



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

STATEMENT OF
ROBERT J. MEYER, M.D.
DIRECTOR
OFFICE OF DRUG EVALUATION II
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE
SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY, AND
HUMAN RESOURCES
COMMITTEE ON GOVERNMENT REFORM
HOUSE OF REPRESENTATIVES

APRIL 1, 2004

FOR RELEASE ONLY UPON DELIVERY

INTRODUCTION

Good afternoon, Mr. Chairman and Members of the Subcommittee. I am Dr. Robert Meyer, Director of the Office of Drug Evaluation II at the Food and Drug Administration's (FDA or the Agency), Center for Drug Evaluation and Research (CDER). I am pleased to be here today with my colleague, Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA). FDA appreciates the opportunity to discuss the need for a science-based approach to evaluating the merits of marijuana for medicinal purposes.

In my testimony today, I will first describe the FDA drug approval process. Second, I will clarify FDA's role in facilitating the objective evaluation of the potential merits of cannabinoids for medical uses as well as FDA's role with respect to enforcement efforts relating to Schedule I Controlled Substances such as marijuana.

FDA APPROVAL PROCESS

FDA's primary mission for over 90 years has been to promote and protect the public health, under the authority of the Federal Food, Drug, and Cosmetic (FD&C) Act and the Public Health Service Act. These statutes were enacted and amended, in part, in response to public health tragedies resulting from the sale to, and use by, an unsuspecting public of unsafe and ineffective products sold as medicines and medical devices. The FD&C Act requires that new drugs be shown to be safe and effective before being marketed in this country.

The single most important public health provision in these statutes is the requirement that a person wishing to sell to the public a product to prevent, cure or mitigate illness or injury must first prove that such product is safe, and actually does what the vendor claims it does. This statutory provision affords patients the most effective protection against untested and unproven products.

A new drug or biologic (referred to in this statement as a drug) may not be distributed in interstate commerce (except for clinical studies under an investigational new drug application) until a sponsor, usually the drug manufacturer, has submitted and FDA has approved a new drug application (NDA) or a biologics license application (BLA) for the product. For approval, an NDA or BLA must contain sufficient scientific evidence demonstrating the safety and effectiveness of the drug for its intended uses.

The evidence of safety and effectiveness usually is obtained through controlled clinical trials. The disciplined, systematic, scientific conduct of such trials is the most effective and certain means of obtaining the data that document safety and efficacy of a drug and how to use the new product so that it will have the most beneficial effect.

A. INVESTIGATIONAL NEW DRUG APPLICATION PROCESS

The first step a sponsor usually must take to obtain approval for a new drug is to test the drug in animals for toxicity. The sponsor then takes that animal testing data, along with additional information about the drug's composition and manufacturing, and develops a plan for testing the drug in humans. The sponsor submits these data, along with proposed studies, the qualifications of the investigators who will conduct the clinical studies, and assurances of informed consent

and protection of the rights and safety of the human subjects, to FDA in the form of an investigational new drug application (IND).

FDA reviews the IND for assurance that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate assurances of informed consent and human subject protection. At that point the first of three phases of study in humans can begin. Phase I studies primarily focus on the safety of the drug in humans. Phase I studies carefully assess how to safely administer and dose the drug with an emphasis on evaluation of the toxic manifestations of the therapy, how the body distributes and degrades the drug, and how side effects relate to dose. Phase I studies typically include fewer than 100 healthy volunteers or subjects.

Phase II studies are clinical studies to explore the effectiveness of the drug for a particular indication over a range of doses and to determine common short-term side effects. Phase II studies typically involve a few hundred subjects. Once Phase II studies are successfully completed, the drug's sponsor has learned much about the drug's appropriate dosing and its apparent safety and effectiveness. The next step is to conduct Phase III studies involving up to several thousand subjects. These studies establish efficacy for a particular indication, examine additional uses, may provide further safety data including long-term experience, and consider additional population subsets, dose response, etc. FDA strongly encourages sponsors to work closely with the Agency in planning definitive Phase III clinical trials to help assure that the trials are designed to have the greatest likelihood of producing results sufficient to provide adequate data and permit the Agency to make appropriate decisions about the safety and efficacy of the product.

Once Phase III trials are completed, the sponsor submits the results of all the relevant testing to FDA in the form of an NDA. FDA's medical officers, chemists, statisticians, and pharmacologists review the application to determine if the sponsor's data in fact show that the drug is both safe and effective. The drug's manufacturing process is evaluated to confirm that the product can be produced consistently with high quality. It is common to allow subjects in Phase II and III studies to continue on a therapy if it seems to be providing benefit. This practice provides long-term safety information at an early stage in this process. At present, there are literally thousands of clinical trials ongoing, involving hundreds of thousands of subjects. There are over 15,000 active INDs for drugs, therapeutic biologics, and biologics filed with the Agency.

Results of controlled clinical trials are the basis of evidence-based medicine. These allow physicians and patients to use therapies with a clear understanding of their benefits and risks and, in some cases, a basis for strong public health recommendations for treatments.

Clinical trials also have saved us from unwanted public health consequences. For example, when azidothymidine (AZT) was the only approved AIDS treatment, dideoxycytidine (ddC) was made available under treatment-IND for the several years while clinical trials were underway. These trials were to assess whether ddC was superior to AZT or if it was effective for patients intolerant of AZT. Although the product, ddC, could cause permanent, sometimes severe nerve damage, there was great demand for early access to the product. It was even manufactured by sources other than the company (probably by amateur chemists) and this "bathtub" ddC was made available through buyers clubs when the demand exceeded the sponsor's supply. FDA

acted with the sponsor, the buyers clubs, patient advocates, and investigators to make more of the drug available and get the illicit, poorly manufactured product off the market.

What did the ddC clinical trials show? In a head-to-head comparison versus AZT as initial therapy, an independent data safety monitoring board stopped the trial early because the death rate in the ddC group was at least twice higher than in the AZT group. For patients intolerant to AZT, a clinical trial compared switching to ddC versus dideoxyinosine (ddI). In this study the trend was that ddC had superior survival to ddI. Later studies showed that ddC in combination with AZT had superior survival to AZT alone. Each of these studies involved hundreds of patients and was essential to determining where ddC improved survival and where it did not. Although some of the early access uses were later found to be poor choices, physicians considered it reasonable at the time to provide the drug while the question was still being answered. The important point is that patients are only well served by early access when the controlled clinical trials proceed in parallel with early access.

A second example that illustrates the importance of conducting clinical trials is the recently announced results of the Women's Health Initiative (WHI) study of estrogen and progesterone in treating post-menopausal women conducted by the National Institutes of Health. This large (more than 16,000 women), scientifically rigorous clinical trial was done to confirm the widely held belief that estrogen/progesterone therapy in post-menopausal women would significantly reduce the risk of cardiovascular events, such as heart attacks and strokes. There was also some hope that this post-menopausal therapy might lessen the onset of Alzheimer's disease. These widely held beliefs were based on scientific evidence that was not from clinical trials, such as

epidemiology. On the strengths of these beliefs, post-menopausal hormone therapy was very widely used and growing in popularity.

The WHI trial of post-menopausal estrogen/progesterone preceded but was stopped early due to an excess of harm in women taking these drugs compared to placebo. Surprisingly and importantly, women given the active drugs were more likely to suffer heart attacks and strokes and appeared to be more likely to develop dementia. This study not only failed to prove the widely held notion that this therapy was good for preventing these types of occurrences, but actually confirmed harm. These important results have led to significant changes in the use of post-menopausal hormones.

FDA sometimes uncovers individuals who do not comply with statutory and regulatory drug approval requirements. This puts patients at risk of using unproven products and also denies to all patients the knowledge of whether the untested therapies may actually work. Distribution of unproven products and subsequent widespread use combined with little accountability or liability reduces the incentive for manufacturers and health care practitioners to conduct studies of safety and effectiveness. We constantly work to find ways to make safe and effective products available to patients as quickly and efficiently as possible, consistent with the protections established in the law. It is essential to preserve the system of controlled clinical trials that provides the information necessary to make the final determination on the safety and effectiveness of unapproved products. The two concepts, the protection of public health and making available treatments for individuals, can and must co-exist.

B. HUMAN SUBJECT PROTECTION

The FD&C Act and its implementing regulations are one part of a complex system of safeguards designed to protect human subjects. Each participant in a research effort -- the company that sponsors the research, the clinical investigator who conducts the research, and the Institutional Review Board (IRB) is obliged to protect the interests of the people who are taking part in the experiments. FDA's responsibility is to see that the safeguards are met. FDA monitors the activities of research sponsors, researchers, IRBs and others involved in the trial. We take very seriously our role to protect people enrolled in clinical trials.

The sponsors of research -- usually, manufacturers or academic bodies, but sometimes individual physicians -- must select well-qualified clinical investigators, design scientifically- sound protocols, make sure that the research is properly conducted, and make certain that the clinical investigators conduct the research in compliance with all pertinent regulations, including requirements for obtaining informed consent and review by an IRB. The primary regulatory obligations of the clinical investigator are to: 1) conduct or supervise the study; 2) conduct the study according to the approved protocol or research plan; 3) ensure that the study is reviewed and approved by an IRB that is constituted and functioning according to FDA and other Federal requirements; 4) obtain informed consent; 5) maintain adequate and accurate records of study observations (including adverse reactions); 6) administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator; 7) report to the sponsor adverse experiences that occur in the course of the investigation; and 8) promptly report to the IRB all unanticipated problems involving risks to humans or others.

The core of FDA's informed consent regulations, Title 21, Code of Federal Regulations (CFR) Part 50, is that the clinical investigator must generally obtain the informed consent of a human subject or his/her legally authorized representative before any FDA-regulated research can be conducted. The researcher has to make sure that, whenever possible, the study participants fully understand the potential risks and benefits of the experiment before the experiment begins. The information provided must be in a language understandable to the subject, and must not require the subject to waive any legal rights, or release those conducting the study from liability for negligence. The clinical investigator must tell the human subjects important information about the study and its potential consequences so that the person can decide whether to be in the experiment. The entire informed consent process involves giving the subject all the information concerning the study that he or she would reasonably want to know, ensuring that the subject has comprehended this information, and obtaining the subject's written consent to participate.

An IRB is a group (consisting of experts and lay persons) formally designated to review, approve the initiation of, and periodically review the progress of, research involving human subjects. The primary function of IRBs is to protect the rights and welfare of the people who are in trials. FDA's regulations, 21 CFR Part 56, contain the general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations submitted to FDA under sections 505(i), and 520(g) of the FD&C Act. IRBs must scrutinize and approve each of the clinical trials that are conducted on FDA-regulated products in this country each year. IRBs must develop and follow procedures for their initial and continuing review of the trials. Among other requirements, IRBs must make sure that the risks to subjects are minimized and do not outweigh the anticipated study benefits, that the selection of participants is equitable, that there are adequate plans to monitor data gathered in the trial and provisions to protect the privacy of

subjects and the confidentiality of data. The IRB has the authority to approve, modify, or disapprove a clinical trial. The IRB must approve the informed consent form that will be used. If the researchers fail to adhere to IRB requirements, the IRB has the authority and the responsibility to take appropriate steps, which may include termination of the trial. The IRB is required to conduct continuing review of ongoing research at intervals appropriate to the degree of risk, but not less than once per year. It also has the authority to observe or have a third party observe the consent process and the research.

IRBs are currently not required to register with FDA nor inform FDA when they begin reviewing studies. However, FDA performs on-site inspections of IRBs that review research involving products that FDA regulates, including IRBs in academic institutions and hospitals as well as those independent from where the research will be conducted. The primary focus of FDA's IRB Program is the protection of the rights and welfare of research subjects, rather than validating the data obtained from research.

Marijuana

FDA has not approved marijuana for medical use in the United States. Despite its status as an unapproved new drug, there has been considerable interest in its use for the treatment of a number of conditions, including glaucoma, AIDS wasting, neuropathic pain, treatment of spasticity associated with multiple sclerosis, and chemotherapy-induced nausea. Under the Controlled Substances Act (CSA) Congress listed marijuana in Schedule I. Schedule I substances have a very high potential for abuse, no accepted medical use in the United States, and lack accepted safety data for use under medical supervision. Schedule I substances can still be the subject of an IND; however, the conditions for its use are more restrictive.

Pursuant to the FD&C Act, FDA is responsible for the approval and marketing of drugs for medical use, including controlled substances. DEA is the lead Federal agency responsible for regulating controlled substances and enforcing the CSA. The CSA separates controlled substances into five schedules, depending upon their approved medical use and abuse potential. Unlike Schedule I controlled substances, Schedule II substances are approved for medical use, although they also have a very high potential for abuse. Schedules III, IV, and V include those controlled substances that have been approved for medical use, but whose potential for abuse is diminished.

FDA's Office of Criminal Investigations (OCI) is responsible for managing and conducting the Agency's criminal investigations. As a part of its duties, OCI has worked closely with DEA on a number of criminal investigations involving the illegal sale, use, and diversion of controlled substances including controlled substances sold over the Internet. OCI's close working relationship with DEA and local law enforcement agencies has led to many successful criminal cases involving controlled substances. FDA cooperates with DEA and other state and Federal agencies. OCI is often requested by these entities to provide assistance. Both OCI and DEA have worked together in the past to utilize the full range of regulatory and administrative tools available to them to pursue cases involving controlled substances. However, the primary responsibility for enforcing the CSA resides with DEA, and, FDA generally defers to DEA on criminal enforcement efforts related to Schedule I controlled substances. The criminal penalties related to Schedule I controlled substances are far greater under the CSA than those available under the FD&C Act for the distribution of an unapproved new drug.

The Department of Health and Human Services (HHS) and FDA support the medical research community who intend to study marijuana in scientifically valid investigations and well-controlled clinical trials, in-line with the FDA's drug approval process. HHS and FDA recognize the need for objective evaluations of the potential merits of cannabinoids for medical uses. If the scientific community discovers a positive benefit, HHS also recognizes the need to stimulate development of alternative, safer dosage forms. In February 1997, an NIH-sponsored workshop analyzed available scientific information and concluded that "in order to evaluate various hypotheses concerning the potential utility of marijuana in various therapeutic areas, more and better studies would be needed."

In March 1999, the Institute of Medicine (IOM) issued a detailed report that supports the absolute need for evidence-based research into the effects of marijuana and cannabinoid components of marijuana, for patients with specific disease conditions. The IOM report also emphasized that smoked marijuana is a crude drug delivery system that exposes patients to a significant number of harmful substances and that "if there is any future of marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives." As such, the IOM recommended that clinical trials should be conducted with the goal of developing safe delivery systems.

In May 1999, HHS released "*Guidance on Procedures for the Provision of Marijuana for Medical Research*," a document intended to provide the medical research community who intend to study marijuana in scientifically valid investigations and well-controlled clinical trials on HHS procedures for providing research-grade marijuana to sponsors.

The HHS guidance is intended to facilitate the research needed to evaluate pending public health questions regarding marijuana by making research-grade marijuana available for well-designed studies on a cost-reimbursable basis. The focus of this HHS program is the support of quality research for the development of clinically meaningful data regarding marijuana. An appropriate scientific study of a drug requires, among other things, that the drug used in the research must have a consistent and predictable potency, must be free of contamination, and must be available in sufficient amounts to support the needs of the study. NIDA allocates resources to cultivate a grade of marijuana that is suitable for research purposes. The HHS Guidance outlines the procedures for obtaining research-grade marijuana including: 1) the researcher must make an inquiry to NIDA to determine the availability and costs of marijuana, and NIDA has to determine that marijuana is available to support the study; 2) researchers who propose to conduct investigations in humans must proceed through the FDA process for filing an IND application: and 3) all researchers must obtain from DEA registration to conduct research using a Schedule I controlled substance.

FDA regulates smoked marijuana, a botanical product, when it is being investigated for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals, as a drug, under the FD&C Act. Botanicals include herbal products made from leaves, as well as products made from roots, stems, seeds, pollen or any other part of a plant. Botanical products pose some issues that are unique to this class of product, including the problem of lot-to-lot consistency. These unpurified products, which may be either from a single plant source or from a combination of different plant substances,

often exert their reported effects through mechanisms that are either unknown or undefined. For these reasons, the exact chemical nature of these products may not be known. In addition, issues of strength, potency, shelf life, dosing and toxicity monitoring need to be addressed. If a product varies greatly, as can occur with botanicals, it is critical to obtain lot-to-lot product consistency. Without this it is difficult to determine if the product is causing the change in a patient's condition, or the change is related to some other factor. Because of the problems associated with obtaining lot-to-lot consistency with botanical marijuana, it is not surprising that IOM recommended that clinical trials should be conducted with the goal of developing safe delivery systems.

HHS performed a scientific and medical evaluation of marijuana in 2001 and concluded with a recommendation to DEA that marijuana should remain in Schedule I pursuant to section 201(b) of the CSA. HHS's scientific and medical evaluation and scheduling recommendation can be found at Volume 66, *Federal Register* page 20038 (April 18, 2001). After receiving an HHS evaluation and recommendation, DEA is responsible for scheduling substances and as noted previously, has primary responsibility for the regulation and distribution of Schedule I substances.

FDA Approval of Safer Dosage Forms of Cannabinoids

FDA has approved two drugs, Marinol and Cesamet, for therapeutic uses in the U.S., which contain active ingredients that are present in botanical marijuana. On May 31, 1985, FDA approved Marinol Capsules, manufactured by Unimed, for nausea and vomiting associated with cancer chemotherapy inpatients that had failed to respond adequately to conventional antiemetic

treatments. Marinol Capsules include the active ingredient dronabinol, a synthetic delta-9-tetrahydrocannabinol or THC, which is considered the psychoactive component of marijuana. On December 22, 1992, FDA approved Marinol Capsules for the treatment of anorexia associated with weight loss in patients with AIDS. Although FDA approved Cesamet Capsules for the treatment of nausea and vomiting associated with chemotherapy on December 26, 1985, this product was never marketed in the U.S. Cesamet Capsules contain nabilone as the active ingredient, a synthetic cannabinoid. Nabilone is not naturally occurring and not derived from marijuana, as is THC.

These products have been through FDA's rigorous approval process and have been determined to be safe and effective for their respective indications. It is only through the FDA drug approval process that solid clinical data can be obtained and a scientifically based assessment of the risks and benefits of an investigational drug is made. Upon FDA approval for marketing, consumers who need the medication can have confidence that the approved medication will be safe and effective.

CONCLUSION

Having access to a drug or medical treatment, without knowing how to use it or even if it is effective, does not benefit anyone. Simply having access, without having safety, efficacy, and adequate use information does not help patients. FDA has and will continue to use its IND and other expanded access programs to provide patients freedom to choose investigational medical treatments while reasonably ensuring safety, informed choice, and systematic data collection that allows us to review drug applications.

FDA will continue to be receptive to sound, scientifically based research into the medicinal uses of botanical marijuana and other cannabinoids. FDA will continue to facilitate the work of manufacturers interested in bringing to the market safe and effective products.

I would like to thank the Subcommittee again for the opportunity to testify today on this important issue. I would be happy, at this time, to answer any questions Members of the Subcommittee may have.

