerning the medical use of THC as directed by the Court of Appeals in NORML v. DEA & DHEW, No. 79-1660 (D.C. Cir., Oct. 16, 1980). In addition, before making the evaluation and scheduling recommendations for THC, DHHS held a hearing before FDA's Drug Abuse Advisory Committee on the rescheduling status of THC as a proposed marketed drug for nausea and vomiting in patients receiving cancer chemotherapy. The advisory committee recommended that upon NDA approval THC should be controlled in CSA Schedule II. Following receipt of this recommendation, FDA published proposed scientific and medical findings and recommendations in the FEDERAL REGISTER of March 9, 1982. We have enclosed a copy of this document (attachment B), the comments received (attachment C), and a document that summarizes the comments and responses to them (attachment D).

Should you have any questions concerning this issue, the FDA Drug Abuse Staff is prepared to respond.

Sincerely yours,

Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

Attachment A - Scientific & medical findings & recommendations on THC
Attachment B - FR Notice of March 9, 1982
Attachment C - Comments to the Notice
Attachment D - FDA's Summary of the Comments & Responses

Attachment A

Recommendation to the Drug Enforcement Administration Regarding the Scheduling Status of Tetrahydrocannabinol

I. Background

The full chemical name for tetrahydrocannabinol, or THC, is (-)-delta-9-(trans)-tetrahydrocannabinol. THC, the principal active ingredient in the marihuana plant, Cannabis sativa, is present in the plant at varying concentrations. THC can be extracted from plant material or synthesized independently. However, it was not until 1970, after THC synthesis, that sufficient quantitites of THC, in purified form, became available for medical research. Investigators have studied THC primarily for its use in treating the nausea and vomiting of some patients receiving cancer chemotherapy. In addition, investigators have studied THC's use in treating glaucoma and muscle spasticity. Medical or investigational use of a drug such as THC that has potential for abuse is regulated under two principal Federal statutes, the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 301 et seq.) and the Controlled Substances Act (CSA) (21 U.S.C. 801 et seq). Under the FFDCA a drug may be marketed only if (1) it has received an approved new drug application from FDA; or (2) the drug is generally recognized by qualified experts as safe and effective on the basis of adequate and well-controlled clinical investigation by well-qualified experts; or (3) the drug is subject to the "grandfather" provisions of the statute.

Enacted in 1970, the CSA establishes domestic control schedules I through V for substances of abuse (21 U.S.C. 812(b)(1) through (5)). Congress placed THC into schedule I, the schedule providing the most stringent controls. The findings required for schedule I are that the substances have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. The major schedule I controls are: dispensing for research use only, separate recordkeeping, and maximum quotas on amounts produced during a given year. The latter two controls also apply to schedule II substances.

In addition to controls under the FFDCA and the CSA, medical or investigational use of a drug that has a potential for abuse also may be subject to control under international treaties: the Single Convention on Narcotic Drugs, and the Convention on Psychotropic Substances. Detailed discussion of control applicable to THC under the Psychotropic Convention are beyond the scope of this document. However, THC is currently controlled in the most restrictive schedule of the Psychotropic Convention, Psychotropic schedule I. Schedule I of the Psychotropic Convention also includes certain other hallucinogenic substances, e.g., mescaline, parahexyl, and LSD. The major controls for substances in Psychotropic Convention schedule I are: prohibition of use except for scientific and limited medical purposes, and

restriction of the amount supplied to a duly authorized person to the quantity required for an authorized purpose. The Psychotropic Convention also requires the United States to impose certain domestic controls on THC. The United States' responsibilities under the Psychotropic Convention are assigned by the CSA, as amended by the Psychotropic Substances Act of 1978 (Pub. L. 95-633).

The CSA contains procedures by which changes in domestic scheduling can be effected (21 U.S.C. 811(a)), including "on petition of any interested person." In May 1972, the National Organization for the Reform of Marijuana Laws (NORML) petitioned the Bureau of Narcotics and Dangerous Drugs (now the Drug Enforcement Administration (DEA)) to remove marihuana and its components from control under the CSA or to move marihuana and its components to a less restrictive schedule. DEA denied NORML's requests (see 37 FR 18097, Sept. 1, 1972). NORML sought judicial review of the denial, and the United States Court of Appeals for the District of Columbia in NORML v. Ingersoll, 497 F. 2d 654 (D.C. Cir. 1974), ordered DEA to hold hearings and reconsider the NORML petition on the basis of evidence introduced at these hearings. Following these hearings, DEA again denied the NORML petition and ruled that the substances at issue must remain in CSA schedule I (40 FR 44164, Sept. 25, 1975). NORML sought judicial review of the second denial, and the appellate court remanded the matter to DEA with instructions to refer the NORML petition to the Secretary of Health, Education and Welfare (now Health and Human Services) for medical and scientific evaluations and recommendations for rescheduling. See NORML v. DEA, 559 F. 2d 735, 750 (D.C. Cir. 1977). The court also directed DEA to comply with the rulemaking procedures in 21 U.S.C. 811(a) and (b) after DEA received the Secretary's evaluation and recommendation. Although the original NORML petition requested a change in the scheduling status only of marihuana leaves and other plant components, the court allowed NORML to amend its petition to include THC. Id. at p. 757.

The court directed the Secretary to make separate evaluations and recommendations for each of the following cannabis materials: "Cannabis" and "cannabis resin" (minimum control - CSA II); cannabis leaves (minimum control - CSA V); cannabis seeds capable of germination (minimum control - CSA V); THC (no minimum control under CSA). The "minimum control" schedules relate to the least restrictive domestic schedules which the court in 1977 stated were consistent with treaty obligations under the Single Convention on Narcotic Drugs, 1961. Each of the "cannabis" materials, other than THC, is controlled by the Single Convention.

The Psychotropic Convention, which requires the United States to impose controls on THC, did not become effective in this country until July 1980. Thus, although the court in 1977 in NORML v. DEA concluded that no minimum domestic control for THC was required by virtue of international treaty, the court's decision did not take into account the present obligations of the United States under the Psychotropic Convention. [See Psychotropic Substances Act of 1978 (amending the CSA to include United States obligations under the Psychotropic Convention)].

In June 1977, DEA referred the NORML petition to the Secretary of Health and Human Services (DHHS). FDA's Controlled Substances Advisory Committee (CSAC) considered NORML's petition in November 1977 and March 1978. The CSAC (now FDA's Drug Abuse Advisory Committee (DAAC)) recommended that the marihuana plant materials remain in CSA schedule I and that THC be rescheduled to CSA schedule II. The CSA schedule II recommendations were based on the advisory committee's view that placement in schedule II would facilitate research. On June 4, 1979, the Secretary transmitted to DEA DHHS' evaluation and recommendation that each of the cannabis materials listed above and THC remain in schedule I. DHHS differed with the advisory committee recommendation because the substances met the legal criteria for CSA schedule I and because control of the substances in schedule I was not viewed as a significant impediment to research. On June 20, 1979, DEA denied NORML's petition and request for a hearing on the ground that there was a lack of substantial evidence to support lesser control of the substances in question (44 FR 36123).

NORML petitioned the Court of Appeals for review of DEA's final order denying the petition. On October 16, 1980, the court ordered that the case once again be remanded to DEA and that DEA refer all the substances at issue to DHHS for scientific and medical findings and recommendations on scheduling. The court directed that the DHHS review take into account new evidence concerning medical use of the substances at issue. NORML v DEA & DHEW, No. 79-1660 (D.C. Cir., Oct. 16, 1980). On April 22, 1981, DEA referred the NORML petition to DHHS for review.

On June 25, 1981, FDA received a new drug application (NDA) seeking approval to market THC for the antinausea indication described above. (The sponsor, however, subsequently withdrew the application, intending to resubmit it in the near future). Since it was anticipated that the recommendations for control of the cannabis substances included in the petition would take a significant time to complete, proposed scheduling and recommendations on THC were prepared and published first. The proposed control of cannabis was published June 29, 1982. If FDA approves the NDA, THC could not become commercially available until its scheduling status under the CSA was changed.

DHHS adopted the following special procedures in making its evaluation and scheduling recommendation for THC (a separate procedure applies to the other cannabis-containing substances covered by the court order):

(a) Hearing before FDA's DAAC on the scheduling status of THC as a proposed marketed drug for nausea and vomiting in patients receiving cancer chemotherapy.

(b) Review by FDA of evidence concerning THC for this use, including the DAAC recommendation and comment from other appropriate units in DHHS.

(c) Publication of a Federal Register notice for public comment of the proposed scientific and medical evaluation and recommendation.

(d) Consideration of the comments received in response to the Federal Register notice in preparing FDA's evaluation and scheduling recommendation for transmittal to the Assistant Secretary for Health, DHHS.

(e) Review of the evaluation and recommendation by the Assistant Secretary for Health, DHHS, and transmittal to DEA.

To accomplish the first of these steps, FDA issued a Federal Register notice on May 15, 1981 (46 FR 26869-70), announcing that the DAAC would meet to consider the scheduling status of THC. An NDA was submitted to the agency on June 25, 1981 seeking approval to market THC for treatment of nausea and vomiting in patients undergoing cancer chemotherapy. The DAAC met on June 29, 1981 and was asked to make a recommendation for appropriate scheduling if the NDA for THC were approved. The DAAC recommended that upon NDA approval THC should be controlled in CSA schedule II. Transcripts of the June 29, 1981 DAAC meeting as well as the November 1977 and March 1978 CSAC meetings are on file at the FDA Dockets Management Branch.

Following the DAAC meeting, FDA conducted the review referred to in the second step above. The third step, notice of FDA's proposed scientific and medical evaluation and scheduling recommendation, was published in the Federal Register notice of March 9, 1982 (47 FR 10080-86). Comments were received (Attachment C) and evaluated by FDA (Attachment D) in preparing the recommendation for transmittal to the Assistant Secretary for Health, DHHS.

II. Scheduling Recommendation

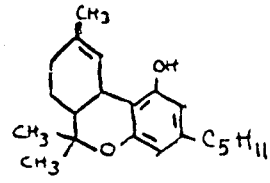
FDA recommends to the Assistant Secretary for Health, DHHS, that THC remain in schedule I, but that if the NDA for THC marketing is approved by the agency, THC be rescheduled under the CSA to schedule II.

FDA notes that several members of the DAAC voted against the majority's recommendation for CSA schedule II and implied that they prefer a schedule with lesser controls. The agency has carefully considered schedule III especially, but also schedules I, IV, and V, and no control, and has concluded that, on balance, THC as a marketed drug would fit best in CSA schedule II.

FDA also notes that any rescheduling of THC from schedule I to II will be influenced not only by the results of this proceeding but also by U.S. treaty obligations under the Psychotropic Convention. As a matter separate from this proceeding but still related to domestic scheduling, FDA is considering with the other interested agencies of government involved in international scheduling whether rescheduling of THC to schedule II domestically could be accomplished without international rescheduling. The agency is not seeking comment on this legal issue.

In making a scheduling recommendation, consideration must be given to the eight factors listed at 21 U.S.C. 811(c). FDA's consideration of these eight factors with respect to THC follows:

(1) Its actual or relative potential for abuse 21 U.S.C. 822(c)(1)). The natural source of (-)-delta-9-(trans)-THC is the plant Cannabis sativa, also called marihuana (Refs. 1 through 4). THC as a single active substance also can be synthesized chemically. THC's chemical structure is:



THC occurs in the plant material at concentrations up to approximately 9 percent of the weight of the leaves. Most cannabis contains less than 3 percent THC (Ref. 6). THC is the major active psychotropic substance in the marihuana plant material.

The legislative history of the Comprehensive Drug Abuse Prevention and Control Act of 1970 defines potential for abuse as:

(1) Evidence that individuals are taking a drug or drugs containing a substance in amounts sufficient to create a hazard to their health or to the safety or other individuals or of the community;

(2) Significant diversion of the drug or drugs containing the substance from legitimate drug channels;

(3) Individuals taking the drug or drugs containing the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or

(4) The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse as to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions of the drug from legitimate channels, significant use contrary to or without medical advice, or that the drug has a substantial capability of creating hazards to the health of the user or to the safety of the community (Ref. 5).

The assumption is made that the potential for abuse of THC is due to its effects on the central nervous system. The pure substance can be applied to any cigarette material and smoked as cannabis is smoked; it can also be put in smoking paraphernalia for use or baked with brownies or other food. In this form THC provides full psychoactive effects. Thus THC can be utilized by the drug-using population in ways similar to the ways cannabis is used, with the advantage of being of high potency and consistent in composition. The substance is not being abused when it is taken orally as dispensed by a licensed medical practitioner in the course of research or practice.

Pure THC has not been available in the United States except in research settings. However, because THC is the major psychoactive ingredient of cannabis, the potential for abuse of THC is indicated by the actual abuse of cannabis. This relation is supported by the practice among abusers of rating the quality of cannabis according to THC content. The higher the THC content, the more desirable the cannabis becomes and the more expensive it becomes on the illicit market (Ref. 6). As an estimate of the magnitude of the actual abuse of cannabis, approximately 10,000 to 15,000 tons of cannabis were smuggled into the United States in 1978 with a value of approximately $15 to $23 billion (Ref. 7). The price on the illicit market in 1978 for cannabis was approximately $35 to $50 per ounce or $375 to $800 per pound (Ref. 8). The usual concentration of THC in illicit cannabis is 1 to 4 percent THC. By comparison, the price of sinsemilla, which is a specially grown high-potency marihuana with a THC content of up to 8 percent, has been reported to be $1,000 to $3,000 per pound (Ref. 7). At that price per unit of THC, the illicit market value of 100 percent THC would be $12,500 to $37,500 per pound. This is equivalent to the illicit value of cocaine, which sells for approximately $2,000 per ounce or $32,000 per pound. To the extent that the illicit price of a substance is a measure of its potential for abuse, THC would have a high potential for abuse.

Further supporting the conclusion that pure THC has a potential for abuse is the presence on the illicit market of substances alleged to be pure THC but which in fact contain other hallucinogenic substances, such as PCP or LSD (Ref. 9). Thus, FDA concludes that there exists a high potential for abuse of THC.

(2) Scientific evidence of its pharmacological effect, if known (21 U.S.C 811(c)(2)). The pharmacological effects of THC have been investigated since it became available in sufficient quantity for extensive studies in the early 1970's. The effect primarily responsible for THC's desirability as a substance of abuse is its ability to produce euphoria. The effects of pure THC are essentially similar to those of cannabis containing THC in equivalent amounts. Responses to THC vary with dosage, frequency of use, and attitude toward the drug (Ref. 10). External factors such as setting or environment, previous drug experience, and age also affect the response to cannabis. A study of subjective marihuana experience revealed that frequent use of

cannabis was associated with reports of increased "creative lucidity," which includes original ideas and greater insight into self, "somatosensory enhancement," which includes more sensual and new touch qualities, and "social withdrawal," which includes a more quiet activity and less talking (Ref. 11). An individual's perception of space and time (which influences sensory perceptions) is also changed by cannabis (Ref. 12). Cannabis can produce a slowing or even a stopping of time perception. At high doses THC produces hallucinogenic effects, paresthesias (abnormal sensations), altered perceptions, difficulty with thinking, concentrating, or speaking, and depersonalization (Ref. 13).

Two physiological effects of cannabis and THC are an increase in heart rate and reddening of the eyes. The increase in heart rate is dependent on the dose of THC in marihuana with a peak effect about 20 minutes after smoking and a duration of about 85 minutes (Ref. 12). Reddening of the eyes reaches a peak about one hour after smoking and slowly declines. THC acts on both the central and autonomic nervous systems (Ref. 12).

(3) The state of current scientific knowledge regarding the drug or other substance (21 U.S.C. 811(c)(3). THC synthesis was first reported in 1964 (Ref. 1). By 1970 there had been sufficient work on the chemistry of THC to produce the material in purified form in sufficient quantities for research (Ref. 15). Since 1970, the scientific and medical literature concerning THC and THC as a component of cannabis has been extensive (Refs. 14 and 16). Under the Marijuana and Health Reporting Act of 1970 (Pub. L. 91-296), Congress receives reports on the health consequences of marihuana and marihuana constituents. These reports present summary information of scientific knowledge accumulated on THC and include an extensive bibliography of research with THC (Ref. 17). The Institute of Medicine of the National Academy of Sciences conducted an independent assessment of the physiological and behavioral effects mainly of marihuana but also of THC. The results of this assessment have recently become available. (Ref 28). Much of the scientific work done with THC was performed under contract from the National Institute on Drug Abuse and is compiled in FDA's Drug Master File No. 1631 (Ref. 19).

The National Cancer Institute (NCI) distributes THC as a group C drug under an investigational new drug application for the indication of nausea and vomiting resulting from cancer chemotherapy. Group C drugs are investigational drugs with sufficient evidence of safety and effectiveness that they may be useful in the care of cancer patients who are not enrolled in formal clinical trials. Group C drugs are not yet marketed, in part because full documentation of safety and/or effectiveness is still being compiled. THC was classified as a group C investigational new drug on the basis of clinical studies indicating its effectiveness in the treatment of some cancer chemotherapy patients with nausea and vomiting refractory to standard antiemetics and because the benefits of treatment with THC exceed the risks

identified to date (Ref. 27). Group C distribution is intended both to provide anti-cancer drugs to patients for humanitarian reasons and to acquire additional information on adverse effects in the context in which the drug is likely to be used in clinical practice after marketing. Under group C distribution, THC remains an investigational drug and is provided only to properly trained physicians who have registered with NCI as clinical investigators.

The precise mechanism of action of THC at the cellular level is unknown. One of the major metabolites of THC is 11-hydroxy-delta-9-THC. This metabolite produces effects similar to those of THC, but appears to have a more rapid onset and to be more potent (Ref. 14). Studies have indicated, however, that THC has activity separate from that of the metabolite 11-hydroxy-delta-9-THC (Ref. 14).

(4) Its history and current pattern of abuse 21 U.S.C 811(c)(4). Pure THC has not been available in the United States except in research settings, and there are no reports of significant diversion or abuse of synthetic THC from scientific and research institutions.

Typical THC values obtained from plant materials in the illicit market and reported in the literature (Ref. 20) are as follows:

	Percent
Fiber-type cannabis	0.05 THC
Drug-type cannabis	1.0 to 4.0 THC
Hashish (resin)	10.0 THC
Red oil (cannabis distillate)	20.0 THC

As the concentration of THC increases, the monetary value of the substance on the illicit market also increases. See the above discussion of factor one, potential for abuse. Attempts have been made to increase the THC content of plant materials which are available on the illicit market. It is reasonable to conclude that the pattern of abuse of synthetic THC would be similar to that of cannabis materials with high concentrations of THC.

(5) The scope, duration, and significance of abuse (21 U.S.C. 811(c)(5)). There has been no actual abuse of THC reported, either from diverted material or in patients given the drug under the stringent controls that apply to investigational drugs. However, cannabis, which contains THC, is widely abused. See the above discussion of factor one.

(6) What, if any, risk there is to the public health (21 U.S.C. 811(c)(6)). The risks to the public health from the illicit use or smoking of THC are likely to be similar to those of smoking marihuana at similar concentrations. Further, the dosage form proposed in the NDA is a capsule for

oral use containing THC in sesame oil. If this dosage form were diverted and injected intravenously, it could cause severe problems to the individual from oil embolism. Taken orally, as intended, the THC capsule would produce psychotropic effects and, like marihuana, could adversely affect job performance and automobile driving. Studies utilizing pure THC or cannabis indicate that the substances impair skills and behavior related to driving (Ref. 21).

(7) Its psychic or physiological dependence liability (21 U.S.C. 811(c)(7). Physical dependence on THC has not been demonstrated. Although one investigator (Ref. 14) reported withdrwawal signs and symptoms after large doses of THC, other investigators have failed to observe a withdrawal syndrome in chronic abusers of marihuana or THC (Ref. 22).

With respect to psychological dependence, there is evidence to suggest such dependence in some individuals. Concentrated forms of cannabis such as hashish or red oil have been reported to produce an acute neurological syndrome which include the clouding of mental processes, disorientation, confusion, and marked memory impairment (Ref. 23). Illicit marihuana has shown a trend in recent years toward higher concentrations of THC in illicit cannabis-containing plant substances. This material commands a high price and is particularly attractive to certain individuals. A recent report of the American Medical Association's Council on Scientific Affairs, as adopted by the AMA House of Delegates, concluded that marihuana is hazardous to health and that there was a growing prospect of an appreciable number of marihuana users incurring physiological and psychological impairment (Ref. 24).

FDA concludes that some individuals should be considered manifesting sufficiently strong drug-seeking behavior to be severely psychologically dependent on cannabis and that a similar potential dependence should be anticipated for THC. Therefore, FDA concludes that THC poses a risk to the public health.

(8) Whether the substance is an immediate precursor of a substance already controlled under this title (21 U.S.C. 811(c)(8). THC is not an immediate precursor to a substance already controlled under this title.

III. Criteria for Scheduling

The eight factors discussed above are used to determine which of the five CSA schedules, if any, is appropriate for a given drug or substance. Each of the five CSA schedules has three criteria to aid in this determination. To assign a substance to a specific schedule, the Attorney General must find that the substance meets the statutory criteria for that schedule (21 U.S.C. 811(a)(1)(B)).

Criterion A for all five schedules is a series of descriptions of abuse potential, declining from high to low. Schedules I and II are identical in this regard, both requiring a finding of "high" potential for abuse. Schedules III through V require findings of lower, though still some, abuse potential.

Criterion B for all five schedules is whether the drug, or other substance, has a currently accepted medical use. Schedule I drugs must be found to have "no currently accepted medical use in treatment in the United States" while schedules II through V all require a "currently accepted medical use in treatment in the United States." In addition, criterion B for schedule II allows an alternative finding, "currently accepted medical use with severe restrictions."

Criterion C is different for schedule I than for the other schedules. For schedule I, the criterion requires a finding of "lack of accepted safety for use of the drug or other substance under medical supervision." For schedules II through V this criterion consists of a sliding scale of the drug's dependence-producing capacity, either physical or psychological. Schedule II drugs require a finding of the highest dependence-producing capacity while schedule V drugs require the lowest.

The "accepted medical use" status of a drug, therefore, plays a significant role in the scheduling analysis, as one of the three criteria for each schedule. Because the NDA for THC has been temporarily withdrawn by its sponsor, two separate proposed scheduling recommendations are made: one which would take effect if the drug is approved for marketing (which would signify that there is an accepted medical use for THC), and a second recommendation for THC absent NDA approval.

1. Upon NDA Approval:

a. Criterion A. - On the scale of abuse potential, FDA concludes that THC has a high potential for abuse and thus meets this criterion for schedules I and II (the criterion is identical for these two schedules).

As noted above, THC is the major active ingredient in the plant Cannabis sativa. As a plant constituent, it has been shown to have a high potential for abuse (see discussion of factor one above). As a single active chemical entity, THC has not been abused because it has been subject to stringent controls as an investigational drug and a schedule I substance under the CSA. The abuse potential of THC must be presumed to be at least as great as that for marihuana. THC has marked psychotropic effects and, if freely available, would very likely to be a major drug of abuse (see discussion of factors two and four above). If THC is marketed as a drug product, it can be anticipated that there will be attempted thefts, that attempts will be made to divert the drug from legitimate channels, and that any drug so diverted will command premium prices in the illicit market.

The conclusion that THC has a high potential for abuse (thus meeting criterion A for schedules I and II) logically precludes THC from meeting criterion A for schedules II through V, because drugs in each of these three schedules have a progressively lower abuse potential than schedule I and II drugs.

b. Criterion B. - As with any drug, upon approval of an NDA for marketing, THC would have a "currently accepted medical use in treatment in the United States." FDA interprets the term "accepted medical use" to mean lawfully marketed in this country under the Federal Food, Drug, and Cosmetic Act.

The mechanism established by Congress for a company lawfully to market a new drug is for the company (the "sponsor") to submit an NDA to FDA and for FDA to approve that application. Before FDA can approve an NDA, however, the drug's sponsor must submit data from a battery of experimental tests on both animals and humans which establish the drug's safety and effectiveness for its proposed uses. In addition, the sponsor must submit data on manufacturing controls demonstrating that standards of identity, strength, quality, and purity are met. Finally, the sponsor must submit labeling which states adequately the proper conditions for use. See 21 U.S.C. 355(d) and 21 CFR 314.1. Only after FDA has evaluated this array of information can the agency make a decision whether the NDA should be approved and the drug marketed.

Thus, FDA's approval of an NDA clearly establishes that a drug has an "accepted medical use", and THC would, therefore, fall into this category if an NDA were approved.

c. Criterion C. - Because an approved NDA for THC would be based, in part, on an FDA finding of THC's safety for its proposed use, in that situation THC would clearly not meet criterion C for schedule I ("lack of accepted safety under medical supervision"). Rather, with an approved NDA the question is where THC fits on the sliding scale of dependence-producing capacity for the remaining schedules, II through V.

Criterion C for schedule II provides that "(a)buse of the drug or other substance may lead to severe psychological or physical dependence" (emphasis added). FDA proposes to recommend the conclusion that abuse of THC may lead to severe psychological dependence in some individuals (see discussion above under factor seven). Whether this psychological dependence might better be characterized as "high" (the schedule III criterion) rather than "severe" (the schedule II criterion) is a subject of scientific controvery. However, FDA agrees with a majority of its DAAC members that THC's psychological dependence-producing ability lies at the top end of the spectrum and is most appropriately characterized as "severe", thus, meeting the criterion for schedule II.

In terms of possible physical dependence, FDA believes the available information at this time is insufficient to determine with certainty whether phsyical dependence occurs. As noted above under factor seven, physical dependence on THC has not been demonstrated clearly; the finding of physical dependence by one investigator has not been confirmed by others.

d. Summary Chart. - FDA's proposed findings for the scheduling of THC, if an NDA is approved, are summarized as follows:

Note. - The criteria vary according to the schedule.

	Criterion A	Criterion B	Criterion C
Schedule I	Met	Not met	Not met
Schedule II	Met	Met	Met
Schedule III	Not met	Met	Possibly met
Schedule IV	Not met	Met	Not met
Schedule V	Not met	Met	Not met

e. Conclusion. - For the reasons stated above, FDA concludes that if an NDA were approved for THC, all three criteria of schedule II would be met and, therefore, at that time DEA should reschedule the drug accordingly.

2. Without NDA Approval:

In 1979, FDA stated that from a medical and scientific standpoint, THC "could be placed in either schedule I or schedule II" (44 FR 36127) but that for policy reasons the agency recommended schedule I. Although certain new developments have occurred with respect to THC in the intervening years (i.e., investigational group C status and enabling legislation in some States providing for various degrees and kinds of more relaxed research controls), these developments do not change FDA's opinion that THC (without an approved NDA) meets all three criteria for both schedule I and schedule II. Accordingly, because there appears to be no advantage to rescheduling THC at this time, FDA recommends for policy considerations that THC remain in schedule I.

a. Criterion A. - As explained above, FDA recommends that THC has a high potential for abuse, and, thus, meets this criterion for both schedules I and II but does not meet this criterion for schedules III through V.

b. Criterion B. - This criterion involves the "accepted medical use" of the drug and has three variations among the five schedules as follows:

(1) Schedule I: " The drug or other substance has no currently accepted medical use in treatment in the United States."

(2) Schedule II: "The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions" (emphasis added).

(3) Schedules III through V: "The drug or other substance has a currently accepted medical use in treatment in the United States."

For the following reasons, FDA recommends that THC currently meets equally well criterion B in both schedule I and schedule II.

As explained above, FDA defines "currently accepted medical use * * * " (schedules III through V and schedule II, first clause) to mean lawfully marketed under the Federal Food, Drug, and Cosmetic Act. Conversely, "no currently accepted medical use * * * " must mean not lawfully marketed. THC fits into the latter category because there is not an approved NDA for the drug, and because it cannot be legally marketed without an approved NDA. Therefore, THC meets criterion B for schedule I.

THC also, however, meets the second clause of criterion B for schedule II involving "a currently accepted medical use with severe restrictions." Although this clause is not defined in the statute or the legislative history, the agency believes that certain investigational drugs, such as THC, in the later stages of the investigational process may fall within this statutory language.

Investigational drugs progress from experimentation in a very limited, closely supervised setting involving only a few individuals to use in a broader investigational protocol using hundreds of patients. Under FDA regulations, reports of these clinical studies are periodically sent to FDA so that the agency can properly monitor the ongoing research and progression to broader clinical trials. See 21 CFR Part 312.

The placement of THC in NCI's group C distribution scheme represents an example of clinical research that has progressed sufficiently far to be termed "currently accepted medical use with severe restrictions." As stated in the Surgeon General's September 10, 1980 press release announcing the placement of THC in group C, the new plan would make THC available to an estimated 4,000 cancer specialists for use in combating nausea and vomiting in cancer patients undergoing chemotherapy (Ref. 25). FDA decided to authorize this broader distribution plan because, among other reasons, the supervision required by the study protocol appeared to provide adequate safeguards for patient safety, and sufficient evidence of effectiveness existed to support broader availability for treatment of patients. This decision was based on review of a significant amount of clinical testing already performed on THC and on the advice of FDA's Oncology Advisory Committee. Thus, although FDA does not propose to define "accepted medical use with severe restrictions" as limited to group C drugs, because that definition would improperly limit the statutory

language to drugs involved in cancer therapy, FDA believes that THC's placement in group C fits the statutory language of "accepted medical use with severe restrictions."

Group C distribution of THC, however, should not be confused with the "accepted medical use" standard of lawful marketing. Group C drugs such as THC remain investigational drugs requiring research protocols, informed consent of patients, availability to a limited number of physicians registered as clinical investigators, and reports of adverse effects to FDA. These requirements together constitute "severe restrictions" under the statutory language that distinguish investigational drugs like THC from marketed drugs.

Similarly, enabling laws in over 20 States that now authorize the use of marihuana and THC in the context of medical research do not satisfy the "accepted medical use" standard of lawful marketing. For example, at least 11 States have FDA-approved protocols for THC research use. Moreover, such State-enabling laws should not be confused with State laws which "decriminalize" the possession or transfer of certain marihuana materials for personal use, including recreational uses. The latter State laws involve reductions in criminal penalties and do not relate directly to the use of these substances in medical research.

FDA concludes that THC meets Criterion B for both schedules I and II.

c. Criterion C - As discussed above, on the sliding scale of dependence-producing capacity (schedules II through V), FDA recommends that THC fits into schedule II because abuse of the drug may lead to severe psychological dependence.

FDA also proposes that THC meets criterion C for schedule I because there is "a lack of accepted safety for use of the drug or other substance under medical supervision." FDA believes that "accepted safety", like "accepted medical use", refers to an attribute possessed only by drugs lawfully marketed under the Federal Food, Drug, and Cosmetic act. Accordingly, because THC is not so lawfully marketed, there is a "lack of accepted safety * * * ".

As noted above, the FFDCA directs FDA to approve an NDA based upon scientific evidence that the drug has been shown to be safe and effective for its proposed uses. See 21 U.S.C. 355(d). Because no drug is ever completely safe in the absolute sense, FDA considers "safe" to mean (in the context of a human drug) that the therapeutic benefits to be derived from the drug outweigh its known and potential risks under the conditions of use prescribed in the labeling. For this reason, FDA requires, before approval of an NDA, that extensive clinical and preclinical testing be conducted to establish the safety of the drug. Indeed, FDA must refuse approval of an NDA if inadequate information about adverse reactions is presented. See 21 U.S.C. 355(d)(1).

Another factor considered by FDA in assessing the drug's safety is the proposed labeling, which is approved at the time of approval for marketing. A drug might be considered safe under some labeling but not others. Physicians depend on detailed labeling for information on when and how a drug should be used, and any claims in the labeling must be supported by clinical studies. False or misleading proposed labeling also precludes FDA approval of an NDA. 21 U.S.C. 355(d)(6).

Clearly, the further along a drug is in the investigational process, the more information about safety and effectiveness there will be. But it is only upon approval for marketing that there has been a decision, based on scientific judgment by the regulatory agency charged with the responsibility of evaluating the safety and efficacy of new drugs, that a drug becomes "accepted" as safe under medical supervision.

THC for use in cancer chemotherapy is a drug near the end of the investigational phase, but FDA has not completed its evaluation of the drug's safety and effectiveness. THC is currently distributed to physicians only as an investigational drug under the group C plan for cancer drugs operated by its sponsor, NCI. NCI's drug master file describes the purpose of group C, in part, as follows: The purpose of this distribution is to acquire information on safety in the context in which the drug is likely to be used in clinical practice after marketing. (Ref. 26 at p. 21) (emphasis added). Thus, participating physicians are required to submit reports directly to NCI when adverse reactions to THC are encountered (Ref. 27).

THC is also being investigated under IND's for both safety and effectiveness. Only when full information is received and reviewed by FDA can a responsible, scientific judgment be made about THC's "accepted safety for use * * * under medical supervision". Accordingly, FDA concludes that THC meets criterion C for schedule I.

d. Summary Chart - FDA's recommendation on scheduling of THC, without an approved NDA, is summarized in the following chart:

Note. - The criteria vary according to the schedule.

	Criterion A	Criterion B	Criterion C
Schedule I	Met	Met	Met
Schedule II	Met	Met*	Met
Schedule III	Not met	Not met	Possibly met
Schedule IV	Not met	Not met	Not met
Schedule V	Not met	Not met	Not met

*The conclusion that THC meets criterion B for schedule II must be qualified because the decision that THC's group C distribution satisfies the requirement for "accepted medical use with severe restriction" represents the first time that a substance still in investigational status has been considered to meet Criteria B of schedule II.

e. Conclusion - FDA proposed that THC remain in schedule I until an NDA is approved, and asked for written comments on the scheduling proposal. Seven parties responded to the request published in the Federal Register (47 FR 10080-86, March 9, 1982 (Docket 81N - 0168)). The comments received are appended in Attachment C. FDA has summarized and evaluated the comments received (Attachment D). The Commissioner concludes that there were no convincing or compelling arguments to change the proposed recommendation. Therefore, it is recommended that THC remain in schedule I until an NDA is approved. If and when an NDA is approved for THC, FDA will recommend that the drug be rescheduled to schedule II.

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