Petitioning the FDA:

"Grandfather it in!"

When marijuana was legalized for medical use by California voters in 1996, Tod Mikuriya, MD, decided to start a company called "Classic Pharmaceuticals" that would market tinctures and ointments based on formulations that were commercially available prior to the federal prohibition in the late 1930s.

Mikuriya hired attorney Robert Raich to set up the company as a for-profit. Then, with legal researcher Paul Klopper, he petitioned the Food and Drug Administration to summarily "grandfather in" cannabis on the grounds that its removal from the formulary in 1940 was based on factual misrepresentation to Congress.

Klopper drafted the following petition to the Dockets Management Branch of the FDA (which is under the Department of Health and Human Services), and it was filed in May, 1999. The response from the FDA came 19 months later.

What follows is the petition and the government response. —*Fred Gardner*

TO: Docket Management Branch
Food and Drug Administration
Department of Health and Human Services
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

PETITION and NOTICE OF EXEMPTION

The undersigned, Paul Klopper —doing business as Farmacy, and Dr. Tod Mikuriya, M.D.— submit this petition and notice of exemption under 21 U.S.C. § 321(p) to request the Commissioner of Food and Drugs to issue a ruling that the products listed below are exempt from all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938 (more commonly known as the "grandfather clause"). 21 CFR § 314.200(e)(2)

A. Products Subject to Exemption

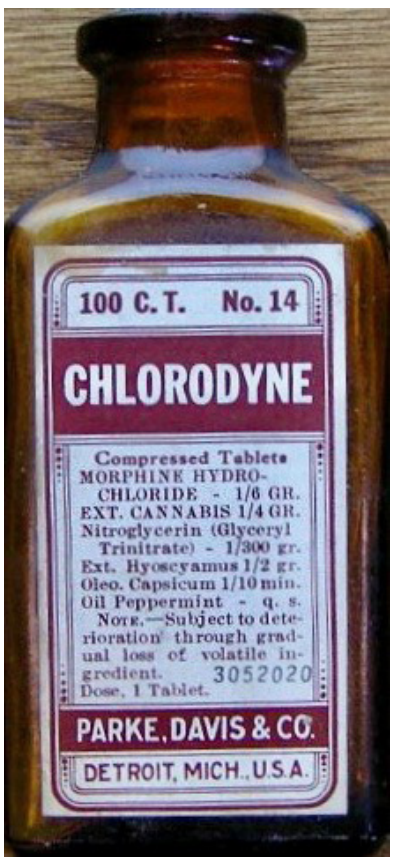
1. Flowering Tops, prepared from Home-Grown Cannabis (HGC)
2. Powdered Extract, prepared from HGC
3. Solid Extract, prepared from HGC
4. Fluid Extracts, prepared from HGC
5. Tinctures, prepared from HGC
6. Pressed Flowering Tops, prepared from HGC
7. Ground Flowering Tops, prepared from HGC
8. Oil with Infused Tops, prepared from HGC
9. Tablets, prepared from HGC
10. Chocolate coated tablets, prepared from HGC
11. Pill and/or Capsule, prepared from HGC
12. Pilular Extract, prepared from HGC
13. Poultice, prepared from HGC

B. Formulations, uses, labeling, and marketing

Attached hereto are copies of pertinent documents and records that establish the formulations, the uses, the labeling, and the marketing of the above identified products at the time of the initial marketing of those products. These documents and/or records are best summarized as follows:

Parke, Davis & Company

From 1890 through 1937, the Parke, Davis & Company widely marketed various formulations of medical cannabis. The products and formulations were advertised as originating from "home-grown cannabis." Parke, Davis & Company marketed tinctures and fluid extracts sold by the pint or fluid ounce; cannabis tablets and pills sold by the gram; solid and powdered extracts sold by the gram, ounce, or pound; and "pressed flowering tops" also sold by the gram, ounce, or pound. Solid and powdered extracts along with "flowering tops" were sold to practitioners or ultimate users who wished to prepare their own tinctures, fluids, or tablets. The advertised uses of these formulations include the following: analgesic, sedative, corn cures, spasmodic disorders, genito-urinary irritation, persistent cough, insomnia, hysteria, asthma, delirium tremens, acute fevers, cathartics, migraine, gastralgia, pruritus, neuralgia, and as a narcotic "used in place of opium."



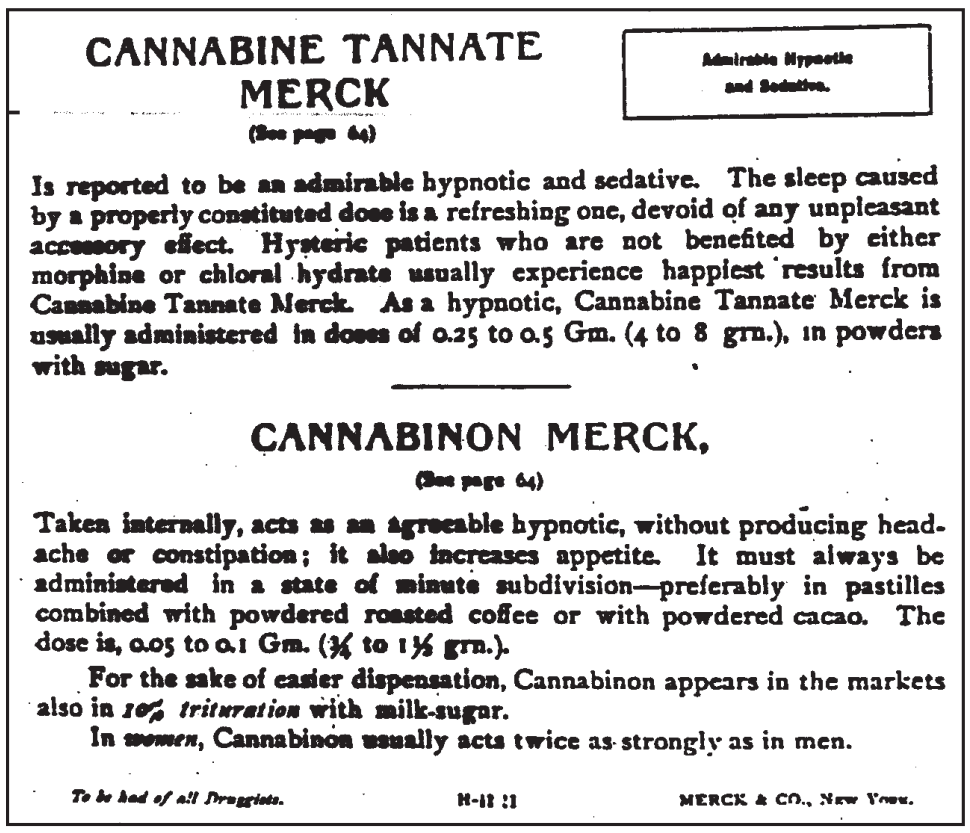
The Eli Lilly Company

From 1877 through 1935, the Eli Lilly Company marketed fluid, solid, and powdered extracts, all ofwhich were manufactured from the "flowering tops of the pistillate plants of *Cannabis sativa L.*" The advertised uses include: antispasmodic, analgesic, sedative, aphrodisiac, narcotic, delirium tremens, insanity, hysteria, migraine.

Merck

In the late 1800's to early 1900s, Merck manufactured and sold the "flowering top of the female plant" by the pound. They also sold, by the pound, tops that were "ground for percola" as well has cannabis oil with "infused tops." In addition, Merck sold fluid extracts, tinctures, and pilular extracts. The Advertised uses included increase appetite, anodyne, antispasmodic, and rheumatism.

Squibb


CANNABINE TANNATE
MERCK
(See page 64)

Admirable Hypnotic and Sedative.

Is reported to be an admirable hypnotic and sedative. The sleep caused by a properly constituted dose is a refreshing one, devoid of any unpleasant accessory effect. Hysteric patients who are not benefited by either morphine or chloral hydrate usually experience happiest results from Cannabine Tannate Merck. As a hypnotic, Cannabine Tannate Merck is usually administered in doses of 0.25 to 0.5 Gm. (4 to 8 grn.), in powders with sugar.

CANNABINON MERCK,
(See page 64)

Taken internally, acts as an agreeable hypnotic, without producing headache or constipation; it also increases appetite. It must always be administered in a state of minute subdivision—preferably in pastilles combined with powdered roasted coffee or with powdered cacao. The dose is, 0.05 to 0.1 Gm. (¾ to 1½ grn.).

For the sake of easier dispensation, Cannabinon appears in the markets also in 10% *trituration* with milk-sugar.

In *women*, Cannabinon usually acts twice as strongly as in men.

To be had of all Druggists. H-11 :1 MERCK & CO., New York.

In the late 1800's to early 1900's, Squibb manufactured and sold tinctures and tablets as well as "the dried flowering tops of the female plant" which could be "ground for pecolation (sic)." The advertised uses include anodyne, epilepsy, hysteria, sedative, neuralgic attacks.

Apex/Frederick Stearns

Sometime prior to 1938, Apex and Federick Stearns marketed a poultice (cannabis combined with alcohol and ether; cannabis combined with salicylic acid and collodion). The advertised use was for a Corn Remedy. Upon information and belief, the formulations —identified above as more fully set forth in the attached — have never been changed.

Those formulations and the marketing of those products were discontinued on the dates noted above.

In addition to the commercial manufacturing and marketing of these products, the medical journals of the time described these products as follows:

Dispensatory of the United States of America (1937)

This describes cannabis as "the dried flowering tops of the pistillate plants of Cannabis sativa Linne" and then further describes cannabis in its various forms —unground flowers and leaves, the stem, and powdered cannabis. American cannabis known as "Cannabis Americana" is "yielded from the Cannabis sativa plants cultivated in various sections of the United States... It occurs on the market in the form of broken segments of the inflorescence and more or less crumpled and broken leaves, varying in color from brownish-green to light brown... Only the female plant produces the drug... Cannabis is used in medicine to relieve pain, to encourage sleep, to soothe restlessness ... and will often relieve migranic headaches." The text notes that "the only way of determining the dose of an individual is to give it ascending quantities until some effect is produced."

The formulations noted are "exctractum, fluidextractum, and tinctura."

Pharmacopoeia of the United States of America (1926)

This text describes cannabis as "the dried flowering tops of the pistillate plants of Cannabis sativa Linne" and then explains how to "assay" the fluidextract in gelatin capsules using dogs to determine the appropriate strength.

Pharmacopoeia of the United States of America (1936)

This discusses "extratum cannabis": "Prepare an extract by percolating 1000 Gm. of cannabis in moderately coarse powder, using alcohol as the menstruum. ..." Eventually, the practitioner/ultimate user will "evaporate the percolate to a pilular consistence ..."

Materia Medica: Pharmacology: Therapeutics Prescription Writing For Students and Practitioners (1914)

This text notes the various formulations; to wit, extract, fluidextract, and tincture, and further notes that Dixon [a well known British authority] "recommends inhalation of the vapor as most soothing." Though "Cannabis indica is very little employed", common usage include: "allaying nervous excitability, pain of neuralgia or migraine, promoting sleep in the presence of pain."

Materia Medica and Pharmacology (1927)

This text details how to prepare the various extracts and lists cannabis use for "neuralgia, distressing cough, quiets tickling in throat, does not constipate or depress like opium, gout, delirium tremens, tetanus convulsions, chorea, hysteria, mental depression, epilepsy, morphine and chloral habits, softening of the brain, nervous vomiting."

Therapeutics Materia Medica and Pharmacy (1926

This explains that "cannabis and its preparations must be standardized by physiological assay according tothe U.S. Pharmacopoeia. The assay is based upon the amount of drug which is required to produce symptoms of incoordination in the dog." The text also explains that "cannabis contains a resin named cannabin" and there are solid extracts, fluid extracts, and tinctures which are used as an "antispasmodic, analgesic, anesthetic

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'Grandfather it in!' from previous page

and narcotic, a cebro-spinal stimulant and a powerful aphrodisasc." "A ravenous appetite is usually one of its early effect."

Pocket Therapeutics and Dose-book (1910)

Notes cannabis is available in tinctures and extracts and also available is "cannabinon" —the "resin from Cannabis indica" and "cannabin tannas" — "a powdered prepared from Cannabis indica." The solid extract and the cannabinon and cannabin tannas are available by the gram. Uses include antispasmodic, antineuralgic, anodyne, cough sedative in tuberculosis, and migraine or sick headache."

Also included, but not separately summarized here, are cannabis references found in: Pharmacopoeia of the United States (1936), Remington's Practice of Pharmacy (1936), A Text-Book of Practical Therapeutics (1916), Textbook of Materia Medica (1931), and Textbook of Materia Medica (1928).

C. Relevant Statutory, Regulatory, and Judicial Decisions

The Administrator for the Drug Enforcement Agency has recognized that formulations prepared from Cannabis were marketed as medicine prior to 1938: "Cannabis sativa L. was one of the first plants to be used by man for fiber, food, medicine, and in social and religious rituals. There were approximately 20 traditional medicinal uses of cannabis ... in Western medicine from the mid-19th to the early 20th century ... In 1941, marijuana passed out of the National Formulary and the United States Pharmacopeia." 54 Fed. Reg. 53767, 53774 (1989).

The Controlled Substance Act, 21 U.S.C. § 801 et seq., currently lists "marihuana" as a schedule I substance. See 21 U.S.C. § 812(I)(c)(10). Petitioner contends Congress did not "un-grandfather" the above listed products when it decided to place "marihuana" (generally) into the schedule I category. At the beginning of the statute setting forth the list of schedule I substances, Congress declared its intent to recognize previously grandfathered substances: "Unless specifically excepted... any material, mixture, or preparation, which contains any quantity of the following... (10) Marihuana." 21 U.S.C. § 812(I)(c). The "unless specifically excepted" clause must be read to refer to 21 U.S.C. § 321(p) which "excepted" and accepted as medicine those products marketed prior to 1938. If Congress had intended to repeal marijuana's pre-1938 exemption as cannabis medicine under § 321(p), it would have made clear its intent to repeal that exemption. *Tennessee Valley Authority v. Hill,* 437 U.S. 153, 189-90 (1978) ("intention of the legislature to repeal must be clear and manifest.").

In *Rutherford v. United States,* 542 F.2d 1137, 1142n4. (10th Cir.1976), the court notes that a pre-1938 product could be un-grandfathered, but only when that previously grandfathered drug is found to be "dangerous to health." To date, neither Congress, the FDA, the DEA, nor the recently commissioned panel from the Institute of Medicine (see Marijuana and Medicine: Assessing the Science Base, 1999) have declared cannabis/marijuana "dangerous to health." Since the decision as to what is or what is not medicine rests with the FDA, the Controlled Substances Act (§ 801 et seq.) did not transfer or otherwise diminish the FDA's authority and responsibility to determine whether a product is a "new" or "exempt" drug or medicine under the grandfather clause: "Clearly, the Controlled Substances Act does not authorize the Attorney General, nor by delegation the DEA Administrator, to make the ultimate medical and policy decision as to whether a drug should be used as medicine." ... "The FDA has both the experts and the statutory mandate to resolve conflicts over safety and efficacy of new drugs." 57 Fed.Reg. 10499, 10505 (1992)

D. Hearing Requested/Required Prior to any Adverse Ruling

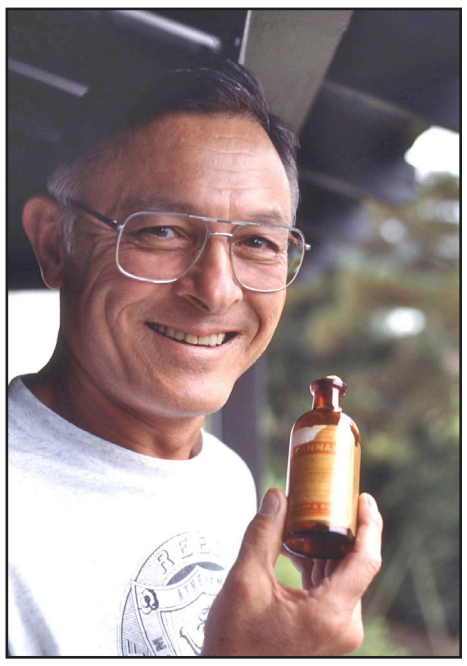
A noted above, as more fully set forth in the attachments, there are genuine and substantial issues of fact regarding the exempt status of the products listed in this petition. As such, a full hearing is required prior to any adverse ruling on the issues contained within this petition. See 21 CFR § 12.87(a) ("The objective of a formal evidentiary hearing is the fair determination of relevant facts consistent with the right of all interested persons to participate and the public interest in promptly settling controversial matters affecting the public health and welfare."). In controversial matters affecting the public health and welfare, the Commissioner of the Food and Drug Administration is required to produce a "full administrative record" which includes a "full hearing" to give "proponents an opportunity to express their views." Rutherford, 542 F.2d. at 1143; accord Breitmeyer v. Califano, 463 F.Supp. 810, 815 (E.D.Mich 1978) ("Under 21 CFR § 314.200(d), any interested person may request a hearing. The hearing, once granted, would extend to all issues relating to [the product's] status as a new drug, including exemption under the grandfather clause. 21 CFR § 314.200(e)(2).").

E. Certification and Verification

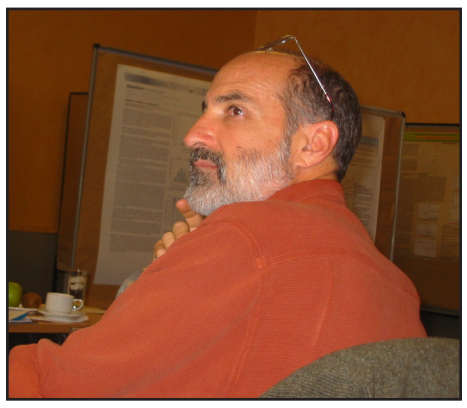
The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition and notice of exemption includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are both favorable and unfavorable to the petition.

The undersigned verify that all appropriate records have been searched and to the best of their knowledge and belief it includes a true and accurate presentation of the facts. Signed:

Paul Klopper. Farmacy, Forestville, CA
Tod H. Mikuriya M.D., Berkeley, CA
Dated May _____, 1999



Tod Mikuriya, MD, with a bottle of cannabis extract made by Sharpe, Dohme.



Legal researcher Paul Klopper

What part of 'no' don't you understand?

The FDA Response

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 29 2000

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Paul Klopper
c/o Farmacy
Post Office Box 242
Forestville, CA 95436

Tod H. Mikuriya, M.D.
1168 Sterling Avenue
Berkeley, CA 94708

Re: Docket No. 99P-1865/CP1

Dear Mr. Klopper and Dr. Mikuriya:

This letter responds to your petition dated May 21, 1999, requesting that the Food and Drug and Administration (FDA) determine that 13 different cannabis-containing drugs are not new drugs, as defined in the Federal Food, Drug, and Cosmetic Act (the 1938 Act), and therefore are not subject to the new drug provisions of the 1938 Act. For the reasons set out below, your petition is denied.

In your petition, you correctly state that, under the 1938 Act's "grandfather" clause (21 U.S.C. 201(p)), if a drug was marketed under the Federal Food and Drugs Act of 1906 (the 1906 Act) prior to the enactment of the 1938 Act, and the drug's labeling regarding its use is the same as it was before the enactment of the 1938 Act, the drug is not a new drug. If it is not a new drug, it is not subject to the new drug provisions of the 1938 Act, such as the new drug application provisions found in section 505 of the 1938 Act (21 U.S.C. 355). For the Agency to determine that a drug product is not a new drug under the grandfather exemption, the following two questions must be answered affirmatively:

1. Was the drug product marketed between January 1, 1907, the effective date of the 1906 Act, and June 25, 1938, the enactment date of the 1938 Act?

2. Is the drug product at issue the same drug product that was marketed between January 1, 1907, and June 25, 1938, and does its labeling describe the same conditions of use?

Your petition presents significant evidence that versions of the 13 different cannabis-containing drug products were marketed between January 1, 1907, and June 25, 1938. The FDA will assume, for purposes of this response, that versions of all 13 drug products were marketed

99P-1865

PDN 1

Mr. Klopper and Dr. Mikuriya
Page 2

between January 1, 1907, and June 25, 1938. However, you do not present any evidence that the drug products at issue are the same drug products that were marketed between January 1, 1907, and June 25, 1938. For this reason, your petition must be denied.

The person seeking to show that a drug product comes within a grandfather exemption must prove every essential fact necessary for invocation of the exemption. See *United States v. An Article of Drug * * * "Bentex Ulcerine,"* 469 F.2d 875, 878 (5th Cir. 1972), *cert. denied*, 412 U.S. 938 (1973). Furthermore, the grandfather clause will be strictly construed against one who invokes it. See *id.*; *United States v. Allan Drug Corp.*, 357 F.2d 713, 718 (10th Cir.), *cert. denied*, 385 U.S. 899 (1966). A change in composition or labeling precludes the applicability of the grandfather exemption. See *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 663 (1973).

Section 314.200(e)(2) (21 CFR 314.200(e)(2)) specifies the information that must support a contention that a drug product is not a new drug because it was marketed under the 1906 Act. The required information addresses both when the drug in question was originally marketed and whether the drug that is currently marketed is the same as the drug marketed between January 1, 1907, and June 25, 1938. Section 314.200(e)(2) requires data showing the "exact quantitative formulation of the drug (both active and inactive ingredients) on the date of initial marketing of the drug" and a "statement whether such formulation has at any subsequent time been changed in any manner. If any such change has been made, the exact date, nature, and rationale for each change in formulation . . . should be stated . . . . If no such change has been made, a copy of representative documents or records showing the formula at representative points in time should be submitted to support the statement."

Additionally, § 314.200(e)(2) requires a "copy of each pertinent document or record to establish the identity of each item of written, printed, or graphic matter used as labeling on the date the drug was initially marketed" and

> A statement whether such labeling has at any subsequent time been discontinued or changed in any manner. If such discontinuance or change has been made, the exact date, nature, and rationale for each discontinuance or change and a copy of each pertinent document or record to establish each such discontinuance or change should be submitted . . . . If no such discontinuance or change has been made, a copy of representative documents or records showing labeling at representative points in time should be submitted to support the statement.

Finally, § 314.200(e)(2) requires a "copy of each pertinent document or record to establish the exact date the drug was initially marketed" and a "statement whether such marketing has at any

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Mr. Klopper and Dr. Mikuriya
Page 3

subsequent time been discontinued. If such marketing has been discontinued, the exact date of each such discontinuance should be submitted, together with a copy of each pertinent document or record to establish each such date."

As can be seen from the material quoted above, the determination of whether a drug product is or is not a new drug under the grandfather provision of the 1938 Act is a fact-intensive determination of whether a ***specific*** drug product is the same drug product marketed between January 1, 1907, and June 25, 1938. See *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 663 (1973).[1] Your petition and supporting documentation simply do not come close to giving the quantity and quality of information required for FDA to make a determination. To give just one example, you do not give the "exact quantitative formulation . . . (both active and inactive ingredients)" of any of the drugs marketed between January 1, 1907, and June 25, 1938, nor do you provide that data for any drug product whose new drug status you wish determined. Without this information, and much more, FDA cannot determine whether any specific drug product that is a member of one of the classes of drugs mentioned in your petition is or is not a new drug.[2]

FDA notes that marihuana is currently listed in Schedule I under the Controlled Substances Act (21 U.S.C. 812(c), 21 CFR 1308.11(d)(19)).[3] The labeling for all Schedule I drugs is required to bear the "C-I" symbol (21 CFR 1302.03). FDA would regard the inclusion of the "C-I" symbol on a product as a labeling change regarding the conditions of its use. This would mean that the drug product no longer qualified for the grandfather clause. This would be true even if marihuana were rescheduled and placed in Schedules II through V: the inclusion of the "C" symbol on the product would be viewed as a labeling change regarding the conditions of its use.

The Agency also denies your request that you be given a hearing prior to any adverse response to your petition (Petition at 5-6). There is no material issue of fact that requires a hearing. See 21 CFR 314.200(g).

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[1]The protection of the grandfather exemption extends only to the specific drug products on the market on the relevant date. A product marketed by a different manufacturer is not entitled to the exemption, even if the later product is virtually identical to the grandfathered product. See the *Federal Register* of May 4, 1982 (47 FR 19224).

[2]Note that the 1938 grandfather clause applies only to the new drug provisions of the Act and not to the adulteration or misbranding provisions (Sections 501 and 502 of the Act (21 U.S.C. 351 - 352)). Thus, the grandfather provision does not prevent the Agency from ensuring that any drug product, even if it might be grandfathered, is not adulterated or misbranded.

[3]Drugs in Schedule I have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and there is a lack of accepted safety for use of the drugs under medical supervision (21 U.S.C. 812(b)(1)). Drugs listed in Schedule I may only be used in research (21 CFR 1301.13).

Color graphics courtesy Don E. Wirtshafter and The Cannabis Museum.

Mr. Klopper and Dr. Mikuriya
Page 4

For the reasons stated above, your petition is denied.

Sincerely yours,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs

Explanations

Cannabis medicine could be bought
At drug stores none of us were taught
Till Reefer Madness came on wings of Hollywood
Woodward and the AMA
Said a ban was not the way
But explanations never do no—
Explanations explanations explanations explanations
Explanations never do no good.

The mayor of New York City
Told the Medical Society
Report on marijuana —every aspect they could
But LaGuardia put no lies to rest
Anslinger had the report suppressed
Explanations never do no—
Explanations explanations explanations explanations
Explanations never do no good.

War on drugs was Nixon's cry
Sent Shafer out to mollify
Here is your commission tell me what we should do
Shafer said "Decriminalize!"
Into the garbage Schafer flies
Explanations never do no… good

ALL those public hearings
all those witnesses appearing
Always they keep nearing
Conclusions none can reach

NORML sued back in 72
Got the runaround, at last got through
Judge Francis Young held hearings leading him to conclude:
"The safest medicine known to man!"
What part of that could DEA not understand?
Explanations never do no—
Explanations explanations explanations explanations
Explanations never do no good.

Doctor Varmus, white medical knight
Said Science smites your Plebescite
And the Institute of Medicine came flying out to our hood!
Tod Mikuriya and Dennis Peron
Tried to make their findings known
But explanations never do no....

And now it's 2017
A new report has hit the scene
The National Academy of Sciences has reviewed
The evidence —meaning clinical trials
No truth was sought in doctors' files
Cause explanations never do no...

All those expert speakers
and lawyers' briefs amicus
Pharma-funded tweakers
addicted to their grants!

Groucho Marx was hip and wise
He said, "Believe me or your own eyes"
A line that top psychiatrists well understood
So now it is with our favorite plant
We know we can but they say we can't
And explanations explanations explanations
explanations explanations never do no good!