

CHAPTER 3
THE RISE AND FALL OF FDA'S PILOT DRUG EVALUATION STAFF

For scientists interested in conducting psychedelic research in the United States, the establishment in 1989 of FDA's Pilot Drug Evaluation Staff was the single most important event in the last 30 years. By 1970, FDA and NIMH had closed down almost all psychedelic research projects in human subjects, as had their regulatory counterparts around the world. By 2000, a handful of researchers had reentered the clinics to administer psychedelics to human subjects in the context of FDA-approved studies. The policy permitting the resumption of this research was developed and initially supervised by Pilot Drug.

In Chapter 2, Pilot Drug's decisions and policies regarding psychedelic and medical marijuana research were reviewed, and the long-term impact of those policies was discussed. This Chapter focuses on Pilot Drug itself and on its broader mission and activities. Much of the basis for the analysis in Chapter 2 evaluating current FDA policies and attitudes toward psychedelic and medical marijuana research comes from research conducted for this chapter about Pilot Drug itself.

The primary goals of the research conducted for this chapter were to determine how and why the dramatic revision of FDA policies toward psychedelic and medical marijuana research took place and also whether the elimination of Pilot Drug had anything to do with these policies and actions. The larger story of Pilot Drug involves an analysis of the personal, bureaucratic and political forces that resulted in the establishment of Pilot Drug in 1989, that impacted on the performance of its primary mission during its existence, and that led to its elimination in 1995. As a result, this chapter is more about bureaucratic processes within FDA than psychedelic and medical marijuana research.

This chapter addresses the following questions:

- 1) Who established Pilot Drug and why?
- 2) How and why did Pilot Drug gain authority over the regulation of psychedelics and marijuana?
- 3) What was Pilot Drug's primary mission and how did it fulfill that mission?
- 4) Why was Pilot Drug eliminated?

This chapter is based on a series of interviews conducted in 1999 with key FDA personnel involved in Pilot Drug's establishment, operation and elimination. Additional sources include published literature in trade press, media, peer-reviewed journals, and publicly available as well as unpublished governmental investigations of Pilot Drug by General Accounting Office (GAO) and the Office of Inspector General (OIG). Especially valuable was an "Internal Assessment" of Pilot Drug not available in the public record or obtainable through FOIA request.

As research proceeded, it became increasingly evident that Pilot Drug represented both a bold search for solutions at a time FDA was in crisis as well as a fundamental challenge to FDA's standard methods of operation. While an entire dissertation could be written about Pilot Drug, this chapter seeks to provide only insight into a remarkable experiment undertaken by an unusual group of civil servants who, among other things, permitted the renewal of psychedelic and marijuana research.

BACKGROUND

FDA Review- A Balancing Act

There are a variety of ways of looking at the balancing act that FDA must perform when it reviews scientific data to determine whether to approve a new drug for prescription use, delay and ask for more tests, or reject the drug. One way of describing the balancing of interests is to note that FDA seeks to avoid making either a false negative Type 1 error, in which it rejects a drug for marketing with a favorable risk/benefit ratio, or a false positive Type 2 error in which it approves a drug for marketing with an unfavorable risk/benefit ratio.⁶⁸⁵

Ever since FDA was empowered in 1962 in the wake of the Thalidomide tragedy to evaluate drugs for efficacy as well as safety, it has been more sensitive to the need not to make a false positive Type 2 error. This is in part a lesson FDA learned when it received widespread public approval and new regulatory powers after it refused to approve Thalidomide in the United States, avoiding what would have been a torrent of criticism if it had allowed the Thalidomide tragedy that took place in Europe, Japan and Canada to occur with the same magnitude in the United States. FDA's incentives to prioritize the avoidance of false positives are also influenced by the fact that it is rather easy for the general public and media to see the damage caused when a drug with an unfavorable risk/benefit ratio has been approved and needs to be withdrawn from the market. Becoming aware of the absence in the marketplace of a drug with a favorable risk/benefit ratio is much more difficult. However, with the increasing interconnection between the US and Europe, there is also a growing public awareness of drugs that are approved in other countries but not in the US. This knowledge increased public disapproval of FDA's historical lag in approving drugs that were available to patients in other countries with perceived positive effects but were not available to patients in the United States.⁶⁸⁶

FDA's regulatory challenge has also been described as a tension between the speed with which FDA reviews data submitted by pharmaceutical companies seeking approval to market their new drug and the quality of its review.⁶⁸⁷ Though not an exact parallel, the

⁶⁸⁵Grabowski H, Vernon J. *The Regulation of Pharmaceuticals- Balancing the Benefits and Risks* Washington, DC: American Enterprise Institute for Public Policy Research, 1983: 10.

⁶⁸⁶Coppinger P, Peck C, Temple R. Understanding comparisons of drug introductions between the United States and the United Kingdom. *Clin Pharmacol Ther* 46 (Aug 1989) 2:139-45.

speed of FDA review is related to the length of time FDA makes a Type 1 error by not approving a drug with a favorable risk/benefit ratio. The quality of FDA review is related to whether FDA avoids making a Type 2 error, mistakenly deciding to approve a drug with an unfavorable risk/benefit ratio. While the speed of FDA review is easy to measure, quality is more difficult to determine.

One factor is the extent of the proof that FDA requires sponsors to provide for FDA review. Another factor is the length of time FDA takes to process the evidence submitted to it while it comes to a decision. A more rapid review, perhaps but not necessarily involving data from fewer or smaller studies, could result in beneficial medicines getting to patients sooner, though some drugs in which the costs outweighed the benefits might also be approved. On the other hand, a slower, more deliberate review, perhaps but not necessarily involving data from more numerous or larger studies, might delay the use of drugs that were socially beneficial but could help prevent the approval for marketing of drugs whose costs outweighed the benefits. The approval/rejection decision-making process in turn interacts with the Secretary of HHS's post-approval ability to withdraw a drug⁶⁸⁸ when post-marketing data reveals a greater than expected number and/or severity of side effects or less than expected efficacy.^{689 690 691 692 693 694}

⁶⁸⁷Lurie P, Woodcock J, Kaitin K. FDA Drug Review: The Debate over Safety, Efficacy, and Speed. *Med Crossfire*1 (April 15, 1999) 3:52-60.

⁶⁸⁸Only the Secretary of HHS has the legal authority to withdraw a drug from the market due to "imminent hazard." FDA can suggest to pharmaceutical companies that products be withdrawn "voluntarily" but it does not have legal authority to withdraw a drug that has already been approved. FDA can withdraw foods from the market and can legally seize the products, but not so with drugs. FDA has the authority to approve drugs for marketing since that authority has been delegated from the Secretary of HHS to FDA, down as far as review staff during the Pilot Drug era. According to Ms. Tyson (2/23/2000 interview), in at least one instance (with the drug Oraflex marketed by Eli Lilly), FDA has requested that a company keep a drug on the market but the company withdrew it anyway. Oraflex was the first FDA-approved NSAID and was implicated in several serious adverse reactions. Nevertheless, FDA wanted to keep the drug on the market since it benefited a large number of patients who at the time had no alternative medications. Eli Lilly nevertheless decided to withdraw the product for reasons of public relations and possible legal liability.

⁶⁸⁹FDA requires quarterly reports (Periodic Safety Update Reports- PSURs) summarizing the adverse event reports of marketed drugs for the first three years of marketing, with annual reports thereafter. 21 CSF 314.80(c) (2) (i). See also FDA Guidance For Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (Nov. 1996, ICH). <http://www.fda.gov/cder/guidance/index.htm>

⁶⁹⁰The FDA Modernization Act of 1997, 105 P.L. 115; 111 Stat. 2296. November 21, 1997, Sec. 112, Expediting Study and Approval of Fast Track Drugs, established procedures for the expedited withdrawal of approval of drugs approved by FDA under fast track provisions. A drug may be withdrawn from the market if a) the sponsor fails to conduct required post-approval studies, b) a post-approval study fails to demonstrate clinical benefit, c) other evidence demonstrates that product is not safe or effective, d) the sponsor disseminates false or misleading promotional materials.

Cost, both in terms of the regulatory review process itself and of the end cost to the consumer of the products approved, is another dimension involved in the effort to design a socially optimal regulatory review process. Determining with any degree of precision how much money the FDA would need to save in regulatory review costs in order to justify it to review somewhat smaller datasets in a somewhat expedited fashion, just like asking an individual to decide how much money he or she would need to save in order to choose to take a slightly less effective or riskier drug, presents difficult tradeoffs that need to be made under significant amounts of uncertainty. The developing field of pharmacoeconomics seeks in part to address these issues, though the field is focused more on the comparative costs and value of particular drugs than on the costs of alternative regulatory review processes.⁶⁹⁵

From October 1988 to November 1993, Dr. Carl Peck was Director of FDA's Center for Drug Evaluation and Research (CDER). Dr. Peck was the person who established Pilot Drug, and was responsible for managing FDA's regulation of all medicines used in human beings. Dr. Peck described FDA's mission in yet another way, in terms of

⁶⁹¹ FDA Modernization Act of 1997, Sec. 506 (b). Reports of Post-Marketing Studies, establishes the obligation of the sponsor to submit annual reports on the outcomes of post-marketing studies.

⁶⁹²For an evaluation of FDA's performance reviewing post-marketing studies, see Office of Inspector General (OIG) report, Post-Marketing Studies of Prescription Drugs. May 1996 OEI-03-94--00760. Roughly 70% of new drugs approved in the 1990's were the subject of post-marketing studies while only about 30% were the subject of such studies in the 1970s. The OIG report was not enthusiastic about FDA's performance in monitoring these studies. However, it determined that FDA was in the process of improving its performance and could do even better as FDA meets its PDUFA goals of reducing or eliminating its backlog and obtains the additional staffing which PDUFA and the FDA Modernization Act of 1997 will continue to provide.

⁶⁹³For a discussion of the purposes and designs of post-approval studies, see Decoster G, Buyse M. Clinical Research After Drug Approval: What is Needed and What is Not. *Drug Info J* 33 (1999) 2:627-634.

⁶⁹⁴In addition to post-marketing studies, data gathered about adverse effects as part of standard "pharmacovigilance" efforts may also result in the withdrawal of drugs from the marketplace. For slides from a talk entitled, "Pragmatic Approaches to Some Current Challenges in Pharmacovigilance," given at the DIA Euro2000 meeting, Nice, France, March 9, 2000 by FDA's Dr. Murray Lumpkin, Deputy Center Director, CDER, see <http://www.fda.gov/cder/present/dia-nice2000/dianice2/index.htm>. For examples of drugs removed from the marketplace as a result of adverse event reports, see March 21, 2000 FDA press release about Rezulin, marketed for the treatment of type 2 diabetes mellitus and removed after FDA request, <http://www.fda.gov/bbs/topics/NEWS/NEW00721.html>, and also FDA's March 23, 2000 Talk Paper on Cisapride, marketed for severe nighttime heartburn and removed voluntarily by the manufacturer, <http://www.fda.gov/bbs/topics/ANSWERS/ANS01007.html>.

⁶⁹⁵For more information, see any issue of the journal, *Pharmacoeconomics*.

increasing the efficiency of the FDA review process and improving the quality of the drugs that get approved. He defined efficiency as, “minimizing the duration of drug development, minimizing the cost of drug development, minimizing the number of patients involved, the number of clinical trials -- all while preserving and even improving the information gain.”⁶⁹⁶ Efficiency as used by Dr. Peck is an operation that seeks to optimize the combination of the speed and quality of the review process. Dr. Peck also wanted FDA to improve the quality of the drugs themselves that were approved, by refining the experimental process through which the proper doses were determined. He noted, “Many drugs are first introduced into the market at doses that are far too high. AZT is the most recent, most important example... I could give you a whole list. Obviously, patients would be better off if the doses were right at the start.”^{697 698}

FDA Prior to the Creation of Pilot Drug

Throughout the 1970s and 1980s, FDA was subjected to an ever increasing amount of criticism by the pharmaceutical industry, some members of Congress and public interest groups for what was perceived as an excessively lengthy and cautious review process.⁶⁹⁹ FDA faced tremendous pressure to reduce the backlog of unreviewed New Drug

⁶⁹⁶Staff. Keep your NDA's 'lean' to cut drug development time. *Med Market & Media*.26 (February 1991) 2:34.

⁶⁹⁷Ibid.

⁶⁹⁸ Statistics on post-approval alterations in the Defined Daily Dose (DDD) of all prescription drugs approved in the US, Europe and Japan (participants in the International Conference on Harmonization) are kept by the WHO Collaborating Centre of Drug Statistics Methodology (<http://www.whocc.nmd.no/>). From 1988, when Dr. Peck arrived at the FDA, through February 2000, the DDD of about 100 drugs has been altered, with 2/3 involving reductions and 1/3 increases. No causal connection is implied between the number of post-approval alterations in the DDD and Dr. Peck's arrival at the FDA. The data is intended to demonstrate the importance of Dr. Peck's concern over determining the most appropriate dose of prescription medicines. According to a March 4, 2000 personal communication to the author from John Urquhart, MD, FRCP (Edin) Professor of Pharmaco-epidemiology, Maastricht University, Maastricht, NL, Professor of Biopharmaceutical Sciences, UCSF, “the last 18 years have seen on average probably about 25 new chemical entities a year being registered, and so the number of DDD changes would signify that between 1 in 4 and 1 in 3 new drugs later underwent a DDD change, mostly (except for the anti-infectives) in the downward direction. According to a 2/29/2000 communication to the author from Ms. Hanne Strom, WHOCC staff, “DDD is NOT synonymous with “recommended dosage.” The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD does not necessarily reflect the Recommended or Prescribed Daily Dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations.”

⁶⁹⁹FDA Drug Approval—A Lengthy Process that Delays the Availability of Important New Drugs, GAO Report No. HRD-80-64 (1980).

Applications (NDAs) and speed up the drug review process. Dr. Kenneth Kaitlin, then Assistant Director of The Center for the Study of Drug Development, Tufts University, remarked in 1992 that, “Over the past two decades, the FDA has been under growing pressure to accelerate its new drug review procedures and hasten the availability of important new medicines.”⁷⁰⁰

In 1979, Dr. Louis Lasagna, a leading analyst of the pharmaceutical industry and then Director of the Center for the Study of Drug Development, Tufts University, blamed excessive regulation for the lengthening review process, commenting, “A lot of unfortunate things have been happening to drug development in recent years, and I believe that many of them can be attributed to excess regulatory zeal...I believe that our current “drug lag” is attributable to excessive regulation and that on balance this is not in the interest of the American public.”⁷⁰¹ According to Dr. Lasagna, in 1979, FDA review of a New Drug Application (NDA) took a relatively constant average of around two and half years between the submission of all clinical data to FDA (marking the beginning of the NDA process) and final approval for marketing,⁷⁰² five times as long as the 180-day target specified in the statutes.⁷⁰³

Despite the pressure on FDA to expedite its review process, prior to the spread of the AIDS epidemic in the mid-1980s, all but one Congressional hearing over 25 years criticized FDA for being too quick to approve drugs for marketing.⁷⁰⁴ After AIDS became a public issue, FDA began to be regularly criticized for moving too slowly to approve new drugs.

A comprehensive study of mean drug development times for new drugs approved from 1963 to 1992,⁷⁰⁵ based on a survey of twenty-two U.S.-owned pharmaceutical firms and 14 U.S. subsidiaries of foreign firms, was conducted by Dr. Joseph DiMasi, also

⁷⁰⁰Kaitlin K, Walsh H. Are Initiatives to Speed the New Drug Approval Process Working? *Drug Info J.*26 (1992): 341.

⁷⁰¹Lasagna L. The impact of regulation on the development of psychoactive drugs. *National Institute on Drug Abuse Research Monograph Series 27. Problems of Drug Dependence.* Proceedings of the 41st Annual Meeting. Washington, D.C: NIDA, 1979:30,34.

⁷⁰²Ibid., 31.

⁷⁰³Kefauver-Harris Amendments of 1962 to the 1938 Food, Drug, and Cosmetic Act. Sec. 104 (c). “Within 180 days after the filing of an application under this subsection, of such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either 1) approve the application... or 2) give the applicant notice of an opportunity for a hearing...”

⁷⁰⁴personal communication, Mr. Peter Hutt, February 28, 2000.

⁷⁰⁵This study focused only on New Chemical Entities (NCE’s), referring to drugs that were going through the FDA review process for the first time. Supplemental New Drug Applications (SNDA) refers to drugs that had already been approved by the FDA for one clinical indication and were subsequently approved for a new clinical indication, based on additional data submitted to FDA.

affiliated with the Center for the Study of Drug Development.⁷⁰⁶ Dr. DiMasi's study showed that the mean time from the submission of the initial application to conduct human studies (the IND, or Investigation New Drug Application) to FDA approval for marketing had been consistently increasing over the decades, with mean development time of 4.7 years for the period from 1963 to 1969, 6.5 years for the period from 1970-1979, 8.3 years for the period from 1980-1989, and 8.6 years for the period from 1990-1992. Dr. DiMasi noted that while FDA has been criticized for the length of time it takes to review the New Drug Application (NDA), the period of time between synthesis and submission of the NDA consumes more than 80% of the drug development process, suggesting that "the potential for societal gain, therefore, appears substantial if the efficiency of the other four-fifths of the process (discovery to NDA submission) can be enhanced."⁷⁰⁷

In a 1989 speech to the US Food and Drug Law Institute's Annual Pharmaceutical Update, Ms. Dorothy Pease, an FDA Consumer Safety Officer who would soon join Pilot Drug, remarked, "The slowness of the US Food and Drug Administration drug approvals process costs pharmaceutical companies money, denies needed drugs to the public and makes the agency look bad."⁷⁰⁸ Congress, though more than willing to criticize the operations of the FDA, was not enthusiastic about increasing FDA's budget in order to allow it to hire more staff.⁷⁰⁹ Although under intense pressure to increase its output, there were no easy answers for FDA management as they sought to balance a variety of competing interests and to find some way of doing more with less.

Dr. Peck's Arrival at FDA

In 1987, the job of Director of FDA's Center for Drug Evaluation and Research (CDER) needed to be filled.⁷¹⁰ The CDER Director's responsibilities included the supervision of FDA's review of all drugs for human use. Dr. John Harter, who had been working at FDA since 1973 and was Anti-Inflammatory Group Leader in FDA's Oncologic

⁷⁰⁶DiMasi J, Seibring M, Lasagna L. New Drug Development in the United States 1963-1992. *Clin Pharm Ther*5 (June 1994) 6:609-22.

⁷⁰⁷Ibid., 24.

⁷⁰⁸Staff. FDLI Hears of FDA Pilot Evaluation. *Marketletter* June 12, 1989: 24.

⁷⁰⁹Funding for additional staff would become available after Congress passed the Prescription Drug User Fee Act (PDUFA) of 1992. PL 102 P.L. 571; 106 Stat 4491. October 29, 1992. This act set user fees for the drug review process to be paid by pharmaceutical companies, with funds restricted to the hiring of new staff for the purpose of expediting the drug review process. This interaction between this Act and the fate of Pilot Drug is discussed later in this Chapter.

⁷¹⁰There were a total of 7 Centers, with CDER being the largest in terms of staff and budget. The other Centers were for Food Safety and Applied Nutrition, Biologics Evaluation and Research, Veterinary Medicine, Devices and Radiological Health, National Center for Toxicological Research, and Center of Field Operations.

and Radiopharmaceutical Drug Products Division,⁷¹¹ learned that FDA Commissioner Dr. Frank Young was having trouble finding qualified candidates for the job. Dr. Harter mentioned the job opening to Dr. Carl Peck, who taught clinical pharmacology at the Uniformed Services University of the Health Sciences (USUHS), in Bethesda, Maryland, and encouraged him to apply. Dr. Harter and Dr. Peck shared a long-standing interest in clinical pharmacology and pharmacokinetics,^{712 713} and had met during the 8 years Dr. Peck had been teaching at USUHS.

Dr. Peck expressed interest in applying for the job, with one major attraction being the opportunity to institutionalize the practice of clinical pharmacology in medicine.^{714 715}
^{716 717} Dr. Harter, along with his wife Ms. Mary Doug Tyson, another long-time FDA employee, began extensively coaching Dr. Peck with background information about FDA. They strategized with him at their home about how he might improve his chances of getting the job. If he got the job, they talked about how he might contribute to the improvement of FDA's standard operating procedures and respond to FDA's need for substantial organizational innovation.⁷¹⁸

In October 1987, Commissioner Young appointed Dr. Peck to be CDER Director. Ms. Tyson became Dr. Peck's principal assistant (She is currently FDA Associate

⁷¹¹Dr. Harter began working at FDA in 1973, after working as a medical researcher at Harvard and in the pharmaceutical industry. Staff. John Gamble Harter Dies, Guided Pilot Drug Program. *News at the Pike* (July 15, 1996): 4.

⁷¹²Harter J. Application of pharmacokinetic data to clinical trials during the IND/NDA process. *J Clin Pharmacol* 16 (Oct 1976) 10 Part 2:560-4.

⁷¹³Harter J. Symposium on pharmacologic and clinical control of cardiovascular drugs. Comments from the Food and Drug Administration. *Am J Med* 58 (April 1975) 4:477-8.

⁷¹⁴Peck C, Crout J. Current status of clinical pharmacology training in the United States. *Clin Pharmacol Ther* 39 (Apr 1986) 4:451-8.

⁷¹⁵Clinical pharmacology is now a recognized Board-certified speciality. This happened during Dr. Peck's time at FDA. According to Ms. Mary Doug Tyson (3/17/1999 interview), the first exam for this field attracted about 120 people, about 75 of whom were FDA review staff. Dr. Peck and Dr. Temple grandfathered themselves into the certification but Dr. Harter decided he should take the exam. He was 63 at the time. He took the exam and passed it.

⁷¹⁶This goal has been achieved. Sec. 128 of the FDA Modernization Act of 1997 reauthorized \$3 million per year for fiscal years 1998-2002 for " grants for a pilot program for the training of individuals in clinical pharmacology at appropriate medical schools." In addition, FDA now has a formal Pharmacology/Toxicology Staff.

⁷¹⁷Temple R. The clinical pharmacologist in drug regulation: the US perspective. *Br J Clin Pharmacol* 42 (July 1996) 1:73-9.

⁷¹⁸personal communication, Ms. Mary-Doug Tyson, March 17, 1999. Ms. Tyson works within FDA as Associate Director, Africa and the Middle East, Office of International Affairs, Office of the Commissioner.

Director, Africa and the Middle East, Office of International Affairs, Office of the Commissioner.) Dr. Peck negotiated a 6 year contract even though Commissioner Young, Dr. Harter and others wanted him to agree to stay 8 years. As a result, Dr. Harter knew that Dr. Peck would quite likely be leaving in 6 years, leaving them with only a relatively short window of time within which to foster organizational change.

New Pressure For Change

By the mid to late 1980s, new and intense pressure on FDA to expedite its review process was generated by a highly motivated and effective lobby of AIDS patients. Their terminal status made many AIDS patients unwilling to accept FDA's lengthy review process as the only way of evaluating the potentially life-saving drugs they needed.⁷¹⁹ In 1987, FDA did revise its regulations to provide a mechanism by which some patients with serious diseases for which there were no alternative therapies could obtain easier access to experimental drugs.⁷²⁰ These changes were not considered far-reaching enough by many AIDS activists. On October 11, 1988, more than 1000 AIDS activists from around the country, organized by the AIDS activist group ACT UP, demonstrated outside FDA's headquarters in Rockville, MD. They demanded streamlined procedures for the review of and access to drugs being tested for the treatment of AIDS. The demonstration effectively shut down much of FDA for the day, as well as much of NIDA and a host of other agencies within HHS whose offices are in the large Parklawn building. Police arrested more than 150 people and the protest generated international publicity.⁷²¹

Inside the building, Dr. Harter did some math in his head, calculating the monetary costs of bringing all those demonstrators to Rockville, and feeding and housing them. He determined that a substantial clinical trial could have been funded with all that money, and thought that there must have been some way for FDA to have channeled the energy of the AIDS activists in a more productive direction, in effect turning protests into protocols.⁷²²

⁷¹⁹Shilts R. *And the Band Played On: Politics, People and the AIDS Epidemic* New York: Penguin Books, 1987.

⁷²⁰Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale. 52 FR 19466. May 22, 1987. 21 CFR Part 312. "These new procedures are intended to facilitate the availability of promising new drugs to patients as early in the drug development process as possible, and to obtain additional data on the drug's safety and effectiveness. These procedures are intended to provide sufficient incentives for drug manufacturers to make investigational new drugs available to patients before general marketing begins, but under sufficient safeguards so as to prevent commercialization of the product as well as to ensure the integrity of clinical trials."

⁷²¹Staff. ACTUP/NY 1988. <http://www.actupny.org/documents/cron-88.html>

⁷²²personal communication, Dr. John Harter, April 1991. From 1990-1994, this author had several discussions about Pilot Drug with Dr. Harter. After being awarded a Presidential Management Internship (PMI) in 1990, this author sought to obtain a position within Pilot Drug, which almost succeeded. Later,

The protest further motivated him to do whatever he could from within the FDA to change what he considered to be some of FDA's "ossified" procedures.

On October 18, 1988, just one week after the ACT-UP protest, FDA issued an interim rule designed to "speed the availability of new therapies to desperately ill patients, while preserving appropriate guarantees for safety and effectiveness...These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses...The procedures apply to products intended to treat acquired immunodeficiency syndrome (AIDS), some cancers, and other life-threatening or severely-debilitating illnesses."⁷²³ These regulations became known as Subpart E -- Drugs Intended to Treat Life Threatening and Severely-debilitating Illnesses.

Who Established Pilot Drug and Why?

According to Dr. Peck, "The AIDS activists were an important influence on the establishment of Pilot Drug, impressing on both myself and Dr. Harter the need for expedited drug review and creative, collaborative drug development policies."⁷²⁴ ⁷²⁵ Dr. Peck freely acknowledged that he had established Pilot Drug at the urging of Dr. Harter and was its initial champion in the face of substantial bureaucratic opposition from within FDA.⁷²⁶ Dr. Peck reported that he, Dr. Harter and Ms. Tyson had discussed the ideas behind the establishment of Pilot Drug for about a year or so before they were ready for it to be formally established. They decided to create Pilot Drug to search for ways to improve

this author assisted various researchers in their efforts to obtain permission for their protocols from Pilot Drug. Unless otherwise noted, all statements attributed to Dr. Harter come from his Founder's Commentary in Pilot Drug's Internal Assessment document.

⁷²³Investigational New Drug, Antibiotic, and Biological Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses. 53 FR 41516 (October 21, 1988).

⁷²⁴personal communication, Dr. Carl Peck, February 22, 1999. Dr. Peck is now Director of the Center for Drug Development Science, Georgetown University Medical Center.

⁷²⁵For efforts to expedite access to new drugs for AIDS patients, see 55 FR 20856 (May 21, 1990), Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and HIV-Related Disease. Also, in 1991, "FDA published regulations to accelerate reviews of drugs for life-threatening diseases." FDA CDER Timeline: Chronology of Drug Regulation in the United States. <http://www.fda.gov/cder/about/history/time1.htm>. see also 57 FR 58942 (December 11, 1992) Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval [for serious or life-treating diseases]. For developments after Dr. Peck's tenure at FDA, see Sec. 112 of the FDA Modernization Act of 1997, which further codified fast track provisions and Sec. 561, which dealt with expanded access to unapproved therapies and diagnostics.

⁷²⁶personal communication, Dr. Peck, February 22, 1999.

innovation, experimentation, access, economy and speed of drug review. From the outset and throughout the experiment, Dr. Harter's vision had the firm and enthusiastic support of Dr. Peck. Dr. Peck in turn was supported in this experiment by his boss, FDA Commissioner Francis Young, who told Dr. Peck when he came to him for approval, "Well, if you think you can explain this to a Congressional committee if something goes awry, OK."⁷²⁷

According to Dr. Peck, Dr. Harter drove the process. Ms. Tyson reported that Dr. Harter loved to review data about drugs and was reluctant to take on management responsibilities. However, he realized that he couldn't make change happen within FDA without having the formal authority that comes with management positions and duties.

Dr. Peck did encounter some opposition to his decision to support Dr. Harter's project from outside FDA, from Mr. Peter Barton Hutt, pharmaceutical industry lawyer and ex-chief counsel of the FDA. Dr. Peck and Mr. Hutt had discussed the creation of Pilot Drug when the concept was still in its early stages. Mr. Hutt recommended to Dr. Peck that he not place Dr. Harter in such an important position of responsibility, which he feared would only exacerbate what he perceived to be Dr. Harter's stubborn and authoritarian tendencies.⁷²⁸ Dr. Peck reported that Dr. Harter remained his clear choice for Director of Pilot Drug due to his high standards and technical competence, despite the fact that he had a mixed reputation with industry as a result of these standards and was sometimes difficult to work with. Dr. Peck considered Dr. Harter to be "disturbingly creative."⁷²⁹

There were also personality conflicts between Dr. Harter and other senior FDA officials. Dr. Temple, Associate Director for Medical Policy and Director, Office of Drug Evaluation I, called him "a difficult man,"⁷³⁰ while Mr. Gerald Meyer, Deputy Director of the Center for Drug Evaluation and Review under Dr. Carl Peck, said that Dr. Harter "was viewed as a difficult personality."⁷³¹ Dr. Leber, Director of the Division of Neuropharmacological Drug Products remarked, "Harter was one of the biggest authoritarians, in terms of lines of control. He acted in an autocratic method. Pilot Drug was similar in design to Five-Year Plans in the old Soviet system."⁷³²

Ms. Tyson reported that once the decision was made to appoint Dr. Harter director of the new Division, that she tried to stay out of as many meetings as possible between Dr.

⁷²⁷ personal communication, Dr. Peck, February 22, 1999.

⁷²⁸ personal communication, Mr. Hutt, February 28, 2000.

⁷²⁹ personal communication, Dr. Peck, February 22, 1999.

⁷³⁰ personal communication, Dr. Robert Temple, March 18, 1999. Dr. Temple currently works within FDA as Associate Director for Medical Policy and Director, Office of Drug Evaluation I.

⁷³¹ personal communication, Mr. Gerald Meyers, March 16, 1999. Mr. Meyers has retired from FDA and works as a private consultant.

⁷³² personal communication, Dr. Paul Leber, March 5, 1999. Dr. Leber recently retired from FDA and works as a private consultant.

Peck and Dr. Harter. Her intention was to avoid the appearance in the eyes of other Division Directors of favoritism, nepotism or conflict of interest.⁷³³

On March 31, 1989, after Dr. Peck had been at FDA for five months, he sent a memo to CDER staff announcing the impending creation of a new organizational unit whose primary mission was to experiment with the drug review process itself, in the hope that policies and procedures could be developed and tested that would improve the speed and/or quality of FDA's drug review process. According to Dr. Peck, the new unit was to "serve as one focus for 'pilot testing' innovations in new drug review. John Harter...will serve as the acting head of this division."⁷³⁴ Dr. Peck wanted to avoid creating a situation whereby FDA staff would leave all the innovating to the new division, so his memo went on to state, "Let me emphasize that the new division is not intended to be a "sole site" for experimentation or a privileged community. Continued leadership and innovation in all divisions will be encouraged and supported, and we will all try to learn from one another."⁷³⁵ Dr. Peck's memo immediately attracted the attention of the pharmaceutical industry, which was alerted to the change four days later by the appearance of articles in two of the major trade newsletters.^{736 737}

Though Dr. Peck called Dr. Harter's new organizational unit a division in his initial memo, and this term was widely used inside and outside FDA, bureaucratically the new unit was not structured as a formal division but was rather only a "staff." In practice, it was somewhat easier to recruit personnel and get a staff going more rapidly, since divisions were encumbered by a larger number of internal FDA regulations and procedures. Even so, Dr. Peck noted that there were still some initial difficulties in acquiring space and personnel for Pilot Drug. On the other hand, the designation of Dr. Harter's group as a staff also made it a little easier to disband later on, since more is required to dissolve a division than a staff.

On April 20, 1989, three weeks after Dr. Peck's internal memo, FDA issued a press release highlighting the creation of the Pilot Drug Evaluation Staff and the consequent reorganization of the divisions. In the press release, Dr. Peck was quoted as endorsing Pilot Drug's plans to test innovative organizational methods. Commissioner Young was quoted as saying the overall reorganization was in response to the need to expedite drugs for life-threatening diseases such as AIDS and cancer, which had been called for by the President's Task Force on Regulatory Relief, chaired by then Vice-President Bush. Commissioner Young was quoted as remarking, "By placing the oncology group in a

⁷³³personal communication, Ms. Tyson, March 17, 1999.

⁷³⁴Staff. Harter to Head New FDA Analgesics, Anti-Inflammatories Division. *Pharma Manufac Assoc Newslet* 31 (April 3, 1989) 13:1.

⁷³⁵Ibid.

⁷³⁶Staff. FDA Anti-Inflammatory/Analgesic Drug Review Division. *Pink Sheet Trade and Government Memos* April 3, 1989: 1.

⁷³⁷Staff. *Pharma Manufac Assoc Newslet*(April 3, 1989): 1.

smaller division, under the direction of an oncologist, we will be allowing greater focus on drugs to treat cancer.”⁷³⁸

What was Pilot Drug’s primary mission?

The Pilot Drug mission statement, as printed in the Federal Register, was, “to facilitate improvements in the quality, efficiency and speed of CDER’s drug review process. Pilot Drug responsibilities are to analyze barriers to innovation, develop new methods of review, and evaluate alternative methods of conducting the review process, all with effective management controls.”⁷³⁹

With the Bush White House advocating regulatory reform and the pharmaceutical industry lobbying Congress to expedite the FDA review process, Dr. Harter began his experiment in FDA reform with just about as much upper-level and outside support as any innovator could hope for. Though Dr. Harter personally lacked some support from some quarters of the pharmaceutical industry, his biggest challenge would be to work with opponents and skeptics within FDA. According to Dr. Peck, “opponents to Pilot Drug were the entire establishment, with its resistance to change, opposition to delegating responsibility downward, and bureaucratic inertia.”⁷⁴⁰ As Dr. Peck acknowledged, the primary legitimate reason to oppose Pilot Drug was the fear that its new techniques might compromise the quality of FDA reviews, and hence public safety, as a result of the elimination of layers of review or of other innovative approaches it would test.

Dr. Harter also faced challenges in motivating FDA staff at lower bureaucratic levels. These FDA employees would be called upon to act in new ways, increase output, take on greater responsibilities and redefine their mission as not just to keep “bad” medicines off the market but also to expedite the approval of “good” medicines for the benefit of the public. If anything went wrong, they were the ones who would have to shoulder a large share of the blame, though as the leader Dr. Harter would bear primary responsibility for mistakes.

As a humorous but telling aside, one of Dr. Harter’s first tasks in establishing Pilot Drug was to choose an identifying number for the new organizational unit, in the form of HFD-XXX. H stood for Health and Human Services, F and D stood for Food and Drug, and the number identified the organizational unit. Dr. Harter inquired as to whether number 7 was still available, which it was. He then took to identifying Pilot Drug as HFD-007, a sly reference to fictional secret agent James Bond’s identifying number and to his “license to kill.” Dr. Harter meant to communicate to people inside and outside of Pilot Drug that he had the freedom to kill layers of bureaucracy and any FDA policies he felt justified in

⁷³⁸Staff. Pilot Drug Review Division. FDA Press Release. April 20, 1989.

⁷³⁹Delegations of Authority and Organization; Center for Drug Evaluation and Research (CDER). Final Rule. 55 FR 51687 (December 17, 1990).

⁷⁴⁰personal communication, Dr. Peck, February 22, 1999.

shredding. It isn't difficult to see how Pilot Drug was perceived by some FDA staff as being more of a threat or a loose cannon than a permanent part of the FDA structure.

How and why did Pilot Drug gain authority over the regulation of psychedelics and marijuana?

When Dr. Peck was appointed Director of CDER, he inherited an organization in which the direct review of drugs was divided into eight divisions.⁷⁴¹ [organizational charts, before and after Pilot Drug, on next two pages] Each division had the responsibility for reviewing specific classes of drugs based on the uses of the drugs (i.e. Oncology or Coagulation) or parts of the body (i.e. Cardio-Renal or Gastrointestinal). The directors of five of the eight review divisions were subordinate to the director of the Office of Drug Evaluation I, and the directors of three divisions were subordinate to the director of the Office of Drug Evaluation II. The directors of the Office of Drug Evaluation I and 2 reported to Dr. Peck, who reported in turn to a deputy commissioner of FDA within the Commissioner's Office.⁷⁴²

Pilot Drug required a portfolio of drugs to review so that the impact of any innovations in the drug review process that it decided to "pilot test" could be evaluated. This necessitated that the review over certain classes of drugs be taken from other divisions and reassigned to Dr. Harter's newly created staff. Dr. Peck's initial intention for Pilot Drug was to give Dr. Harter authority over drugs that he was already reviewing.⁷⁴³ As a result, Dr. Harter was given authority over anti-inflammatory drugs since he had previously been in charge of reviewing those drugs within the Oncologic and Radiopharmaceutical Drug Products Division. The Oncology/Radiopharmacology group lost anti-inflammatory drugs but exchanged radiopharmacology for pulmonary drugs with the Surgical/Dental Division. These reshufflings at FDA resulted in nine review divisions.⁷⁴⁴

The review of anesthetic drugs was also moved into Pilot Drug, from the Surgical-Dental Drug Products Division. The decision to move these drugs into Pilot Drug was due in part to Dr. Peck's unpleasant experience during his first testimony to Congress as Director of CDER. Dr. Peck was questioned about an anesthetic drug whose dose had been

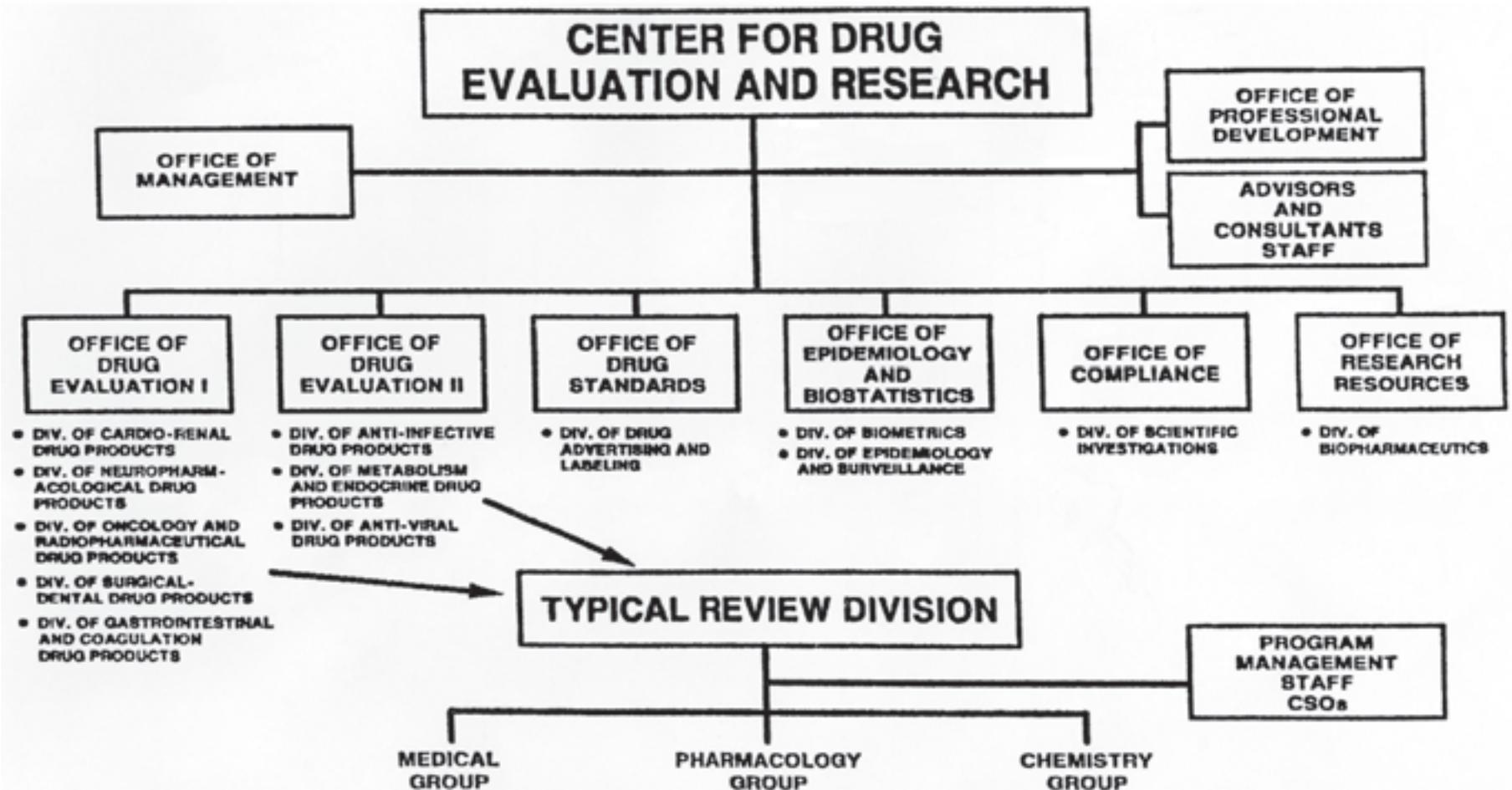
⁷⁴¹ 1) Cardio-Renal, 2) Gastrointestinal and Coagulation, 3) Anti-Virals, 4) Anti-Infective, 5) Metabolism and Endocrine, 6) Neuropharmacologic, 7) Surgical and Dental, 8) Oncology/Radiopharmaceutical. The review of OTC Drugs and Generic Drugs were Divisions in different Offices.

⁷⁴²The Deputy Commissioner to whom Dr. Peck reported was Dr. Jane Henney, current Commissioner of FDA.

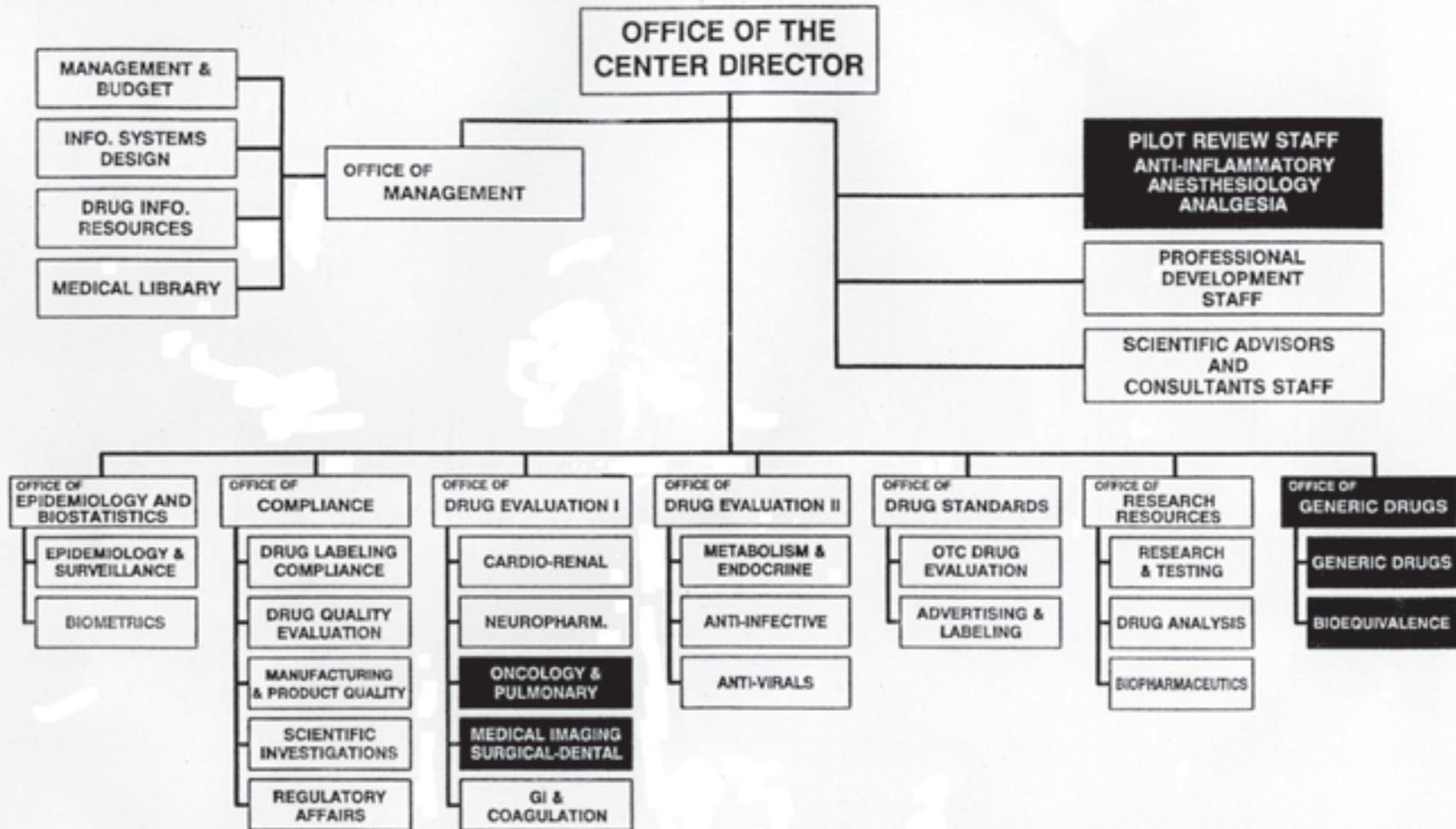
⁷⁴³personal communication, Ms. Tyson, February 23, 1999.

⁷⁴⁴1) Cardio-Renal, 2) Gastrointestinal and Coagulation, 3) Anti-Virals, 4) Anti-Infective,5) Metabolism and Endocrine, 6) Neuropharmacologic, 7) Medical Imaging and Surgical and Dental, 8) Oncology and Pulmonary, 9) Pilot Drug Evaluation Staff. A 10th review Division, Topical Drug Products, was added before May 1995.

ORGANIZATIONS CONCERNED WITH NDA REVIEW



CENTER FOR DRUG EVALUATION AND RESEARCH



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set too high, as a result causing several patients to die. Dr. Peck had to defend the agency when he considered it outrageous that the FDA's medical reviewers hadn't paid sufficient attention to pharmacokinetic and pharmacodynamic (PK/PD) data that would have offered clues that such adverse reactions might occur.⁷⁴⁵ Dr. Peck was also concerned that the review of another anesthetic drug then under review had been recycled back and forth three times between FDA and the sponsor.⁷⁴⁶ In addition, Dr. Peck was aware that FDA's Anesthetics Advisory Committee had several members who were familiar with PK/PD data. Since one of the purposes of Pilot Drug was to give greater emphasis to the use of PK/PD data in the review process, the review of anesthetic drugs was also moved into Pilot Drug. According to Ms. Tyson, Dr. Peck commented to Dr. Harter that, "It looks like this would be a class of drugs that we could have fun with."⁷⁴⁷

The review of analgesic drugs was moved to the new division from the Division of Neuropharmacologic Drug Products, directed by Dr. Leber. Also moved to Dr. Harter's new division from Neuropharmacologic Drug Products was the drug abuse function, which entailed reviewing the development of drugs for the treatment of drug abuse as well any other research conducted with drugs of abuse, defined as all drugs placed in Schedule I of the Controlled Substances Act, including the psychedelics and marijuana.⁷⁴⁸

Dr. Peck reported that the decision to move the review of Schedule 1 drugs from Dr. Leber's Division to Pilot Drug was Dr. Harter's idea. Ms. Tyson reported that the decision was a shared idea.⁷⁴⁹ According to Ms. Tyson, NIDA's Dr. Charles Grudzinkas had been complaining to Dr. Peck that Dr. Leber was unnecessarily putting Clinical Holds on protocols for drugs that NIDA wanted to research for potential use in the treatment of drug abuse, and was holding up the approval of LAAM, a long-acting methadone that NIDA had been wanting to develop for an extremely long time. Though Dr. Leber had been placing Clinical Holds on psychedelic research for many years, that did not seem to be an issue of concern to Dr. Peck, probably because complaints from researchers or proponents had not come to his attention.⁷⁵⁰

⁷⁴⁵personal communication, Ms. Tyson, February 23, 1999. The drug in question was Versed (midazolam hydrochloride).

⁷⁴⁶personal communication, Ms. Tyson, February 23, 1999.

⁷⁴⁷personal communication, Ms. Tyson, February 23, 1999.

⁷⁴⁸Staff. *Pharma Manufac Assoc Newslet*(April 3, 1989): 1.

⁷⁴⁹personal communication, Ms. Tyson, February 23, 1999.

⁷⁵⁰On February 11, 1987, prior to Dr. Peck's arrival at FDA, this author sent a letter to Dr. Robert Windom, the Assistant Secretary of Health, requesting a reversal of Dr. Leber's placement of a Clinical Hold on an MDMA single-patient protocol in a woman with severe treatment resistant unipolar depression. The rationale was based on the lack of available alternative treatments (ECT had been tried twice and failed, as had all available prescription medications), the devastating consequences of the illness, and the anecdotal evidence and case reports from before MDMA was criminalized suggesting a favorable risk/benefit ratio for

The Neuropharmacologic Drug Products' lack of active interest in the review of drugs of abuse had come to Dr. Peck's attention as a result of an HHS-wide comprehensive review of all advisory committees being conducted by the Secretary of HHS. As a result of this review, the Secretary's office noted that the Neuropharmacologic Drug Products' Drug Abuse Advisory Committee hadn't met in 4 years. Consequently, Dr. Peck was asked to determine whether or not the Drug Abuse Advisory Committee should be disbanded.⁷⁵¹

The Neuropharmacologic Drug Products' resistance to and lack of interest in research with drugs of abuse was apparent to both Dr. Peck and Dr. Harter. The decision to move the review of drugs of abuse to Pilot Drug was a result of Dr. Harter's willingness to accept responsibility for problem areas, combined with his desire to expand the number of drugs/protocols under his review so that he would have more opportunities to test innovative approaches.

There is nothing to suggest that Dr. Harter's decision had anything whatsoever to do with any particular or longstanding interest in the regulation of psychedelic drugs or marijuana. These drugs were not actively being researched and it was extremely unlikely that one or more of them would become the subject of a drug development effort capable of turning them into FDA-approved prescription medicines.

According to Dr. Peck, Dr. Leber seemed glad to be rid of the Schedule I drugs. Dr. Leber confirmed that he didn't mind relinquishing the review of analgesics (mostly in Schedule II) and Schedule I drugs, and was "happy to get rid of it."⁷⁵² The stated purpose of the move was to consolidate controlled substances in one place, which made sense to Dr. Leber. According to Ms. Tyson, the public rationale for the shift of the drug abuse function as well as the review of analgesics from Dr. Leber to Dr. Harter was that there was a value in consolidating in one place the review of all substances with a high potential for abuse including the narcotic analgesics that were scheduled as prescription medicines. However, this public rationale was supplemented by an internal rationale, that being that "people were grumbling about Leber's review of these drugs."⁷⁵³

Mr. Meyer wasn't sure why Dr. Harter wanted to take the drug abuse function from Dr. Leber but said that "Dr. Harter was aggressive in trying to expand his authority."⁷⁵⁴

the use of MDMA in patients with anxiety and depression. In his March 18, 1987 response, Dr. Windom supported Dr. Leber's decision to place the protocol on Clinical Hold, commenting, "Available data suggests that MDMA could pose a real and substantial risk where structural brain damage already exists... Additional animal data must be obtained before it would be reasonable to permit its experimental use in humans...until the safety issue is resolved, experimental use of MDMA in humans must be deferred." The patient (this author's grandmother) eventually refused to eat, had to be hospitalized in order to be force-fed, and died without her physicians being permitted the opportunity to administer MDMA.

⁷⁵¹personal communication, Ms. Tyson, February 23, 1999.

⁷⁵²personal communication, Dr. Leber, March 5, 1999.

⁷⁵³personal communication, Ms. Tyson, March 17, 1999.

He thought that Dr. Leber was probably glad to get rid of it since, “Dr. Leber saw that the political element was involved, not just science.” Mr. Meyer didn’t think that the primary reason for transferring the drug abuse function from Dr. Leber to Dr. Harter was dissatisfaction with Dr. Leber’s review of scheduled drugs. He reported that FDA officials were not that concerned about the number of Clinical Holds in Dr. Leber’s Division and remarked, “I still don’t know whether NIDA concerns over the holdup on LAAM had anything to do with it.”

From Dr. Leber’s perspective, there was no love lost between himself and NIDA. He remarked “LAAM is the biggest joke of all time. LAAM was a failure. It took so long to develop since NIDA was incompetent for many years.”⁷⁵⁵ As for LSD research, he felt that “Research with LSD from one long-running team [Dr. Kurland’s group at Spring Grove] was just an excuse to give people LSD. 1200 people got LSD but no data resulted, just testimonials and beliefs.” While this was Dr. Leber’s opinion, a review of the literature indicates that Dr. Kurland’s group published 19 papers in peer-reviewed journals over the years.⁷⁵⁶ Dr. Leber remarked that, “If I had the power, I would have put the doctor in charge in jail. INDs should be approved to investigate, not just to give drugs to people.” Dr. Leber’s attitudes toward psychedelic research didn’t seem to stem from a puritanical view of drugs of abuse. He stated, “If it were up to me, heroin would be widely available... Medical marijuana should be rigorously tested, and we should get the moralistic bull out of it.”⁷⁵⁷

About a year after Pilot Drug was created, very strong support for its existence came from NIDA, from its Medications Development Division (MDD). MDD was created by Congress in 1988 with a mission to foster the development of new medications to treat addiction.⁷⁵⁸ MDD became operational in 1990 with Dr. Charles Grudzinkas as its first Director.⁷⁵⁹ MDD needed a close working relationship with FDA to conduct human studies to evaluate promising drugs, some of which were useful in the treatment of addiction but also had significant abuse potential, such as LAAM. Dr. Peck reported that it was a “lucky stroke for NIDA that Pilot Drug existed.”⁷⁶⁰

⁷⁵⁴personal communication, Mr. Meyers, March 16, 1999.

⁷⁵⁵personal communication, Dr. Leber, March 5, 1999.

⁷⁵⁶The Yensen, Dryer (1992) review of the published literature that emerged from Spring Grove lists 19 publications in peer-reviewed journals.

⁷⁵⁷personal communication, Dr. Leber, March 5, 1999.

⁷⁵⁸Anti-Drug Abuse Act of 1988. 100 P.L. 690; 102 Stat. 4181. November 18, 1988.

⁷⁵⁹Fulco C. Liverman C, Earley L (eds.) *Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector*. Washington, DC: Institute of Medicine, National Academy Press, 1995: 2.

⁷⁶⁰personal communication, Dr. Peck, February 22, 1999.

By the time Pilot Drug was formally established, its portfolio included the 4 A's, anesthetics, anti-inflammatories, analgesics, and abused drugs, all drugs that needed an innovative approach. As a result of this broad set of responsibilities, Pilot Drug became the only review unit within FDA that had three affiliated advisory committees, the management of which was a burdensome process that required substantial amounts of staff time.⁷⁶¹ Ms. Tyson cautioned Dr. Harter that Pilot Drug could become a lightning rod for many of FDA's problem areas, but Dr. Harter's response was, "We'll handle it."⁷⁶²

Pilot Drug's Organizational Autonomy

Dr. Peck wanted to keep in close touch with the new division, to give it an additional measure of autonomy and protection. Therefore, Dr. Peck pulled Dr. Harter's Division out from under Office of Drug Evaluation I, whose director was Dr. Temple, and arranged for Dr. Harter to report directly to him, thus bypassing Dr. Temple. Dr. Harter became the only Division Director who reported directly to Dr. Peck and not to either the Director of the Office of Drug Evaluation I or the Director of the Office of Drug Evaluation II.

This situation was not enthusiastically welcomed by Dr. Temple. He said it was well known that he resented Dr. Harter, not just for his access but because he considered Dr. Harter to be "a difficult man who had lots of ideas, half of which were good and half were bad."⁷⁶³ According to Dr. Temple, his role was to support that half of Dr. Harter's ideas that were good and suppress the other half. He felt that his efforts to suppress the half of Dr. Harter's ideas that he considered bad explained why Dr. Harter didn't want to work under him.⁷⁶⁴ According to Ms. Tyson, Dr. Harter greatly valued Dr. Temple's expertise and input, appreciated his perspective, and wasn't actively trying to get out from under his authority. She attributed Pilot Drug's location within CDER to Dr. Peck's desire to send a signal that he valued innovation. She reported that Dr. Temple felt a certain sense of betrayal by Dr. Harter that several classes of drugs had been removed from his sign-off authority.⁷⁶⁵

Mr. Meyer confirmed that Dr. Harter and his new division were resented within FDA. Mr. Meyer noted that Dr. Temple was upset since some authority to sign off on the approval of certain drugs was removed from his jurisdiction. Mr. Meyer said, "Dr. Temple thought that Dr. Harter needed supervision... Dr. Peck decided that Dr. Harter's ideas needed an honest try."

Dr. Leber, who lost some of his portfolio to Dr. Harter, was also not enthusiastic about Dr. Harter or his new Division. Though Dr. Leber claimed to be "happy to get rid

⁷⁶¹personal communication, Ms. Tyson, February 23, 1999.

⁷⁶²personal communication, Ms. Tyson, February 23, 1999.

⁷⁶³personal communication, Dr. Temple, March 18, 1999.

⁷⁶⁴personal communication, Dr. Temple, March 18, 1999.

⁷⁶⁵personal communication, Ms. Tyson, February 23, 1999.

of” his responsibility for reviewing narcotic analgesics and Schedule I drugs, he wasn’t pleased to see the creation of the new division. In his view, Pilot Drug was a political creation established by Dr. Peck as a political sop to the pressure to expedite drug review, and as a personal favor to Dr. Harter, who helped him get his job as Director of CDER. Dr. Leber felt that Dr. Harter was never that successful politically within FDA but since he had helped Dr. Peck get his job, he was given a plum because Dr. Peck came in owing him something.⁷⁶⁶

Pilot Drug-Staffing

Dr. Harter decided not to request authority to select staff from other Divisions but chose to accept only volunteers, mindful both that the innovations he had in mind would require a willingness to experiment and also that there could be long-term career implications for those people who did decide to join with him in the effort to remake the FDA from the inside out. As it turned out, Dr. Harter was able to attract some talented and highly motivated staff who volunteered to be a part of the Pilot Drug experiment.

Surviving Leadership Change

In early December 1990, a year and five months after Pilot Drug was established, FDA Commissioner Frank Young resigned. President Bush subsequently appointed Dr. David Kessler as FDA Commissioner. Though Dr. Kessler did not have a hand in the creation of Pilot Drug or in the appointment of Dr. Peck as Director of the Center for Drug Evaluation and Research (CDER), Dr. Kessler seemingly welcomed both the existence of Pilot Drug and the leadership of Dr. Peck. In a December 11, 1990 speech to the Food and Drug Law Institute after he had been at FDA for about one week, Dr. Kessler remarked, “I am confident that Dr. Peck and his team will develop the structure and systems - and management - so that we can continue to reduce the time required for new drug development and review.”⁷⁶⁷

In a February 1991 interview at the mid-point of his tenure at FDA, Dr. Peck expressed his goals by noting, “My deputy, Gerald Meyer, and I are committed during our term at the FDA to two basic goals. One is to improve the review process, to make it more efficient. The second is to further improve the quality of the drugs that get approved. It’s one of the great shocks of my career, after three years at FDA, to have to say that I think as a whole the level of efficiency in drug development is pitiful. When we review NDAs, we ordinarily have to sift through many unnecessary pieces of data -- data derived from clinical trials that have failed to contribute to either the development process or to regulatory review.”^{768 769}

⁷⁶⁶personal communication, Dr. Leber, March 5, 1999.

⁷⁶⁷Kessler D. Commissioner of Food and Drug Administration. Speech to Food and Drug Institute, December 11, 1990. <http://www.fda.gov/bbs/topics/SPEECH/SPE00021.htm>

The Role of the FDA- Two Different Visions

Ms. Tyson remarked that Dr. Harter had the philosophy that “any drug can be approved, with proper labeling.” She reported that Dr. Harter felt that the ultimate decision to use a drug should be left up to the doctor and the patient.⁷⁷⁰ Ms. Tyson explained that Dr. Harter realized that when FDA reviews data, it looks at aggregate data. He knew that due to the idiosyncratic nature of individual responses to drugs, some subpopulations will respond well to a drug while other subpopulations will not. He also knew that frequently it is not possible to identify these subpopulations ahead of time. As a result, each individual patient needs to experiment on him or herself to learn what works and what doesn’t. Dr. Harter felt that the challenge to the FDA was to figure out a way to communicate information effectively so physicians and perhaps even their patients could make proper judgements about which medications to take. As an example, Dr. Harter thought that FDA should require more information about kinetics and metabolism on drug labels.

Ms. Tyson noted that Dr. Temple had the opposite view of FDA’s role. She reported that Dr. Temple thought that the FDA had an obligation to make risk/benefit evaluations for the general public as well as for physicians, who generally don’t have proper training, time, access to information, or experience to evaluate the data and make an adequate judgement as to whether or not to use a specific drug in a specific individual at a specific time.

Pilot Drug- Dr. Harter’s Four Principles

After spending more than 15 years as a primary reviewer of clinical trials, Dr. Harter felt that he had several core ideas that could expedite the review process at no loss of quality, all the while staying within the resource constraints faced by the FDA. Dr. Harter formulated four core principles and worked from them to design Pilot Drug’s organizational structures and policies. He described them as follows:

- 1) Devolution of Authority - The primary reviewers had insights into the NDA approval process which the managers did not have and therefore they could improve the process, if they could be provided the opportunity.
- 2) Regulatory Research - The NDA approval process would benefit from encouraging Regulatory Research [the study of internal FDA processes] and the

⁷⁶⁸Staff. Keep your NDAs 'lean' to cut drug development time. *Med Market Media* 26 (February 1991) 2:34.

⁷⁶⁹Meyer G. CDER’s Organizational Changes. *Food Drug Law J* 48 (1993) 1:43-46.

⁷⁷⁰For an excellent analysis of an alternative conception of the role of FDA as a provider of reliable information to the public in the context of a consumer choice, free access model, see Gieringer D. *Consumer Choice and FDA Drug Regulation*. Dissertation submitted to the Department of Engineering-Economic Systems. Stanford University. May 1984. See also Higgs R. (ed.) *Hazardous to our Health- FDA Regulation of Health Care Products*. Oakland: The Independent Institute, 1995.

more academic environment it could create for reviewers.

3) The Interactive Approach - The “review and recycle until it is approvable” mode (R&R mode) that underlies the traditional processes is responsible for much of the inefficiency that FDA contributes to the process and is the leading cause of FDA’s contribution to “unnecessary delays” in the process.

4) FDA Involvement at IND Stage - Reviewers, their peers and their company counterparts need to have detected and resolved during the IND process any problems in the NDA which would prevent approval.⁷⁷¹

Principle #1- Devolution of Authority

Dr. Harter ‘s first principle was that there were benefits to be had by empowering primary reviewers. This principle was based on his diagnosis that FDA review time was substantially slowed by the multiple layers of review that needed to take place before all levels of the FDA hierarchy had signed off on the approval of an NDA.⁷⁷² While such redundancy was meant to enhance safety, Dr. Harter felt that several layers of review could be excised from the process, with the devolution of authority producing no loss in the quality of the review while generating substantial benefits in reducing review time.

In an effort to support Dr. Harter’s attempt to eliminate layers of review, Dr. Peck initially took for himself the final sign-off on drugs approved by the Pilot Division, eliminating one layer of review that would have previously taken place in an Office of Drug Evaluation.⁷⁷³ On December 17, 1990, Pilot Drug obtained Federal Register Delegation of Authority to approve NDAs, with the authority delegated all the way down to the supervisory medical officers. The statement read in part, “Inclusions in the delegations of authority listed below will provide the Pilot Drug director with signatory authority for drug evaluation and regulatory activities; it will also provide signatory authority on particular decisions to supervisory consumer safety officers, supervisory medical officers, and other

⁷⁷¹Founders Commentary. *Pilot Drug Evaluation Staff, Internal Assessment, June 1989-December 1992, The 007 Experiment-An Approach to Change.* February 25, 1993. This unpublished document was written by PDES staff, when the long-term fate of PDES was already uncertain. The document was both a review of PDES’ accomplishments and a proposal for its expansion. The founders’ commentary is written by Dr. Harter while the rest of the document is a collective effort which he choose not to edit. Dr. Patricia Love, currently Director of the Division of Medical Imaging and Radiopharmaceutical Drug Products, was one of the primary authors of the document. A Freedom Of Information Act request seeking any internal FDA documents discussing and/or evaluating Pilot Drug resulted in a April 5, 1999 letter (in response to File:F99-1830) saying that no such documents could be found. Fortunately, as result of my interviews, I learned that just such a document did exist. I was able to obtain a copy from Ms. Tyson and have found it to be an invaluable resource.

⁷⁷²Harter J. New Drug Approval—It’s a Whole New Ballgame. *Regulat Affair Prof Soc (RAPS) News* 1 (March 1993): 23-24.

⁷⁷³Staff. Pilot Drug Review Division. *FDA Press Release* April 20, 1989.

supervisory reviewers in Pilot Drug.”⁷⁷⁴ This devolution of authority was unprecedented at FDA.⁷⁷⁵

Still, as Ms. Tyson pointed out, Dr. Harter valued Dr. Temple’s data analysis expertise and also wanted to retain some form of senior level management review so that the quality of the review would remain high. In order to ensure that senior management had the opportunity to challenge any aspects of Pilot Drug’s review, thus sharing expertise and improving quality, Dr. Harter asked Dr. Temple, Dr. Peck and others to participate as consultants in Pilot Drug reviews. Dr. Harter wanted Dr. Temple’s participation primarily to retain the benefit of his expertise in a more efficient manner but also so that Dr. Temple could “maintain his turf” somewhat through his participation in the review process.⁷⁷⁶

In addition to expediting the review process, the devolution of authority stimulated the review team to take ownership of their work product. Dr. Harter instituted a policy whereby each member of the review team was required to sign the NDA review letter that approved the NDA. These letters were known as the summary basis of approval-(SBA letters). Initially, some Pilot Drug staff were nervous about this policy. They worried about the possibility of personal legal liability for their decisions and felt a heavier burden of responsibility as a result of having to sign their name on the official document. Over time, Pilot Drug staff took great pride in being able to sign the SBA letters, creating the sense of personal ownership that Dr. Harter had sought to engender.⁷⁷⁷

Within Pilot Drug, Dr. Harter concentrated on creating an entirely new organizational structure that challenged the traditional organizational hierarchy. As with most divisions, Pilot Drug Evaluation Staff was composed of eight different groups: medical, chemistry, pharmacology, pharmacokinetics, statistics, consumer safety officers (liaisons between FDA and the pharmaceutical industry sponsors of the research being reviewed), secretaries and resource coordinators. One crucial decision Dr. Harter made was to refrain from bringing supervisory review personnel into Pilot Drug. Dr. Harter didn’t like the concept of supervisors for professional staff. He observed that within FDA it discouraged the initial review staff from working hard to resolve difficult issues on their own and encouraged the passing of problem issues up to officials at higher levels. Dr. Harter called this dysfunctional process the “dead cat review,” in which lower level staff identified a problem but put no effort into addressing solutions.⁷⁷⁸ Dr. Harter sought to design a system in which it was everybody’s responsibility both to identify problems and also come up with solutions. Dr. Harter felt it essential to change that aspect of FDA culture

⁷⁷⁴Delegations of Authority and Organization; Center for Drug Evaluation and Research (CDER). Final Rule. 55 FR 51687 (December 17, 1990).

⁷⁷⁵Staff. Pilot Drug Staff Now Can Approve Products. *Wash Drug Let* 22 (December 24, 1990): 52.

⁷⁷⁶personal communication, Ms. Tyson, March 17, 1999.

⁷⁷⁷personal communication, Ms. Tyson, February 23, 1999.

⁷⁷⁸personal communication, Ms. Tyson, February 23, 1999.

that let reviewers identify problems as reasons why a drug couldn't be approved instead of focusing on identifying solutions that could lead to the drug becoming approved.

The decision not to hire supervisory review personnel only partially eliminated another layer of review, since some system was still needed to provide oversight to ensure a quality review. In order to design Pilot Drug to be "reviewer managed," Dr. Harter designed a "Peer Reviewer" system in which primary responsibility was assigned to each reviewer to approve their portion of an NDA application, with the primary reviewer's recommendations evaluated by the primary reviewer's peers (both intra- and inter-discipline). This peer-review process promoted collegiality and was intended to generate a final decision through what Dr. Harter called a process of "institutionalization."

This peer review process was systematized with the development of a rotating schedule by which staff moved in and out of the peer reviewer position every three to six months, depending on the number of staff in each group. The peer reviewer had administrative functions such as "triage of duty assignments; critiques of members' work and related duties; leave approval, coordination of discipline meetings, etc...responsibility in developing a consensus."⁷⁷⁹

This rotating process provided an unusual opportunity for staff development, since the skills required to be an effective peer reviewer were different than those required to be a primary reviewer. The volunteer nature of Pilot Drug, which attracted the kind of people who wanted to experience this sort of work environment, helped to make this structure work, but also limited the generalizability of the organizational structure across an entire agency like the Food and Drug Administration. As Ms. Tyson pointed out, "one difficulty and opportunity with NDA Days [another Harter innovation, discussed in more detail later] was that staff reviewers needed to present the results of their reviews in public with senior management in attendance. This could make some staff very nervous. Some had never had to make a public presentation and defend it publicly in real time. This was a career development opportunity but was also difficult for some people."⁷⁸⁰

The goals of this cross training included greater organizational flexibility and enhanced morale due to the greater variety of tasks and job security that comes with the development of multiple skill sets. The weaknesses of this approach included higher staff development costs and the loss of some of the benefits of specialization.

The Federal Register Delegation of Authority to approve new drugs down to the reviewer level lent a sense of ownership to the peer reviewer system, since power actually had been devolved to those staff conducting the primary, secondary and tertiary reviews. In order for this fluid system to remain coherent and focused on quality, certain internal controls needed to be maintained. These controls were primarily the emphasis on team decisions, group collaboration, and voluntary and standing committees. Ms. Madeline Van

⁷⁷⁹*Pilot Drug Evaluation Staff, Internal Assessment, June 1989-December 1992, The 007 Experiment-An Approach to Change.* February 25, 1993: 25.

⁷⁸⁰personal communication, Ms. Tyson, March 17, 1999.

Hoose, a Pilot Drug staff member who left Pilot Drug to work in FDA's Office of the Commissioner developing project management systems, reported that Dr. Harter's establishment of consensus management and decisions did not mean that everyone agreed with each decision, but that everyone agreed not to obstruct the decisions that were made.⁷⁸¹

As described in the self-assessment document prepared by Pilot Drug in February 1993, the Staff was a "self-regulating, (macro and micro, bottom-up and top-down) work process. This system functions through a matrix of peers (all members of the division) who are responsible for not only identifying but also solving problems. There are ad hoc committees, voluntary fixed committees, a rotating peer review position for each discipline and other responsibilities which are used to develop an issue consensus."⁷⁸²

The matrix concept refers to the organizational structure in which staff assume different formal roles at designated times, and can also use informal authority more easily in a flexible environment. The web of relations between the staff members was more complex and more multi-faceted than in a traditional organizational hierarchy. In 1994, the Office of Personnel Management "cited that Division [Pilot Drug] as being the first self-directed, team-based matrix organization established in the Metropolitan Washington, DC area."⁷⁸³

However, as noted by Dr. Temple, a meritocracy emerged even within this context, with some review staff growing to feel and be recognized as more able than others in their ability to review their peers' work. The concept of secondary and tertiary reviewers developed, with these secondary and tertiary reviewers sometimes being distinct from the rotational review leader. Dr. Temple thought that there was less than met the eye in the matrix concept, since the elimination of the titles didn't really eliminate the functions and roles. Informal authority was still invested in specific people. For example, Dr. Temple said that Dr. Wright, a medical review officer in Pilot Drug, functioned just as a "group leader" would in other Divisions, in a formal FDA supervisory role. According to Dr. Temple, those outside of Pilot Drug interacted with Dr. Wright as they would with a "group leader" even though he lacked that formal title. Dr. Temple asked, "How did we know? They had defacto supervisors though not in title."

Dr. Temple also commented that the delegation of authority and the flatter organizational structure did not mean that Dr. Harter actually surrendered control and

⁷⁸¹personal communication, Ms. Madeline Van Hoose, March 16, 1999. Ms. Van Hoose is currently working in the Office of the FDA Commissioner, Management Staff.

⁷⁸²*Internal Assessment* (1993): 5.

⁷⁸³Staff. Toy Ping Tara Plans Showcase Exhibit for Women's History Month. *News Along the Pike* (February 25, 1999): 4. Toy Ping Tara was ex-Deputy Director of Pilot Drug Evaluation Staff and, at the time of the article, was FDA Associate Director of Program Evaluation, Office of Clinical Pharmacology and BioPharmaceutics.

authority. He said that from Dr. Harter's perspective, "if everybody is in charge, then I'm in charge...The idea that he was giving up control was a fiction." Mr. Meyer expressed a similar sentiment, and said that Dr. Harter's idea of interactive was, "You listen and I'll preach."⁷⁸⁴

Whether the management controls that Dr. Harter established were sufficient was questioned by Dr. Temple. He remarked that rotating sign-off wasn't wise since "experience counts, and not everybody is equally capable." Dr. Temple thinks that routing NDAs through multiple layers of review is the best way to protect public health. He acknowledged that Pilot Drug's peer review process involved designated secondary and tertiary reviewers, which provided checks on quality, but still wondered if the secondary and tertiary reviewers really had time to read the voluminous reports, or were as qualified to read them as supervisory personnel who specialize in such reviews.

Dr. Harter also instituted a system of both individual project planning and what he called "strategic synchronization across project planning." These processes were designed to identify staffing needs and critical decision points. Dr. Harter brought in Ms. Van Hoose to help develop what she called "resource management, project management, or portfolio management."⁷⁸⁵ According to Ms. Van Hoose, project management at its simplest is just critical path scheduling. Pilot Drug did sophisticated project management not limited to monitoring the review process but also looking for bottlenecks, making and revising work assignments and finding ways to innovate and make the process move faster and on schedule. Project Manager even became a specified career option, giving Consumer Safety Officers, (CSOs, the old name for the people who were the link between the FDA review staff and the pharmaceutical sponsors and researchers) an option to move up in the bureaucracy to become project managers.⁷⁸⁶ Ms. Van Hoose felt that she was initially resented by CSOs who thought she was trying to do their job, when she felt that she was actually trying to help them do their jobs "better, easier, and faster." While project management had been used in industry for quite some time, Dr. Harter helped introduce it into the FDA and became a major proponent of the technique.

Dr. Temple commented that the entire FDA has moved toward a more formal emphasis on team reviews and the team concept. He thought that some of the innovations in Pilot Drug may have foreshadowed subsequent FDA procedures and policies that are now much more explicit.

Not to be underemphasized was the role that Dr. Harter played in being available when needed for consultation and direction. Though he tried to be a hands-off director and let the staff make their own decisions and work through problems on their own, he was a

⁷⁸⁴personal communication, Mr. Meyers, March 16, 1999.

⁷⁸⁵personal communication, Ms. Van Hoose, March 16, 1999.

⁷⁸⁶For information on the institutionalization of the project manager position within FDA, see Yager J, Kallgren D. Roles of Regulatory Project Managers in the U.S. Food and Drug Administration's Center for Drug Evaluation and Research. *Drug Info J* 34 (2000) 1:289-293.

reassuring presence. The success of such an anti-hierarchical office environment probably depends in large part on a rare mix of capabilities in the person at the top of the hierarchy, another factor that calls into question the replicability of this organizational model throughout an entire agency.

Principle # 2-Regulatory Research

Dr. Harter sought to reward staff members who thought clearly and creatively about the review processes they were engaged in, a reward system he felt the traditional FDA review Divisions made difficult. These rewards were expressed in budgeting time for evaluating process and outcomes, writing papers, and giving speeches, all aimed at organizational learning - a rarity in bureaucratic environments. Dr. Harter possessed the ability to make innovation safe, reward risk-taking, and encourage experimentation.

Pilot Drug's Internal Assessment document is itself one example of the regulatory research that Dr. Harter prioritized. He wrote, "Any change in a process as fundamental as those involved in this experiment takes time to show any promise, usually operates in a hostile environment and only gets four-five years until "judgement day." It is for this latter reason that I have encouraged the division this year to evaluate the experiment from its inception rather than to simply do an annual report." Dr. Harter's mention of the time period of four-five years until judgement day coincides with the time commitment that he knew Dr. Peck had made when accepting the job as CDER Director.

Within the Internal Assessment, the staff reported that they collectively held/produced 13 Advisory Committee meetings, 13 abstracts/posters, five published articles,^{787 788 789} two published, invited book chapters, and 63 invited speeches and panel participations at major scientific or regulatory meetings. Drs. Harter and Peck even published some papers together.^{790 791} According to Dr. Temple, Dr. Harter was successful in getting people to write scientific papers and give presentations and talks.

Ms. Van Hoose said Dr. Harter "brought out the best in people." He was opinionated but brilliant, a good debater "in a class with Dr. Temple." Another enthusiastic opinion of Dr. Harter was offered by Dr. Dan Spyker, a medical review officer who

⁷⁸⁷Katz L. NDA Days. *Reg Affairs*3 (1991): 209-216.

⁷⁸⁸Owens M. NDA Days- An update. *Reg Affairs*3 (1991): 217-222.

⁷⁸⁹Yee J. NDA Days. Presentation at the 14th annual meeting of the Regulatory Affairs Professional Society. October 16, 1990.

⁷⁹⁰Harter J, Peck C. Chronobiology. Suggestions for integrating it into drug development. *Ann NY Acad Sci* 618 (1991): 563-71.

⁷⁹¹Peck C, Barr W, Benet L, Collins J, Desjardins R, Furst D, Harter J, Levy G, Ludden T, Rodman J, et al. Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. *Clin Pharmacol Ther*51 (April 1992) 4:465-73. Also published in *J Pharm Sci* 81(June 1992) 6:605-10 and in *Pharm Res* 9 (June 1992) 6:826-33 and in *J Clin Pharmacol*34 (Feb 1994) 2:111-9.

worked in Pilot Drug.⁷⁹² Dr. Spyker reported that he loved working for Dr. Harter, who created a family atmosphere among the people who worked for him. Dr. Spyker thought Dr. Harter was inspiringly devoted.⁷⁹³ Still, Dr. Spyker understood how others outside the FDA and inside could dislike Dr. Harter, who he thought probably generated more complaints from industry than other division directors. Dr. Spyker estimated that if the standard rate of complaints for FDA Division Directors was 10% of customers, that Dr. Harter was probably at 30%, due to his sometimes arbitrary and authoritarian methods and his willingness to be direct and stir things up. Dr. Spyker characterized Dr. Harter as “born out of the box,” a novel, innovative thinker, who was also “data driven and driven by data,” motivated to think a lot about how to understand and present data. According to Dr. Spyker, Dr. Harter’s actions were always in service to what he thought was best for public health.⁷⁹⁴

Principle # 3- The Interactive Approach

Dr. Harter called the traditional FDA process the R& R mode, review and recycle. FDA review staff evaluate data from a pharmaceutical company, send questions and comments back to the company, then wait for a response, repeating the process through numerous iterations. Dr. Harter’s alternative approach called for FDA reviewers to engage in shared problem-solving, in an “interactive” process between FDA reviewers, the applicant (pharmaceutical company or other sponsor), and the reviewers’ peer reviewers.^{795 796} The goal of the interactive process was to focus on what “can and should be done to make an application approvable.” This approach sees the FDA and the pharmaceutical industry as partners in the drug development process and represents a major change from what some FDA reviewers considered to be their mission – to establish high hurdles and watch to see if their opponent, the pharmaceutical industry, could surmount them. Dr. Harter thought that within FDA he was situated on one pole of this dynamic and that Dr. Leber was situated at the other end.⁷⁹⁷

In a variety of ways since Pilot Drug was established, the FDA has explicitly been moving toward an increasingly interactive approach, especially in the development of a formalized process for requesting and scheduling FDA/sponsor meetings. These meetings have been subjected to evaluation and have been determined to expedite the drug review

⁷⁹²Dr. Spyker left Pilot Drug to work in the Center for Devices and Radiological Health, then left for private industry in 1999.

⁷⁹³personal communication, Dr. Dan Spyker, February 22, 1999.

⁷⁹⁴personal communication, Dr. Spyker, February 22, 1999.

⁷⁹⁵Staff. The Pilot Drug Evaluation Staff’s “Interactive” Review Processes. *US Reg Reporter*10 (May 1994) 11:1-5.

⁷⁹⁶Miller L, Buckley J. The Interactive IND/NDA. *Drug Info J* 30 (1996) 3:593-600.

⁷⁹⁷personal communication, Dr. Harter, April 1991.

process.⁷⁹⁸ In order to improve the drug development process, the FDA Modernization Act of 1997 mandated meetings between sponsor and FDA and an interactive approach, processes quite similar to some of the innovations “pilot tested” at Pilot Drug.⁷⁹⁹

The interactive approach is as much an attitude of mutual cooperation as it is a formalized series of meetings between FDA and the sponsor. According to Dr. Spyker, the main innovation of Pilot Drug was the interactive way that the Division and the pharmaceutical drug company sponsors related to each other. This spirit of collaboration was the essence of Dr. Harter’s style (though he could still act independently and arbitrarily). From Ms. Tyson’s perspective as Dr. Harter’s wife and Dr. Peck’s assistant, one of the most important things that was new at 007 about its interactive approach was that it reviewed data from protocols on an individual basis, and would review new studies on the basis of data from previous studies with the same drug. The use of newly gathered information to update and revise prior choices offered the opportunity to introduce Bayesian efficiencies into the drug testing process. The old interactive approach was simply to discuss with industry good protocol design and a general approach to drug development. It did not involve the use of data analysis from prior studies as a guide to the design of subsequent protocols and to the modification of the overall drug development strategy.

One justification for the old interactive approach, in which drug companies were left to decide how to design their own studies without much FDA input, was the concern that if FDA helped with the design of studies, it then ended up reviewing its own proposed designs, creating a conflict of interest in a sense. In the new interactive approach, the conception of FDA’s role was expanded to include giving companies guidance about what studies to conduct, with the focus shifting to the objective review of whatever data was gathered from well-designed studies.⁸⁰⁰ Pilot Drug pioneered the process of not just offering the opportunity to companies to discuss protocols but proactively contacting industry after studies to reevaluate the overall clinical plan and come up with the most efficient next steps.

Interactive Approach at the NDA Stage

⁷⁹⁸DiMasi J, Manocchia M. Initiatives to speed new drug development and regulatory review: the impact of FDA-sponsor conferences. *Drug Info J* 31 (1997) 3:71-88.

⁷⁹⁹Sec. 119, Food and Drug Administration Modernization Act of 1997. 105 P.L. 115; 111 Stat. 2296; November 21, 1997.

⁸⁰⁰FDA now offers a comprehensive set of written guidances on the design of protocols for virtually all clinical indications, as well as guidances on most interactions that sponsors will need to have with FDA. see <http://www.fda.gov/cder/guidance/index.htm> According to the statement on the FDA web site, “Guidance documents represent the Agency’s current thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office.”

Dr. Wright commented that the "rolling" NDA or interactive NDA, which was also developed by Pilot Drug, refers to a situation whereby FDA reviews independent pieces of an NDA without waiting for the complete package to be submitted. Though he noted that this technique is not currently being practiced within FDA, the concept of heavy interaction of priority reviews is alive and well.⁸⁰¹

The "NDA Day" was started by Dr. Harter in 1988 when he was still Anti-Inflammatory Group Leader in FDA's Oncologic and Radiopharmaceutical Drug Products Division, at a time when the establishment of Pilot Drug was being planned but before it was formally established.⁸⁰² The NDA Day was an early effort to expedite the NDA review process. The idea of the NDA Day was to gather together in person for one long day all FDA staff and industry staff involved in an NDA review process. One goal of the NDA Day process was to make a decision at the end of the day whether or not to approve the drug in question, after real time question and answer sessions. The NDA Day replaced the customary process of formal letters sent back and forth over the course of many months. Another goal of the NDA Day process was to reduce the sense that FDA review of NDA's was a black box with industry unable to divine how FDA made its decisions. During the 1960s and early 1970s, NDA review decisions (SBA reviews) were private, confidential and not even given to the company. When the Freedom of Information Act came into being in 1974, companies were finally able to see SBA reviews.⁸⁰³ NDA Day was one more step to open the black box.

Much work went into preparing for an NDA Day and the outcomes were not preordained. The NDA day concept has been evaluated by outside scholars and found to have been helpful in expediting the review process.⁸⁰⁴ ⁸⁰⁵ The NDA Day has also been favorably reviewed in several trade newsletters.⁸⁰⁶ ⁸⁰⁷ ⁸⁰⁸

Mr. Hutt noted that the NDA Day is not used as much lately since the Prescription Drug User Fee Act of 1992 (PDUFA) established user fees paid by pharmaceutical companies which have allowed FDA to hire more staff.⁸⁰⁹ The increased staffing levels

⁸⁰¹personal communication, Dr. Wright, March 8, 1999.

⁸⁰²Owens M. (1991).

⁸⁰³Freedom of Information Act, Amendment. 93 P.L. 502; 88 Stat. 1561. November 21, 1974.

⁸⁰⁴Kaitin K, Walsh H. (1992).

⁸⁰⁵Miller L. Aboyu-Donia M. Rudd D. Samara B. Schmith V. Huffman C. et al. NDA Day: The Approval of a Neuromuscular Blocking Agent. *J Clin Res Pharmacoevidem*6 (1992): 271-284

⁸⁰⁶Staff. Pilot Drug Review Division: A Profile. *US Reg Repor* (March 1992): 6-8.

⁸⁰⁷Staff. NDA Days Have Been Held By Two FDA Groups Outside of Pilot Drug Evaluation Staff. Pilot Group Convened Six NDA Days in 1990, More Planned. *F-D-C Reports Pinksheet* (October 22, 1990): 14-15.

⁸⁰⁸Staff. NDA Days: Some Divisions Do, Some Don't. *US Reg Report* (August 1991): 3-5.

⁸⁰⁹Prescription Drug User Fee Act of 1992. 102 P.L. 571; 106 Stat. 4491; October 29, 1992. Amended

have sped up drug development by half and lessened the need for NDA Days. But Mr. Hutt believed the NDA Day was a genuine and important innovation at the time.

Another FDA process that Pilot Drug helped to develop was the computer-assisted New Drug Application (CANDA), though the effort had begun before the establishment of Pilot Drug.⁸¹⁰ Dr. Wright noted that while the technology used by Pilot Drug has been rejected, the concept has been accepted.⁸¹¹

Dr. Peck found value in Pilot Drug's decision to reverse the accepted policy of not using Refusal-to-File letters. Refusal-to-File letters are used when FDA rejects an NDA because of serious and substantial omissions in the data that make reviewing the NDA an exercise in frustration and futility. According to Dr. Peck, FDA had a policy under which it retained an option for up to 45 days after a company submitted an NDA to tell the company that it refused to file the NDA due to its being incomplete, confusing, or not convincing.⁸¹² In practice, FDA didn't use this policy and accepted all NDAs. This wasted time on the review of bad NDAs but avoided angering companies, at least at first. According to Dr. Peck, "Companies would spend ten years, conduct 15 or so clinical trials, and would end up with lots of data that sometimes wasn't easy to understand or condense into a clearly defined clinical indication. The company would fill up a semi-truck with paper and send it over to FDA, saying "Maybe they can make some sense of this.""⁸¹³

In the second and third years of Pilot Drug, Dr. Peck and Harter decided to start using FDA's refuse to file powers. In Dr. Harter's enthusiastic way, he proceeded to issue Refusal-to-File letters for a large percentage of the NDAs submitted, generating an intense outcry by companies who then brought pressure to bear on Pilot Drug from the White House, Congress, and HHS. Dr. Peck thought that the end result was an improvement in the quality of NDAs submitted, which helped FDA focus its resources on those NDAs that were most likely to result in drug approval. It also effectively shortened approval time for those NDAs that remained in the system.

Mr. Hutt thought that Pilot Drug's use of the Refusal-to-File letters was a good innovation since it weeded out poor quality, "junk" NDAs earlier in the process. However, Mr. Hutt feels this tactic has been abused by some FDA reviewers who reject NDAs for petty, arbitrary reasons such as data formatting issues. On balance, Mr. Hutt thinks the increased use of the Refusal-to-File letters is a very positive development.

Dr. Peck also pointed out that Pilot Drug pioneered having advisory committees

in 1997 by FDA Modernization Act. 105 P.L. 115; 111 Stat. 2296. November 21, 1997.

⁸¹⁰Kaitin K, Walsh H. (1992).

⁸¹¹For current FDA policies regarding electronic submissions of NDA's as well as INDs and other documents, see Electronic Regulatory Submissions and Review Page.

<http://www.fda.gov/cder/regulatory/ersr/default.htm>

⁸¹²personal communication, Dr. Peck, February 22, 1999.

⁸¹³personal communication, Dr. Peck, February 22, 1999.

more involved in reviewing NDA's. Dr. Peck stated that Dr. Harter thought inclusively and was able to tap into resources that others overlooked. Dr. Temple's perspective was slightly different. He felt that the use of outside reviewers to help with NDA reviews was not new, nor was the use of advisory committee members on reviews, though Pilot Drug used outside reviewers more than had ever been done before. Dr. Temple noted that one review coordinated by PDES was conducted entirely by the advisory committee, which he thought was not a good idea. He felt that the method of review conducted by FDA personnel was of a different sort, better and more thorough than a review done by outside personnel who had other jobs. In Dr. Temple's opinion, a quality review required full time effort. Dr. Temple confessed that even he wasn't able to read all the material for the NDA Days he participated in, and he knew others hadn't either, because they had other responsibilities.

Dr. Temple did see value in Pilot Drug's innovation in the monitoring of reports of adverse drug reactions (ADRs). Reviewing the performance of a drug post-approval is called post-marketing surveillance, and is sometimes formally studied in post-approval studies known as Phase IV studies. Dr. Temple thought that ADR reports weren't monitored that well in most divisions or in epidemiology where they were also routed, and important information was sometimes overlooked. Pilot Drug assigned someone, though not a doctor, to screen the ADR reports and pass on the more important/unusual ones for further review. This person "prioritized" the ADR reports. This expedited evaluation of the ADR reports, reduced backlog, and enhanced public safety, and was thus overall a "good idea."⁸¹⁴ Though Dr. Harter had developed a method that improved upon the evaluation of ADRs once they were submitted to FDA, other solutions would still be required to address the more fundamental problem involved in ensuring that FDA received a good sample of the adverse drug reaction reports.⁸¹⁵

Principle #4- FDA Involvement in the IND Phase

The potential for early interaction between sponsor and FDA to generate substantial savings in time and money is highlighted by Dr. DiMasi's research on drug development

⁸¹⁴FDA's system of monitoring Adverse Drug Reactions (ADRs) relies on voluntary reporting. A December 1999 report from HHS's Office of Inspector General criticized FDA's system and recommended moving to mandatory reporting. see Stolberg, S. Study Finds Faults in Tracing of Drug Reactions. *New York Times*(December 15, 1999): A20. According to Dr. Woodcock (personal communication, Dr. Woodcock, Director, CDER, June 8, 1999), "We have always recognized that this was a problem. We have a fairly serious resource problem in this area, which is why we haven't moved more quickly." Practicing physicians also face resource problems when considering whether to report ADRs, primarily shortage of time.

⁸¹⁵See FDA compliance program discussion, Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations. Guidance to FDA Field Staff. (September 30, 1999).

<http://www.fda.gov/cder/aers/chapter53.htm>

times, which indicate that the IND phase of drug development steadily increased from 1963 to 1992 and represented four-fifths of the drug development process.⁸¹⁶ According to Dr. DiMasi's recent research comparing drugs approved during 1993-1995 with drugs approved from 1996-1998, both time periods after the 1992 passage of the Prescription Drug User Fee Act, (PDUFA) the IND phase of clinical testing has dropped by 18% to 5.9 years and the NDA review time has dropped by 30% to 1.4 years.⁸¹⁷ The IND phase still remains four-fifths of the drug development process, suggesting the importance of looking for increased efficiencies in the IND process.

Dr. Peck thought that a concept called label-driven drug development⁸¹⁸ was one of the most important innovations developed at Pilot Drug. Dr. Peck reported that Harter invented label-driven drug development, in which the sponsor and FDA work together to develop a draft of a proposed label early on in drug development process, then let the label guide and "discipline" protocol development. Label-driven drug development is just one aspect of "project planning," which Pilot Drug enthusiastically helped introduce into FDA. The use of Clinical Plans outlining the entire series of clinical trials that are expected to be conducted is also part of project planning.⁸¹⁹ Dr. Peck observed that the FDA started out behind industry regarding project planning but then raced ahead. This was not solely due to Pilot Drug, but Pilot Drug was among the first to embrace this approach.

Ms. Van Hoose thought that the real institutionalization of project management within FDA took place when Deputy Commissioner Mary Jo Veverka wanted project management to help FDA meet the goals for timely review of NDA's that were set by PDUFA.⁸²⁰ Deputy Commissioner Veverka would have placed this emphasis on project management independently of Pilot Drug efforts, but she looked down into the bureaucracy to see if she could find seeds of it anywhere, found it in Pilot Drug where Ms. Van Hoose was involved in trying to formalize project and resource management within the drug review process. Ms Julie Carlston, who headed up the Management Initiatives Staff under Ms. Veverka brought Ms. Van Hoose to the Commissioners' office to continue her

⁸¹⁶DiMasi J, Seibring M, Lasagna L. (1994).

⁸¹⁷Staff. Clinical Development times for new drugs drop 18%, reversing 12 -yr trend. *Impact Report-Tufts Center for the Study of Drug Development* (July 1999): 1-4.

⁸¹⁸Miller L. Pitfalls in the Drug Approval Process; Dose-Effect, Experimental Design, and Risk-Benefit Issues. *Drug Info J* 26 (1992) 2:251-260.

⁸¹⁹In 1994, Dr. Spyker worked with this author to create a clinical plan to guide the testing of the medical use of marijuana. The Clinical Plan was a helpful tool that promoted strategic thinking and helped with planning and budgeting. Doblin R. A Comprehensive Clinical Plan for the Investigation of Marijuana's Medical Use in the Treatment of the HIV-Related Wasting Syndrome. *Bull MAPS* 5 (Summer 1994) 1:16-18. <http://www.maps.org/news-letters/v05n1/05116cli.html>

⁸²⁰Sec. 102 (3) and Sec. 104, Prescription Drug User Fee Act of 1992. 102 P.L. 571; 106 Stat. 4491; October 29, 1992. See also Wechsler J. Challenging FDA Authority. *Pharmaceu Exec* 14 (1994) 8:18-22.

work. Dr. Temple agreed, saying that “The commitment in Pilot Drug to project management was commendable, and is being replicated throughout FDA, though it is not really due to Pilot Drug. Again foreshadowing but not causing, Pilot Drug was on the right track in this area.”⁸²¹ Project Management was actually started throughout FDA in the early 1970s.⁸²²

Dr. Wright reported that another of the innovations of Pilot Drug was to formalize a policy mandating that when FDA issued a Clinical Hold, it needed to give the investigator a reason why the Hold was placed, along with guidance as to how that Hold could be removed, what studies needed to be conducted or what protocol changes needed to be made. This approach is now practiced by all divisions at FDA.⁸²³ FDA has instituted another policy in which INDs placed on Clinical Hold, some chosen randomly and others by request of the sponsor, are sent for review to a team composed of other division and center level directors, senior managers in CDER and CBER (Center for Biologics Evaluation and Research) and FDA's Chief Mediator and Ombudsman.⁸²⁴ ⁸²⁵ If this policy of reviewing Clinical Holds by senior FDA management had been in place during the 1980s, it might have been possible for some of the MDMA protocols to have been conducted.⁸²⁶

⁸²¹personal communication, Dr. Temple, March 18, 1999.

⁸²²According to Peter Hutt (personal communication, Mr. Hutt, February 28, 2000), FDA's early efforts on project management were directed by Sherwin Gardner and Jake Barkdoll.

⁸²³personal communication, Dr. Wright, March 8, 1999. For more information on Clinical Holds, see Sec. 117 of FDA Modernization Act of 1997.

⁸²⁴Investigational New Drugs; Procedure to Monitor Clinical Hold Process; Meeting of Review Committee and Request for Submissions. 56 FR 49894 (October 2, 1991). The new review policy was proposed as an experiment for several years. The policy was adopted on a permanent basis in Investigational New Drugs; Procedure to Monitor Clinical Hold Process; Meeting of Review Committee and Request for Submissions, 58 FR 32537 (June 10, 1993). See also FDA Guidance for Industry.- Submitting and Reviewing Responses to Clinical Holds. April 1998.

⁸²⁵For information on regulations FDA adopted to make it easier to place clinical holds on drugs being used in expedited access contexts, see Investigational New Drug, Antibiotic, and Biological Product Applications; Clinical Hold and Termination. 57 FR 13244 (April 15, 1992). “Under this rule, FDA may require sponsors to cease distributing an experimental drug in an open, nonconcurrently controlled investigation if any of several specified conditions exist. This final rule is part of the Public Health Services (PHS's) efforts to make promising drugs widely available to people with acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV)-related disease who lack satisfactory alternative therapies, while simultaneously ensuring that the adequate and well-controlled clinical trials essential to establishing a new drug's safety and effectiveness are expeditiously conducted.”

⁸²⁶For additional information on FDA policies regarding dispute resolution, see Formal Dispute Resolution: Appeals Above the Division Level. FDA Guidance for Industry. February 2000.

Not everyone at FDA fully supported the interactive approach, or credited Pilot Drug with making a major contribution to that effort. Dr. Temple pointed out that Pilot Drug did not create the interactive approach. It was first formalized at FDA in 1987, with an end of Phase II conference between FDA review staff and the sponsor of the drug. Since 1987, and really before, companies were able to talk with FDA about overall development plans.⁸²⁷ While Pilot Drug did not develop the interactive approach, Pilot Drug's contribution to the interactive process was the distinction between FDA being willing to meet with sponsors if necessary and FDA proactively meeting with sponsors after every study to review data and help think over the next study.

Dr. Temple was also of the opinion that some interactions are not that valuable, such as the new pre-IND conference mandated by the 1997 FDA Modernization Act.⁸²⁸ Dr. Temple thinks that there is not enough information at that stage with which to evaluate protocol design or drug development strategy. He thinks that FDA isn't supposed to know or impose what the sponsor wants to study – that is the sponsor's business. He prefers sponsors to conduct a Phase I study first in order to get a better idea of what their drug is all about, then work with FDA to create a clinical development plan at a later stage in the drug development process.⁸²⁹

Why was Pilot Drug Eliminated?

Dr. Woodcock, Director of the Center for Drug Evaluation and Research, explained her rationale for dissolving Pilot Drug by noting that FDA is engaged in a complex intellectual endeavor at the limits of scientific knowledge. The inherent difficulty of FDA's mission requires that its scientific reviews be conducted in a clear, consistent and impartial manner. In her view, Pilot Drug had not always upheld this standard and had serious organizational weaknesses in the area of scientific rigor. Dr. Woodcock insisted that she saw the value of Pilot Drug as a laboratory for innovative bureaucratic practices. Nevertheless, she believed that the sacrifice in scientific rigor was not worth the

<http://www.fda.gov/cder/guidance/2740fnl.htm>

⁸²⁷Meyer G. The Food and Drug Administration Perspective on the Importance of Dialogue with Industry. *Drug Info J* 26 (1992): 159-161.

⁸²⁸Sec. 119, FDA Modernization Act of 1997.

⁸²⁹For information on FDA-sponsor conferences before Phase 3 studies, see Special Protocol Assessment. FDA Guidance for Industry, Draft. December 1999. <http://www.fda.gov/cder/guidance/2127dft.htm#I>. According to the Guidance, "Section 119(a) of the Modernization Act amends section 505(b) of the Act (21 U.S.C. 355(b)). New section 505(b)(4)(B) of the Act directs FDA to meet with sponsors, provided certain conditions are met, for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim in a marketing application submitted under section 505(b) of the Act or section 351 of the Public Health Service Act (42 U.S.C. 262)." See also Formal Meetings with Sponsors and Applicants for PDUFA Products. FDA Guidance for Industry, Draft. February 2000. <http://www.fda.gov/cder/guidance/2125fnl.htm>

innovations especially since it was possible for FDA to adopt some of the most important innovations, such as the interactive and proactive approaches and project management, regardless of whether Pilot Drug still existed. Pilot Drug pioneered many excellent changes at FDA, but Dr. Woodcock felt it was no longer needed or worth the cost.⁸³⁰

Dr. Murray Lumpkin, Deputy Center (CDER) Director for Review Management, is Dr. Woodcock's Deputy with direct management responsibility for all drug review divisions within FDA, with 980 people reporting to him. He stated that Pilot Drug was eliminated strictly for management reasons related in part to meeting PDUFA goals and in part to concerns over the "cowboy mentality" of Pilot Drug which resulted in Pilot Drug's failure to follow standard regulations, not permissible in a regulatory agency.⁸³¹

By 1995, Dr. Lumpkin (and Dr. Woodcock) realized that any delays in meeting PDUFA goals for timely review were no longer going to be caused at the initial review levels, since there were more staff to handle the workload. The bottleneck in the NDA review process that they saw was at the Office level.⁸³² Before the 1995 reorganization, FDA was organized into 10 review divisions reporting to 2 Offices, with the Directors of each Office required to review and approve all NDA applications. In order to address this bottleneck, CDER was reorganized by Dr. Woodcock into 15 review divisions under 5 Offices. This effectively divided up the workload at the upper management level.

During the course of this reorganization, Pilot Drug was eliminated and its portfolio was reallocated. Dr. Lumpkin believed that there was no reason to keep Pilot Drug intact to test innovations in the drug review process. While Pilot Drug had implemented many "very good, very important innovations," primarily its focus on the interactive process, FDA needed to and was able to spread the valuable innovations pioneered by Pilot Drug throughout FDA.^{833 834}

Dr. Woodcock's most serious critique of the quality of Pilot Drug's reviews stemmed from an experience she had when she was called in as a consultant to help Pilot Drug review several scleroderma and rheumatic drugs.⁸³⁵ She said that there was even a

⁸³⁰personal communication, Dr. Janet Woodcock, June 8, 1999.

⁸³¹personal communication, Dr. Murray Lumpkin, February 18, 2000. Dr. Lumpkin had been brought into FDA by Dr. Peck at the end of 1989. He was initially a Division manager in Anti-Infectives before assuming senior management responsibilities.

⁸³²personal communication, Dr. Lumpkin, February 18, 2000.

⁸³³personal communication, Dr. Lumpkin, February 18, 2000.

⁸³⁴For a review of current (3/2000) FDA policies regarding the acceleration of the drug development process, see slides from a talk given by Dr. Lumpkin entitled, "Accelerating Drug Development: Regulatory Initiatives in the USA," at the DIA EuroMEETING 2000, Nice, France, March 9, 2000. <http://www.fda.gov/cder/present/dia-nice2000/dianice1/index.htm>. See also FDA Guidance document, Fast Track Drug Development Programs: Designation, Development, and Application, <http://www.fda.gov/cder/guidance/2112fnl.pdf>.

Congressional hearing in 1994 about Pilot Drug's review of one of these drugs. Dr. Woodcock reported that her direct impression of Pilot Drug as being deficient in rigor contributed substantially to her decision to eliminate it. Dr. Lumpkin stated that Pilot Drug's actions in regard to Therafectin was just one such concern, there were others which he didn't specify. He commented that the 007 "license to kill" mentality was illustrative of the attitudes in Pilot Drug, and that senior FDA staff had to spend time, "cleaning up after Pilot Drug."⁸³⁶

What follows is an evaluation of Pilot Drug's track record, both in terms of the speed and quality of its reviews, including a close look at the way it handled the drug that Dr. Woodcock cited in her rationale for eliminating Pilot Drug.

Evaluating the Speed of Pilot Drug's Review

The evaluation of Pilot Drug's organizational performance is based in large part on the standard statistics kept on every division; the size of the backlog, the number of approvals, disapprovals and Clinical Holds, and the speed of review. By this measure, the organizational model worked extraordinarily well.

Pilot Drug began with about 36 NDA applications from the various drug areas that had been incorporated into Pilot Drug. As was the case at the other FDA Divisions, most of these NDA applications were older than the target review time of 180 days. Thus, Pilot Drug began with a substantial backlog. During the first two years of operation from June 1989 to June 1991, the task of building a new staff from scratch while putting in place a very unique and challenging organizational model took a great deal of energy. The rate of new NDA submissions exceeded the rate of decisions (the action rate), resulting in an increase in the backlog. Project management and cross-project synchronization began to be put into place at the end of the second year and the new staff became adept within the Pilot Drug environment. From June 1991 to December 1992, the backlog was completely eliminated, a remarkable achievement. When measured by the standard criteria used throughout FDA, Pilot Drug performed superlatively in terms of the speed of its review process.

Not all NDAs were approved. Some of the backlog was resolved through non-approval of NDAs and through the use of Refusal-to-File letters. Dr. Harter noted that allocating staff time to clear the backlog by rejecting NDAs and issuing Refusal-To-File letters carried the cost of not being able to devote that same staff time to work on NDAs that were approvable. Dr. Harter estimated the cost of getting the Pilot Drug backlog to zero was three to four additional NDAs that could have been approved if staff time had not been reallocated toward reducing the backlog. In an illustrative example of the way Pilot Drug was managed, Dr. Harter noted that the staff revolted, "as is their prerogative under the peer system" and prioritized clearing the backlog over his objections.⁸³⁷

⁸³⁵personal communication, Dr. Woodcock, June 8, 1999.

⁸³⁶personal communication, Dr. Lumpkin, February 18, 2000.

Evaluating Quality of Pilot Drug Review

Assessing the quality of Pilot Drug's reviews is not as easy as assessing the speed of its reviews. The Internal Assessment document lists all the drugs approved by Pilot Drug up to the writing of the document. Dr. Temple didn't think that there were reports of any unusual number of adverse drug reports (ADRs) in any of the NDAs approved by Pilot Drug. Furthermore, Pilot Drug's list of approved NDAs seemed more than he had initially expected. However, he said upon closer inspection that many of the NDAs that emerged from Pilot Drug were for new formulations or uses of old drugs. In those cases, unanticipated adverse effects are unlikely, since these are not new chemical entities (NCE). Dr. Temple went through the list and identified about seven out of thirty as being NCEs. He ended up with the view that the lack of surprises in terms of ADRs in the NDAs approved by Pilot Drug wasn't an argument in support of the acceptability of the elimination of supervisory personnel. Instead, he claimed that Pilot Drug hadn't approved enough NDAs for new chemical entities to evaluate adequately Pilot Drug's use of its peer review system as compared to the traditional supervisory review.

Dr. Jerry Collins, currently Director of FDA's Clinical Pharmacology Lab, had an indirect view of the quality of Pilot Drugs' reviews. Dr. Collins had been brought to FDA in 1989 by Dr. Peck due to his expertise in clinical pharmacology. He was initially Director of the Office of Research Resources. In that capacity, he commented that he thought his title could also have been Vice President for Complaints, with the complaints coming from sponsors who felt that the review of their drug wasn't being conducted in a scientifically appropriate, impartial or fair manner. Dr. Collins noted that FDA was a large place with a great deal going on and that he could have missed something, but he wasn't aware of complaints about the scientific quality of Pilot Drug's reviews.⁸³⁸

GAO Inquiry into Pilot Drug use of Statistical Meta-analysis

Another evaluation of the quality of Pilot Drug's review was conducted in the context of a 1991 investigation by the General Accounting Office (GAO) into Pilot Drug's use of the technique of meta-analysis in the review and approval of three drugs: the transdermal fentanyl patch, toradol, and ketorolac. The GAO review was conducted by Ms. Michele Orza, who reported in an interview that the review was started by Mr. Mitch Zeller, now with FDA but then a health staff member working for Congressman Ted Weiss, Chair of Subcommittee on Investigations, House Commerce Committee.⁸³⁹ Mr.

⁸³⁷*Internal Assessment* (1993): 8-9.

⁸³⁸personal communication, Dr. Jerry Collins, February 15, 2000. Dr. Collins indicated that he wasn't really aware of what Pilot Drug did regarding psychedelics or marijuana, which he said was another data point suggesting that Pilot Drug's work in this area did not generate substantial internal controversy.

⁸³⁹personal communication, Ms. Michele Orza, March 5, 1999. Ms. Orza is still working with the

Zeller had read a trade report indicating that Pilot Drug had approved several drugs using a new technique called meta-analysis.⁸⁴⁰ According to Ms. Orza, Mr. Zeller wanted an investigation to determine if this new technique was some sort of “dubious hocus pocus” that the FDA had found to approve essentially unapprovable drugs. Rep. Weiss wanted to learn whether FDA was being pushed too hard by industry to let drugs out.

Ms. Orza was chosen to conduct the review for GAO since she had recently been hired specifically for her training in meta-analysis. In conducting her review, Ms. Orza interacted with Dr. Harter, Dr. Peck, Dr. Wright, and CSO Dottie Pease. GAO’s preliminary investigation concluded that what FDA was doing was justified, that Pilot Drug had tried to make the most of the data it was given. What Pilot Drug did wasn’t wrong or illegitimate; it performed interesting analyses with pharmacology data trying to create dose-response curves, which looked reasonable. Ms. Orza remarked, “They were just trying to be creative in that division.”⁸⁴¹ Dr. Peck has commented, “FDA took a calculated “regulatory risk” when it approved ketorolac at a specific dosage that had never been tested. It had already been investigated at many different dosages – above and below the final approved dosage. Thus, the agency was confident that the approved dosage was both safe and effective. Subsequent clinical experience bore out the agency’s decision.”⁸⁴²

After Ms. Orza determined that FDA had done its best with the data that had been submitted, the GAO investigations shifted to why companies give FDA “such lame data,” of such poor quality. The GAO investigation shifted to the nature and quality of NDA applications. One response to the poor quality of submissions was to reject them, using Refusal-to-File letters. Ms. Orza remembers Pilot Drug as not being the most aggressive in refusing to file. Rather, she thought that Gastrointestinal and Coagulation Products (nickname: blood and guts) had that honor.

Technically speaking, GAO conducted a “preliminary review to see if there was any need to launch a full scale investigation.” GAO came to the conclusion that there was nothing to warrant a full-scale formal investigation.

Office of Inspector General Evaluation of Pilot Drug’s Review of Therafectin

Dr. Woodcock’s most important critique of Pilot Drug’s scientific rigor was based on her experience as a consultant to Pilot Drug assisting in the review of several scleroderma and rheumatic drugs, one of which she said became the object of a Congressional investigation.

Dr. Wright indicated that the drug in question was Therafectin, a drug to be used

General Accounting Office.

⁸⁴⁰Staff. Data Dredging was Key to Toradol, Lodine, Duragesic Approvals, FDA’s Harter Says: Pharmacokinetics Work in Animal Models Urged by CDER Director. *F-D-C Reports Pinksheet* (February 25, 1991): 10-11.

⁸⁴¹personal communication, Ms. Orza, March 5, 1999.

⁸⁴²Peck C. Drug Development: Improving the Process. *Food Drug Law J* 52 (1997) 2:166.

in the treatment of rheumatoid arthritis. The NDA-seeking company was Greenwich Pharmaceuticals. In Dr. Wright's opinion, Pilot Drug had indeed made some mistakes in handling its review of that drug, but the decision not to approve the NDA for Therafectin had been correct.⁸⁴³ Dr. Wright further indicated that the mistakes were caused in large part by an outside reviewer that Dr. Harter had brought in, not by permanent Pilot Drug staff.

Fortunately, there are some publicly available data that can be used to evaluate what mistakes Pilot Drug made in its review of Therafectin, and to what extent those mistakes reflect tradeoffs that Pilot Drug might have made between organizational innovation, speed of review, and quality, i.e. scientific rigor. A series of publicly available press releases from Greenwich Pharmaceuticals, Inc., as well as from the company it eventually merged with, Boston Life Sciences, provide historical information about Therafectin's clinical development process. Most importantly, though there was no formal Congressional hearing regarding Pilot Drug's review of Therafectin, the HHS Office of Inspector General (OIG) did conduct a thorough investigation of Pilot Drug's review of Therafectin, with the OIG's final report being publicly available.⁸⁴⁴

Background for Therafectin

Greenwich Pharmaceuticals began to conduct research with Therafectin in the late 1980s. Results of an initial efficacy trial were presented to Pilot Drug on March 5, 1990, with a Business Wire article reporting that, "At the meeting, representatives from the FDA confirmed that this study demonstrated efficacy with statistically significant results in favor of Therafectin. The confirmation of Therafectin's efficacy significantly strengthens its potential to be a therapeutic advance in the chronic treatment of rheumatoid arthritis."⁸⁴⁵ Based on the successful outcome of the initial study, planning for a Phase III trial was initiated. On May 24, 1990, Greenwich Pharmaceutical representatives and Pilot Drug staff met with the members of one of Pilot Drug's outside advisory committees, the Arthritis Advisory Committee, to discuss Therafectin.

On May 22, 1992, Greenwich Pharmaceuticals met with Pilot Drug staff to discuss the results of the Phase III trial. Greenwich released the following statement, "Greenwich met with representatives of the U.S. Food and Drug Administration (FDA) to review the results of RA12, an ongoing study in patients with rheumatoid arthritis. At the meeting, the FDA indicated that it will require further analysis of RA12 and an integration of these results into the existing Therafectin (amiprilose HCL) database prior to determining

⁸⁴³personal communication, Dr. Wright, November 16, 1999.

⁸⁴⁴Review of the Food and Drug Administration's Processing of a New Drug Application for Therafectin (A-15-94-00023). Office of Inspector General-Audit. June Gibbs Brown, Inspector General. Report Submitted to Philip R Lee, M.D., Assistant Secretary for Health, August 2, 1995.

⁸⁴⁵Staff. Results of study confirm the Therapeutic potential of Therafectin (amiprilose HC1) as a treatment for Rheumatoid Arthritis. *Business Wire*(March 8, 1990).

whether or not the company will proceed with the filing of the New Drug Application.”⁸⁴⁶ On September 23, 1992, Greenwich Pharmaceuticals and Pilot Drug staff met for a second time with the Arthritis Advisory Committee. Greenwich released a statement saying “At the meeting, a majority of the members of the committee agreed that the company's analysis of the database supports the efficacy of Therafectin in a selected group of rheumatoid arthritis patients.”⁸⁴⁷

On January 11, 1993 Greenwich submitted its NDA to Pilot Drug.⁸⁴⁸ On September 13, 1993, Pilot Drug informed Greenwich Pharmaceuticals that it would not approve Therafectin for marketing due to lack of data supporting a claim of efficacy. However, Pilot Drug offered Greenwich Pharmaceuticals another opportunity to meet with the Arthritis Advisory Committee.⁸⁴⁹ In October 1993, Greenwich Pharmaceuticals complained to Congressman John Dingell, Chairman of the House Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce.⁸⁵⁰ On January 27, 1994, the Arthritis Advisory Committee voted to recommend that Therafectin not be approved.⁸⁵¹ In March 1994, Congressman Dingell requested an Office of Inspector General audit of Pilot Drug’s handling of the Therafectin review. On May 10, 1994, Greenwich Pharmaceuticals announced that it received word that “an independent evaluation of the efficacy of Therafectin and the supervisory review of the Pilot Drug Division’s review of the Therafectin NDA concluded that the application lacks substantial evidence of Therafectin’s effectiveness.”⁸⁵² On May 11, 1994 Greenwich announced that it had settled a shareholders class action lawsuit regarding misleading public statements the company had made about Therafectin, for the sum of \$4.375 million.⁸⁵³

Office of Inspector General Report

On August 2, 1995, the completed OIG report was submitted to Dr. Philip Lee,

⁸⁴⁶Thompson E. Chairman, President and CEO of Greenwich Pharmaceuticals. Statement. *Business Wire*(May 22, 1992).

⁸⁴⁷Staff. Greenwich Pharmaceuticals reports on status of Therafectin (amiprilose HCl). *Business Wire* (September 23, 1992).

⁸⁴⁸Staff. Greenwich Pharmaceuticals submits New Drug Application for Therafectin (amiprilose HCl). *Business Wire*(January 11, 1993).

⁸⁴⁹Staff. Greenwich Pharmaceuticals receives "not approvable" letter from FDA. *Business Wire*(September 13, 1993).

⁸⁵⁰Review of the Food and Drug Administration’s Processing of a New Drug Application for Therafectin (A-15-94-00023): 1.

⁸⁵¹Staff. Greenwich Pharmaceuticals makes announcement about Therafectin. *Business Wire* (January 27, 1994).

⁸⁵²Staff. Greenwich announces negative evaluation of Therafectin. *Business Wire* (May 10, 1994).

⁸⁵³Staff. Greenwich announces settlement of Securities Litigation. *Business Wire* (May 11, 1994).

Assistant Secretary for Health, by June Gibbs Brown, the Inspector General. The IG's cover letter to Philip Lee summarized the findings of the audit as follows, "We found that, in general, FDA properly processed the Therafectin NDA. We noted certain administrative shortcomings, but found no evidence that they affected the approval status of the Therafectin application. In the final analysis, Greenwich was not able to adequately demonstrate – either to FDA or the Arthritis Advisory Committee – that Therafectin was effective in the treatment of rheumatoid arthritis."⁸⁵⁴

The administrative failings of Pilot Drug that the OIG noted consisted primarily of not promptly arranging to meet with Greenwich to discuss scientific disputes and not providing Greenwich with a unified statement of Pilot Drug's concerns regarding the deficiencies in the data. To its credit, Pilot Drug had provided Greenwich with its medical and statistical reviews. The OIG report did not find fault with the scientific rigor of Pilot Drug's review of the Therafectin data.

Postscript on Therafectin

On Sept, 30, 1997, Boston Life Sciences announced the results of another clinical trial of Therafectin. Though there were no statistically significant changes in the primary efficacy variable, some of the secondary efficacy variables did show statistically significant changes.⁸⁵⁵ In July 1998, Boston Life Sciences filed an amendment to its NDA that included the data from its new clinical trial. On November 17, 1999, it was still waiting to hear from FDA about its NDA and its request for one final meeting with the Arthritis Advisory Committee to review of all the data on Therafectin.⁸⁵⁶ On December 29, 1999, Boston Life Sciences announced that the FDA had formally rejected its NDA application for Therafectin.⁸⁵⁷ According to Boston Life Sciences, FDA had concluded that the new data on Therafectin submitted in 1998 "had not provided sufficient evidence of a statistically significant treatment effect," and that an informal meeting with FDA to discuss Therafectin would be scheduled in the first quarter of 2000.⁸⁵⁸

A Multidetermined Demise

Though Dr. Woodcock reported that her decision to dissolve Pilot Drug was based

⁸⁵⁴Brown J. Inspector General, Office of Inspector General. Cover Letter to Philip Lee, Assistant Secretary for Health. August 2, 1995. Review of the Food and Drug Administration's Processing of A New Drug Application for Therafectin (A-15-94-00023).

⁸⁵⁵Staff. Boston Life Sciences Announces Results of its Phase III Trial for Therafectin. *Business Wire* (September 30, 1997).

⁸⁵⁶personal communication, Maria Zapf, investor relations, Boston Life Sciences, November 17, 1999.

⁸⁵⁷Staff. Boston Life Sciences' Drug rejected by FDA. *Boston Globe*(December 30, 1999): D7.

⁸⁵⁸Staff. Boston Life Sciences to Meet With FDA On Therafectin Efficacy Issues. *Healthwire*(December 29, 1999).

primarily on her concerns over Pilot Drug's core competencies, the analysis of Pilot Drug's review of Therafectin suggests that it is likely that there were other contributing factors. The OIG's report does provide evidence supporting Dr. Woodcock's concerns about administrative failings in Pilot Drug's review of Therafectin, and therefore provides sufficient reason to believe that Dr. Woodcock did indeed eliminate Pilot Drug for reasons related in part to her concerns about the quality of its review of Therafectin. However, the OIG report and the subsequent history of clinical research and FDA actions regarding Therafectin do not provide evidence supporting the claim that Pilot Drug made any significant scientific errors in its decision not to approve Therafectin.

Another factor in the dissolution of Pilot Drug was most likely the fundamental challenge Pilot Drug presented to FDA's bureaucratic structure. Dr. Wright reported that many FDA officials were resentful of the attention paid to Pilot Drug and were threatened by its proposals to reorganize FDA review divisions. Dr. Wright noted that the departure of Dr. Peck from FDA permitted Pilot Drug to be attacked, and that the new people at FDA [e.g. Dr. Woodcock] were "more concerned with uniform, transparent practices, and not interested in innovation."

The single event that more than anything else led to the elimination of Pilot Drug took place on October 29, 1992, when Congress passed the Prescription Drug User Fee Act (PDUFA).⁸⁵⁹ PDUFA authorized FDA to collect user fees from the pharmaceutical industry for the purpose of hiring an additional 600 or so review staff. User fees were to provide FDA with an additional \$36 million in 1993, rising to \$84 million in 1997.⁸⁶⁰ As a result of PDUFA's provision of funding for additional staff to expedite the drug review process, FDA was in a position to do with brute peoplepower what Pilot Drug was trying to do with efficiency-driven reform of FDA's standard practices, with all the challenges and opposition that engendered.

On February 25, 1993, several months after the passage of PDUFA, Pilot Drug staff completed an Internal Assessment, evaluating the activities of Pilot Drug from its founding in June 1989 to December 1992.⁸⁶¹ The report concluded that Pilot Drug had been able to completely eliminate its backlog by December 1992 as a result of its innovative organizational approach and dedicated staff. Pilot Drug's recommendations in its Internal Assessment were for the establishment of a new Office of Experimental Drug Evaluation (OEDE), with one additional Division reconfiguring itself in a manner similar to Pilot Drug as a prelude for the eventual reorganization of the entire FDA along the general lines pioneered by Pilot Drug. No formal response was ever written to Pilot Drug's Internal Assessment of the value and implications of the organizational innovations it developed. Needless to say, the recommendations contained in that report were not implemented.

⁸⁵⁹Prescription Drug User Fee Act of 1992. 102 P.L. 571; 106 Stat. 4491. October 29, 1992.

⁸⁶⁰Sec. 736 (g). \$36 million for fiscal year 1993, \$54 million for fiscal year 1994, \$75 million for fiscal year 1995, \$78 million for fiscal year 1996, and \$84 million for fiscal year 1997.

⁸⁶¹*Internal Assessment* (1993).

On May 18, 1993, an FDA press release announced that Dr. Peck would be retiring as Director of CDER as of November 1, 1993.⁸⁶² That date marked his sixth year at FDA, exactly the amount of time that he had pledged to remain at FDA when he accepted the job in October 1987. In that press release, FDA Commissioner David A. Kessler, M.D. remarked, "Dr. Peck brought to FDA the spirit of innovative scientific management." As soon as Dr. Peck departed, he reported that "the sharks came out" after Dr. Harter.⁸⁶³ CDER Deputy Director Gerald Meyer, who Dr. Peck considered the most powerful internal opponent of Dr. Harter,⁸⁶⁴ took over the management of CDER on an interim basis.

At the time Mr. Meyer began to manage CDER, Dr. Harter had voluntarily rotated out of the Division Directorship of Pilot Drug on a temporary basis, as part of his policy of rotating directorships to promote the professional development of his staff. As a result, he was technically classified as simply a medical review officer. Mr. Meyer took advantage of Dr. Harter's temporarily reduced status and transferred him involuntarily to another area of FDA, Pharmaceutical Sciences, where he had virtually no job description, no review responsibilities and no authority. After this treatment, Dr. Harter decided to retire at the age of 67, first filing a lawsuit for age discrimination against FDA.⁸⁶⁵

In an August 1993 reorganization, Pilot Drug lost its special place within CDER's organizational structure as the only review Division reporting directly to the Center Director. It was demoted and placed under the Office of Drug Evaluation II.⁸⁶⁶ According to Dr. Jerry Collins, Director of FDA's Clinical Pharmacology Lab, the key decision that indicated that the Pilot Drug era was going to end was when it was demoted from reporting directly to the CDER Director and was placed under an Office.⁸⁶⁷

With the "resignation" of Dr. Harter from FDA and the removal of Pilot Drug from direct report to the Center Director, the management of CDER focused on the organizational changes brought about by the passage of PDUFA. Pilot Drug's Internal Assessment contained a recommendation from Dr. Harter about how FDA might best use the additional resources that PDUFA would provide. He wrote, "My belief is that we should consider applying more of our resources to interaction during the IND process with the goal of securing better NDA's rather than continuing to put the bulk of our resources into nonapproved actions within the 180 days."⁸⁶⁸ As it has turned out, FDA's increasing

⁸⁶²McLearn D. *FDA Press Release P93-19* (May 18, 1993).

⁸⁶³personal communication, Dr. Peck, February 22, 1999.

⁸⁶⁴personal communication, Dr. Peck, February 22, 1999.

⁸⁶⁵personal communication, Ms. Tyson, March 17, 1999.

⁸⁶⁶Review of the Food and Drug Administration's Processing of a New Drug Application for Therafectin (A-15-94-00023): 2.

⁸⁶⁷personal communication, Dr. Collins, February 15, 2000.

emphasis on an interactive approach has resulted in the adoption of Dr. Harter's recommendation.

In Ms. Tyson's opinion, PDUFA has resulted in an overabundance of reviewers. She noted that Dr. Harter wasn't actually against PDUFA, he just saw several potential problems with it such as a pressure on staff to approve NDAs becoming the highest priority, since those were the measurable goals established by PDUFA. The priority placed on reducing NDA review time at the tail end of the process made Dr. Harter wonder if there would still be time for an interactive IND process at the front end, which he concluded offered the best opportunity to increase efficiencies in drug development. Dr. Harter thought that PDUFA should have permitted FDA staff time to be evaluated no matter what tasks they were doing, but the PDUFA fees were primarily for NDA review, not for the IND process, and no measurable performance goals were related to the IND process.⁸⁶⁹

Created with the goal of doing more with less, Pilot Drug was able to cut its backlog to zero without the additional staff that PDUFA was later to fund. According to Ms. Van Hoose, Dr. Harter was not enthusiastic about PDUFA and felt that "We shouldn't need it." Pilot Drug's track record of success within pre-PDUFA staffing levels perhaps helps partially explain why Pilot Drug has almost totally fallen out of FDA's recorded institutional memory. There remains very little in the way of historical documents about one of the most remarkable and innovative organizational experiments conducted within the federal bureaucracy. The fee-based income and additional staff resources provided to FDA as a result of PDUFA, now amounting to an additional \$100 million per year in PDUFA fees⁸⁷⁰ and roughly 600 new employees,⁸⁷¹ eliminated the need for major organizational restructuring and process redesign. Pilot Drug's success in eliminating its backlog within the pre-PDUFA staffing constraints was less of an inspirational model to replicate and more of a challenge to the perceived need for bureaucratic expansion.

Dr. Wright had a similar view. He remarked, "PDUFA eliminated the need for the agency to improve productivity... It eliminated FDA's need for the innovations at Pilot Drug that challenged bureaucratic structure... Management strategy in response to PDUFA came straight out of classic 1900 texts....Review staff has now even unionized!"⁸⁷² Dr. Wright noted that at the height of the Reinventing Government (REGO) initiative, the FDA post-PDUFA has actually relayered office level bureaucracy, with a Center Director, Deputy Center Director, Office Director, Deputy Office Director, Division Director, Deputy Division Director, and Team Leader all above the primary review staff. PDUFA-funded staff increases have indeed resulted in a dramatic lowering of FDA review times, enabling FDA to meet and exceed PDUFA targets.^{873 874 875 876}

⁸⁶⁸ *Internal Assessment* (1993): 9.

⁸⁶⁹ personal communication, Ms. Tyson, February 23, 2000.

⁸⁷⁰ Sec 103 (f) of Food and Drug Administration Modernization Act of 1997.

⁸⁷¹ Wechsler J. Challenging FDA Authority. *Pharmaceu Exec* 14 (1994) 8:18-22.

⁸⁷² personal communication, Dr. Wright, March 8, 1999.

In October 1995, Pilot Drug was dissolved and the portfolio of drugs it reviewed were redistributed to other Divisions. Five new Divisions were created and a new management structure, with three additional Office level managers, were established. [new organizational charts on next two pages] Dr. Woodcock's statement that she could continue to develop many of Pilot Drug's innovations independent of the existence of Pilot Drug suggests that she did value many aspects of Pilot Drug's innovative approach, but that its elimination of layers of reviewers and its devolving of authority in the review process represented a core incompatibility with her vision of a post-PDUFA FDA. Whether the Pilot Drug model could have been successfully exported throughout FDA, or whether the type of people who can work and thrive in such dynamic environments are few and far between, remains an open question.

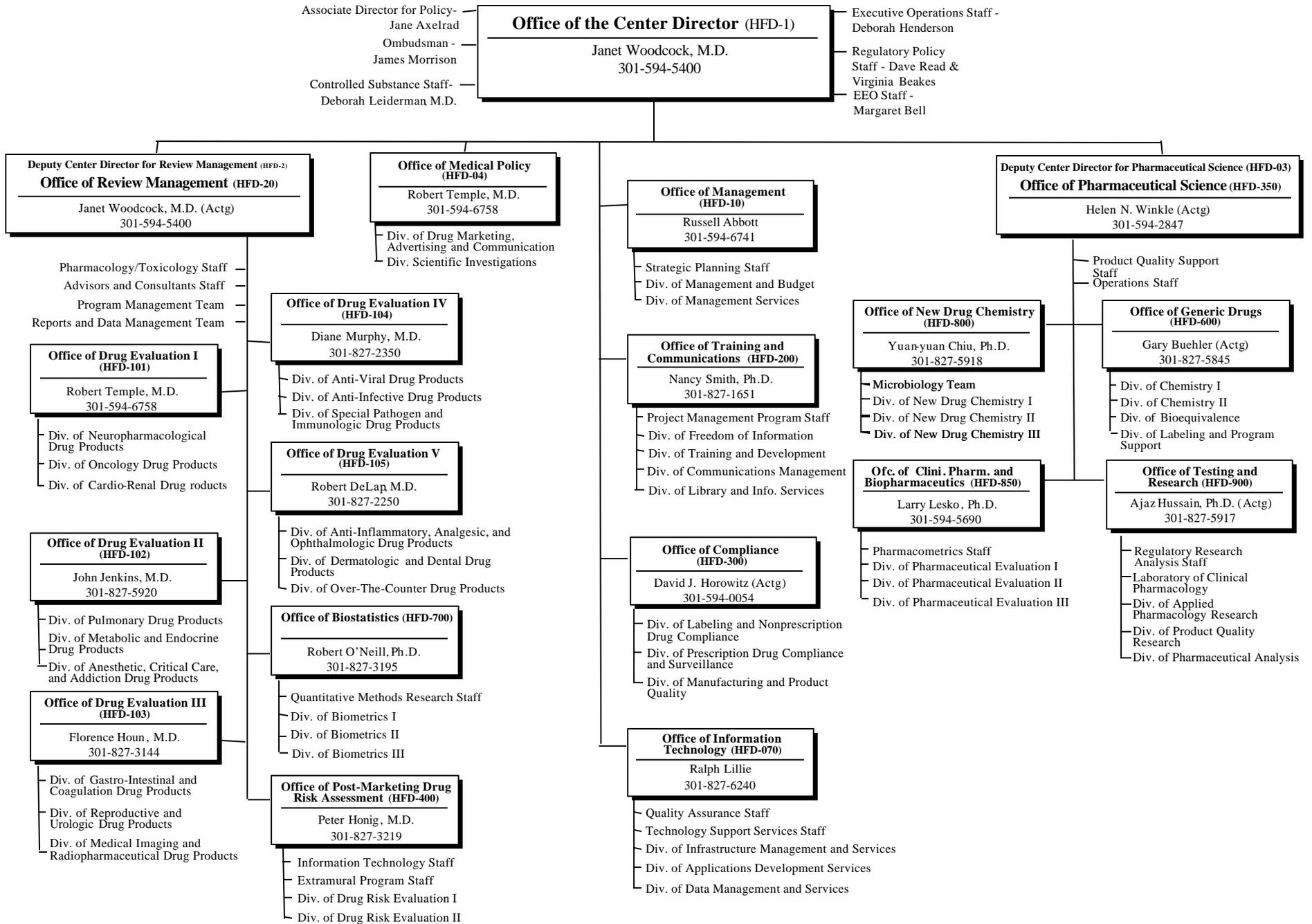
⁸⁷³ Mean NDA review time for New Chemical Entities (NCEs) in the period 1996-1998 was 1.4 years, a 30% decline from 1993-1995. The mean length of the clinical research process (IND Phases) in the period 1996-1998 dropped to 5.9 years, an 18% decline from 1993-1995 and the first decline in this measure since 1984-1986. Staff. Clinical development times for new drugs drop 18%, reversing 12-yr trend. *Impact Report—Tufts Center for the Study of Drug Development* (July 1999): 1-4.

⁸⁷⁴ Mean NDA review time in 1999 declined even further to 12 months. Lumpkin, M. Center Reports Drug Review Statistics for 1999. *News Along the Pike* 6 (February 2000) 2:1,8. For a chart of FDA's reported review times from 1986 to 1999, see Approval times (in months) for NDAs and NMEs approved. Calendar years 1986–1999. FDA Chart. <http://www.fda.gov/cder/rdmt/cy99ndaap.htm>

⁸⁷⁵ Review times in the US are no longer slower than in Europe. Staff. European and U.S. approval times for new drugs are virtually identical. *Impact Report—Tufts Center for the Study of Drug Development* 1 (November 1999): 1-4.

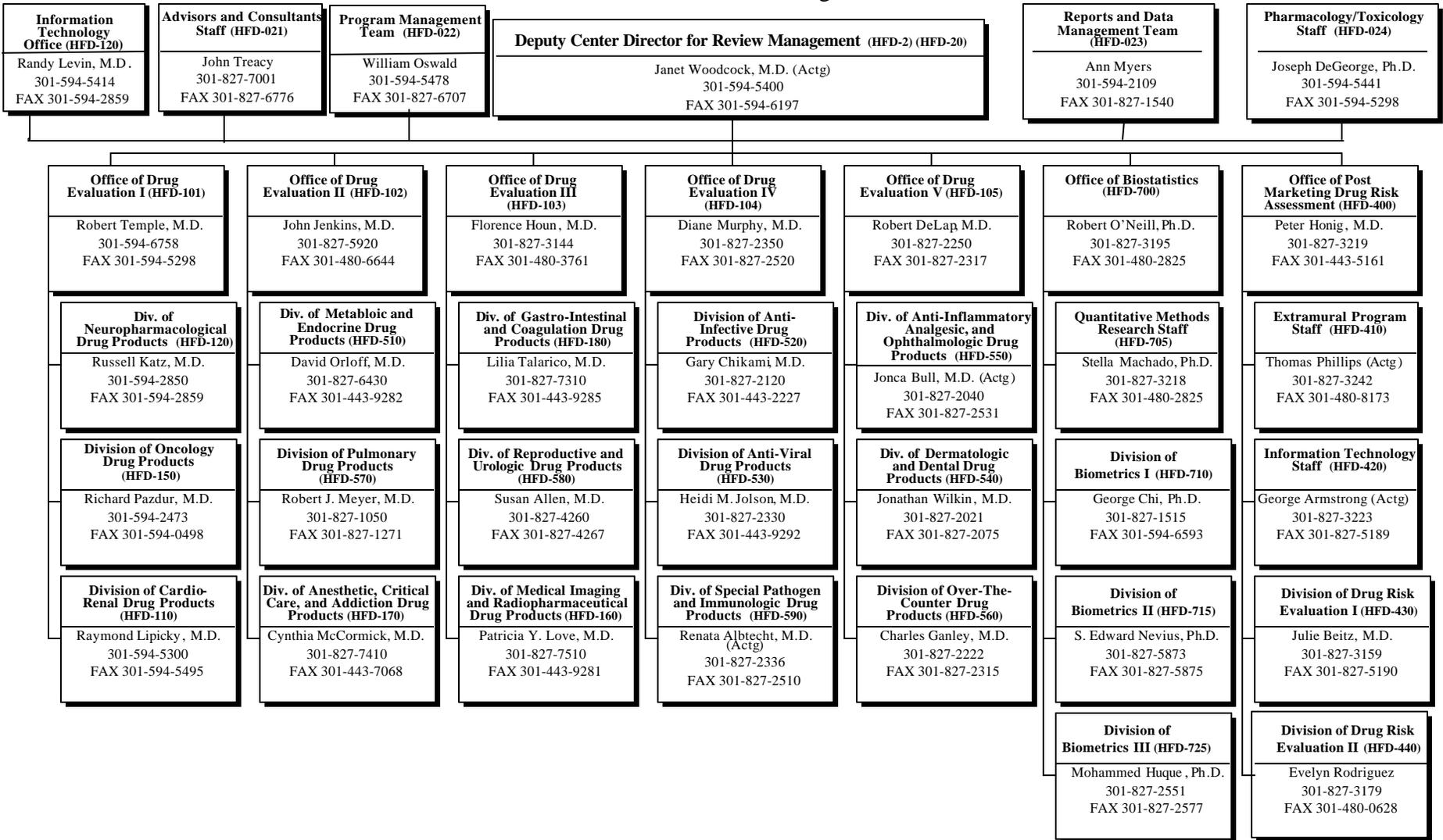
⁸⁷⁶ Questions have been raised, however, about whether FDA's need to meet PDUFA targets and the dramatic reductions in review time have resulted in compromised safety. Lurie P, Wolfe S. Lower Standards Permit Dangerous Drug Approvals—FDA Medical Officers Report. Public Citizen's Health Research Group. (December 1998). <http://www.citizen.org/hrg/PUBLICATIONS/FDASURVEY/FDASURVEY.htm>. For FDA response, see Friedman M, Woodcock J, Lumpkin M, Shuren J, Hass A, Thompson L. The safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA* 281(1999 May 12) 18:1728-34.

CENTER FOR DRUG EVALUATION AND RESEARCH



CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Review Management



The Legacy of Pilot Drug for FDA

Dr. Peck considers Pilot Drug to have been “marvelously successful,” in that many of its innovations have been widely adopted at FDA. As he said in a 1991 interview and reiterated in 1999, “One of the most important decisions I have made was to set up the Pilot Drug Review Division under John Harter.”⁸⁷⁷

Dr. Wright remarked that “almost all of the innovations originated at Pilot Drug have been mainstreamed within FDA, although not in that name.” There were some notable exceptions having to do with the fundamental structural reorganizations tried by Pilot Drug, such as the devolution of authority, the rotating team leaders, peer review, and work group sign-off on letters so as to generate active ownership and personal responsibility. Dr. Wright reported that these have all been soundly rejected with the sentiment, “we don’t do that here.” He felt that these innovations were considered inconsistent with the goals of civil service “which are to fight like hell over trivial differences in authority and span of control.” Dr. Wright said that Pilot Drug was ahead of its time. Dr. Peck used the same words, noting that the failed innovation of rotating group leadership and internal peer review was just way ahead of its time.

Dr. Woodcock said that one of her major accomplishments has been to institutionalize those innovations of Pilot Drug that were valuable and ahead of their time, like the proactive, interactive approach and project management.⁸⁷⁸ In the long-run, she thinks that the speeding up of the review time is only somewhat important compared to the cultural shift that has taken place at the FDA toward a proactive, interactive approach. She thinks that the proactive interactive approach will create more lasting public value than faster review times, especially since the longest times in the drug development process are the pre-IND and IND phases.

As Ms. Van Hoose noted, “it has been observed that experimental islands very seldom survive. The rest of the organization can’t allow experiments to survive, their existing paradigms are too threatened.” Pilot Drug was no exception. She considered Pilot Drug “A glorious experiment...the operation succeeded even though the patient (Pilot Drug) died.”

Dr. Wright’s Departure from FDA

Dr. Wright resigned from FDA in October 1997, just one month before Congress passed the Food and Drug Administration Modernization Act of 1997, on November 21, 1997.⁸⁷⁹ The 1997 Act came into being as a result of the five-year sunset provision in the

⁸⁷⁷ Staff. Keep your NDA's 'lean' to cut drug development time. *Med Market & Media*. 26 (February 1991) 2:34.

⁸⁷⁸ Woodcock J. An FDA Perspective on the Drug Development Process. *Food Drug Law J* 52 (1997) 2:145-150.

original PDUFA. The 1997 Act reauthorized user fees,⁸⁸⁰ retained performance targets,⁸⁸¹ contained a five-year sunset provision⁸⁸² and made numerous other changes in FDA policies.⁸⁸³ The reauthorization of user fees further solidified the previous expansion of FDA staff, eliminated FDA's need to explore further or seriously reconsider any of Pilot Drug's organizational innovations, and reduced the value to FDA of Dr. Wright's formative experiences within Pilot Drug.

Dr. Woodcock reported that her 1997 decision to appoint Dr. McCormick instead of Dr. Wright as Director of DACCADP was independent of Dr. Wright's support for psychedelic and medical marijuana research. Dr. Woodcock also indicated that it would be incorrect to assume that because Dr. McCormick had worked for Dr. Leber that she shared his views or had been appointed in part to restore FDA's old policies toward psychedelic and marijuana research.⁸⁸⁴

When challenged in 1994 by strident DEA complaints about Pilot Drug's decision to approve Dr. Abrams' medical marijuana protocol, Dr. Kessler and Dr. Woodcock provided a vigorous defense of Pilot Drug, then directed by Dr. Wright. In addition, Dr. Lee Brown, Director of the Office of National Drug Control Policy, reaffirmed FDA's primacy in reviewing medical marijuana research protocols. These events further support Dr. Woodcock's contention that Dr. Wright's decision to review medical marijuana and psychedelic research protocols on their merits had not engendered disapproval of his actions within the FDA leadership.

Dr. Wright agrees with Dr. Woodcock that his candidacy was not adversely affected by his work and policies toward psychedelic and medical marijuana research. He attributed his being passed over for the permanent directorship primarily to his being so closely associated with the Pilot Drug experiment, with perhaps additional baggage stemming from his involvement in FDA's controversial and largely unsuccessful effort to regulate tobacco.”

Did Pilot Drug's psychedelic and medical marijuana policies contribute to its demise?

Nothing in the analysis of the establishment, operation and dissolution of Pilot

⁸⁷⁹ Food and Drug Administration Modernization Act of 1997.

⁸⁸⁰ Sec. 103 (f) (3) of the Act provides in excess of \$100 million per year from 1998-2002.

⁸⁸¹ Sec. 101 (4) and Sec. 104.

⁸⁸² Sec. 107. The amendments made by Sections 102 and 103 cease to be effective October 1, 2002.

⁸⁸³ Secs. 111—422. FDA has called these provisions “the most wide-ranging reforms in agency practices since 1938. Provisions include measures to accelerate review of devices, advertising unapproved uses of approved drugs and devices, health claims for foods in agreement with published data by a reputable public health source, and development of good guidance practices for agency decision-making.” FDA CDER

Timeline: Chronology of Drug Regulation in the United States.

<http://www.fda.gov/cder/about/history/time1.htm>

⁸⁸⁴ personal communication, Dr. Woodcock, June 8, 1999.

Drug supports the contention that its approval of psychedelic and medical marijuana research contributed to its demise. Dr. Woodcock explicitly stated that the dissolution of Pilot Drug had nothing to do with its work on psychedelics or marijuana.⁸⁸⁵ Dr. Lumpkin offered a similar denial, stating that Pilot Drug’s renewal of psychedelic and medical marijuana research played no role in its elimination. He further noted that the policies established by Pilot Drug toward the review of psychedelics and marijuana, namely that protocols be reviewed in a manner similar to the way FDA reviews all other drugs, is still intact and there has been no change in these policies since the elimination of Pilot Drug.⁸⁸⁶

This view was supported by Dr. Wright, who agreed that the demise of Pilot Drug “wasn’t related in any way to hallucinogens,” though he allowed that perhaps Pilot Drug’s actions on tobacco may have created some animosity toward Pilot Drug that contributed to the decision to dissolve it.⁸⁸⁷ Dr. Temple, another opponent of Pilot Drug, also shared the view that the “closing of Pilot Drug had absolutely nothing to do with psychedelics or marijuana research. We support science around here.”⁸⁸⁸ Dr. Lumpkin also emphasized that FDA’s focus on scientific research governs its policies toward all drugs that may have therapeutic potential.⁸⁸⁹ These statements by Dr. Temple and Dr. Lumpkin illustrate both their personal and FDA’s organizational commitment to seek wherever possible to prioritize scientific research over political concerns regarding the conduct or outcome of research.

In 1999, Dr. Wright reflected on the 1992 Drug Abuse Advisory Committee meeting that established Pilot Drug’s policies toward psychedelic research. He commented, “The purpose of the Advisory Committee was to ask whether there was anything special about hallucinogens, anything intrinsically different, to make research with these drugs be reviewed differently from other drugs. The answer was no.”⁸⁹⁰ The Advisory Committee’s ratification of Pilot Drug’s approach resulted in the first formal endorsement of the resumption of psychedelic research since Congress held hearings in 1966 condemning LSD research. Pilot Drug had succeeded in establishing the policy framework

⁸⁸⁵personal communication, Dr. Woodcock, June 8, 1999.

⁸⁸⁶personal communication, Dr. Lumpkin, February 18, 2000.

⁸⁸⁷personal communication, Dr. Wright, March 8, 1999.

⁸⁸⁸personal communication, Dr. Temple, March 18, 1999.

⁸⁸⁹personal communication, Dr. Lumpkin, February 18, 2000.

⁸⁹⁰personal communication, Dr. Wright, March 8, 1999.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

Note: * Reports to Deputy Commissioner
 ** Permanently assigned to ORA

New Organization
Effective 6/20/99

Commissioner of Food and Drugs
 Jane E. Henney
Deputy Commissioner
 Michael A. Friedman
 Senior Advisor for Science*

Office of the Senior Associate Commissioner
 Senior Associate Commissioner
 Linda Suydam

- Executive Secretariat
- Public Affairs
- Ombudsman
- Orphan Products
- Tobacco Programs
- Advisory Committee Oversight
- [Internal Affairs] **

Office of International and Constituent Relations
 Deputy Commissioner for International and Constituent Relations
 Sharon Smith Holston

- International Programs
- Consumer Affairs
- Special Health Issues
- Women's Health

Office of Policy, Planning, and Legislation
 Senior Associate Commissioner for Policy, Planning, and Legislation
 William K. Hubbard

- Policy
- Planning
- Legislation
- Evaluation
- Policy Coordination
- Regulations Policy
- Management Initiatives
- Economics

Office of the Chief Counsel
 Chief Counsel
 Margaret J. Porter

Office of Equal Opportunity
 Director
 Rosamelia T. Lecea

Administrative Law Judge
 Administrative Law Judge
 Daniel J. Davidson

Office of Management and Systems
 Deputy Commissioner for Management and Systems
 Robert J. Byrd

- Human Resources and Management Services
- Financial Management
- Facilities, Acquisitions, and Central Services
- Information Resources Management

Office of Regulatory Affairs
 Associate Commissioner
 Dennis F. Baker

National Center for Toxicological Research
 Director
 Bernard A. Schwetz

Center for Biologics Evaluation and Research
 Director
 Kathryn C. Zoon

Center for Drug Evaluation and Research
 Director
 Janet Woodcock

Center for Devices and Radiological Health
 Director
 David W. Feigal, Jr.

Center for Food Safety and Applied Nutrition
 Director
 Joseph A. Levitt

Center for Veterinary Medicine
 Director
 Stephen F. Sundlof

- Medwatch
- PDUFA Waivers
- Patent Term Restoration
- Scheduling of Controlled Subs. [from Health Affairs]
- Health Asses. Policy Staff

for the review of future research protocols.

Mr. Hutt offered the view that the changes at FDA regarding psychedelic and marijuana research were not driven by external pressure or by high-level internal decisions but by the personal attitudes of Drs. Harter, Wright and Spyker, by a few individuals who were able to work together to develop a new policy. Mr. Hutt observed that these decisions were relatively cost-free in that they did not generate much external or internal pressure on FDA. Mr. Hutt felt that Pilot Drug's approval of psychedelic research probably hardly even attracted the attention of FDA Commissioner Kessler. Dr. Spyker also attributed the renewal of psychedelic and marijuana research under Drs. Harter, Wright and himself not to a grand plan directed from above, but to Dr. Harter's vision and Dr. Peck's strong support for Dr. Harter.

The Legacy of Pilot Drug for Psychedelic Research

Dr. Woodcock remarked that she and Dr. McCormick both believe that the FDA should review research with Schedule I drugs in a manner consistent with FDA's review of all other drugs, explicitly endorsing the policy established by Pilot Drug and the 1992 Drug Abuse Advisory Committee. In Dr. Woodcock's opinion, Dr. McCormick does not share Dr. Leber's philosophy of drug review or his antagonism towards research with Schedule I and II drugs. Dr. Woodcock further noted that, with the passage of time, FDA and the culture in general have become more sympathetic to the plight of drug addicts and more aware that drugs with addictive potential can also have therapeutic potentials.

Dr. Lumpkin offered a benign explanation for Dr. McCormick's two year refusal to review Dr. Russo's medical marijuana protocol. According to Dr. Lumpkin, Dr. McCormick's decision not to review marijuana protocols unless NIDA had previously agreed to supply the drug was an FDA staff resource allocation issue and not a reluctance to approve research with marijuana. From FDA's point of view, there was little reason to review a protocol when the supply of the test drug was uncertain. Since NIDA was the only legal source of marijuana, FDA could be wasting valuable staff time if it approved a protocol only to have NIDA refuse to supply marijuana. When pressed, FDA agreed to review the protocol but this was not a reversal of any antagonism toward marijuana research.⁸⁹¹

Dr. Woodcock also pointed out that the reorganization of the Office of the Commissioner (effective June 20, 1999, several days after our interview) shifts FDA's responsibilities for the scheduling of controlled substances into her office from the Commissioner's office.⁸⁹² [current organizational chart, prior page] Dr. Woodcock

⁸⁹¹personal communication, Dr. Lumpkin, February 18, 2000.

⁸⁹²The June 18, 1999 memo, Explanation of the Office of the Commissioner Reorganization, states, "The Office of Health Affairs will be abolished. Some of its functions (health assessments, patent term restorations, and scheduling of controlled substances) are being reassigned to the Center for Drug Evaluation

thought that locating the responsibility for the scheduling and rescheduling of controlled substances in the same office that already reviews research protocols and New Drug Applications (NDAs) for these drugs would facilitate the exploration and development of the medical uses of psychedelics and marijuana.⁸⁹³

On February 16, 2000, Dr. Woodcock announced the establishment of the new Controlled Substances Staff (CSS), operating out of the CDER Director's office and assuming functions that had previously been the responsibility of the Office of Health Affairs in the Commissioner's Office.⁸⁹⁴ The CSS will also take over from the DACCADP the primary responsibility for reviewing non-therapeutic Phase I studies with psychedelics and marijuana.⁸⁹⁵ While it is too early to know for sure whether the CSS will remain open to Phase I studies with psychedelics and marijuana, every indication is that this will indeed be the case.

As psychedelic and medical marijuana research develops, the protocols will increasingly focus on therapeutic applications. As the specific patient populations and disease states to be studied move outside of the areas of expertise of DACCADP's staff, the DACCADP will begin to share the review of INDs and NDAs with FDA personnel in other divisions. The DACCADP will continue to play the primary role in reviewing research using psychedelics or marijuana for the treatment of pain and in the treatment of substance abuse. In the early 1990s, the pioneering attitude necessary for the renewal of psychedelic and medical marijuana research existed initially in Pilot Drug and was largely carried forward by DACCADP. It will soon be determined whether psychedelic and medical marijuana research can flourish throughout FDA.

and Research (CDER).” The reorganization became effective 6/20/1999.

<http://www.fda.gov/oc/reorg/june1999.html>

⁸⁹³personal communication, Dr. Woodcock, June 8, 1999.

⁸⁹⁴The February 16, 2000 memo sent to FDA review staff stated, “This is to announce the formation of a Controlled Substances Staff (CSS) reporting to the Office of the Director, CDER. This new staff will serve as a focal point for all activities related to the domestic and international control of drugs and substances. The CSS will now be responsible for the abuse liability evaluations previously assigned to the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) and formulating recommendations for drug scheduling under the U.S. Controlled Substances Act. They will also serve as the Agency focus of activities in this area, a function previously performed by staff in the FDA Office of Health Affairs. I am pleased to announce that Deborah Leiderman, M.D. has assumed the position of Director of the CSS. Dr. Leiderman is a board-certified neurologist who joins the FDA from NIDA. She will be joined on the new staff by Mike Klein, Silvia Calderon, and Corinne Moody whom many of you already know from their excellent work in DACCADP. Jim Hunter of the Executive Operations Staff is also providing staff support during this time of transition.”

⁸⁹⁵personal communication, Dr. Cynthia McCormick, June 2, 2000.

Conclusion

Pilot Drug was not dissolved due to its policies and actions regarding psychedelic and medical marijuana research. Neither was it eliminated due to systemic failures or errors in its practices, as indicated by its performance on standardized measures. Rather, Pilot Drug was dissolved primarily because the need for its non-hierarchical model, which was fundamentally at odds with standard FDA practices, had essentially disappeared once FDA became able to hire more staff as a result of the increased income that flowed from the passage of the Prescription Drug User Fee Act of 1992. Ironically, while Pilot Drug existed, its work creating the regulatory framework for the renewal of psychedelic and marijuana research was among its least controversial activities.

This analysis lends support to the conclusion that there are few inherent internal obstacles at FDA to the pursuit of research into the therapeutic applications of psychedelic drugs and marijuana, or to the possibility of prescription approval should sufficient research demonstrating safety and efficacy be presented to FDA. A variety of indicators support this view. Among them are 1) FDA's institutional mission, supportive of research into all potential medicines, including Schedule I drugs, 2) the personal values of senior FDA officials, as expressed in their interviews, favoring science over politics 3) the analysis in Chapter 3 which demonstrates that Pilot Drug was not eliminated and Dr. Wright was not passed over for promotion due to the renewal of psychedelic and medical marijuana research, 4) evidence from the 1994 exchange of letters between FDA and DEA over medical marijuana research, 5) DACCADP's commitment to approve the testing of MDMA in cancer patients, 6) DACCADP's 1999 approvals of a study evaluating the therapeutic use of psilocybin to treat patients with obsessive-compulsive disorder as well as a study using mescaline to study brain function with PET scanners, 7) the actions of DACCADP in the summer of 1999 regarding the approval of Dr. Russo's medical marijuana protocol despite NIDA's decision not to provide marijuana to the study, 8) FDA's Office of Orphan Products Development's approval of Orphan Drug status for marijuana for AIDS wasting, and last but not least, 9) the legacy of Pilot Drug and the 1992 Drug Abuse Advisory Committee's recommendations. These internal factors suggest that the policies established by Pilot Drug have been endorsed by senior FDA management and have become institutionalized.

Both by rhetoric and by recent action, the FDA policy towards psychedelic and marijuana research that was established by Pilot Drug seems to have informed and guided current decision-making. The policy basis and precedent for renewed psychedelic and medical marijuana research established under Pilot Drug makes future FDA openness toward such research more likely than it would be if the Pilot Drug experiment had not taken place, if only because it resides in organizational memory and provides formal justification for officials inclined to permit such research in the future.

A confluence of external factors also seem to be developing that may provide support to sustain the continuation of Pilot Drug's open but careful policies toward

psychedelic and medical marijuana research. These factors include 1) external pressure for medical marijuana research from the public, as expressed at the ballot box in state medical marijuana initiatives, 2) support for medical marijuana research (as opposed to ballot initiatives) expressed in the rhetoric of political leaders of both parties, 3) increased support for research into alternative medicines, 4) the gradual development of psychedelic research outside the United States which establishes evidence of safety, and 5) the lack of substantial external pressure on FDA against psychedelic and medical marijuana research.

Problematic factors remain 1) the controversial nature of the research, 2) the potential for unexpected adverse effects in clinical trials, 3) the lack of funding, 4) the shortage of qualified researchers willing to enter this field, and 5) the inherent difficulties involved in conducting rigorous treatment studies with psychedelics and marijuana.

It remains unclear which policies FDA will adopt in the future, or how the field of psychedelic and medical marijuana research will develop. Parts 2 and 3 of this dissertation seek to establish a map of the possible future. Chapters 4 and 5 focus on the design of the large Phase III studies that will be needed to provide FDA with evidence regarding the safety and efficacy of the use of psychedelics and marijuana in the treatment of a variety of clinical indications. Chapter 6 assumes that data proving the safety and efficacy of at least one psychedelic drug for at least one clinical indication has been submitted to FDA, and

proposes an optimal regulatory framework for the prescription use of psychedelics. Perhaps this map will help inform the decisions that are going to be made in the years to come.

Epilogue

On July 11, 1996, Dr. Harter passed away. Ms. Tyson noted that his age discrimination lawsuit against FDA was still ongoing when he died. She settled it after his death. This was “a bitter way to end a career, especially one that had been so productive.”

On January 2, 1997, an application to the Ford Foundation- Kennedy School Innovations in American Government program was submitted by William Hubbard, FDA Associate Commissioner for Policy Coordination, with sign-off by FDA Commissioner David Kessler. The preliminary application claimed three basic innovations that FDA thought worthy of consideration, all of which had been formally implemented in 1992; 1) System of prioritizing drugs based on medical benefits, 2) Novel procedure for accelerating approval for drugs that treat serious and life-threatening conditions – the use of surrogate endpoints, and 3) User fees.

On April 24, 1997, FDA submitted a revised application after having been chosen

as a semi-finalist. The application was submitted by William Hubbard, with sign-off by HHS Secretary Donna Shalala, and Dr. Michael Friedman, FDA lead deputy commissioner. The order of innovative items was reversed, with the users fees first, accelerated approval- surrogate endpoints second, and the ranking of drugs based on medical benefits as a method of expediting review was listed third.

On July 10, 1997, Prof. Jack Donahue conducted a site visit, and came away impressed with the changes at FDA that PDUFA had brought about. He wrote that these changes included, “systematic prioritization, a project-management system, formal timelines and tracking, and more intensive interaction with the drug companies at all levels.” It appears from information in the Innovation program files that Prof. Donahue was not told about Pilot Drug and its pioneering effort to bring to FDA the project management system, more intensive interaction with drug companies, or its remarkable brand of creative innovation and anti-hierarchical, organizational restructuring. Shortly after Prof. Donahue’s visit, FDA CDER received a 1997 Innovations in Government Award.

Dr. Janet Woodcock, Director of CDER, was aware of CDER’s Innovation Award. In a June 1999 interview, she noted that the FDA staff who wrote the original application to the Innovations in American Government program did not consult her or CDER management, which didn’t get involved until the second draft was required for the semifinalist round. Dr. Woodcock thought that the innovation of PDUFA was not a genuine innovation, but perhaps was seen as such because it provided more staff and offered benchmarks that were simple to quantify (reduced review times).

Ms Van Hoose, an ex-Pilot Drug staffer now in FDA’s Office of the Commissioner, observed “PDUFA squashed efforts at innovation by pouring resources into FDA.”⁸⁹⁶ She reported that after Pilot Drug was dissolved, Dr. Harter told the staff, “You have to go out and be missionaries.”⁸⁹⁷ Endorsement of the innovations resulting from the Pilot Drug experiment by some of the strongest opponents of the formal experiment, and decisions to continue or mainstream some of the innovations suggest that this has occurred.

⁸⁹⁶personal communication, Ms. Van Hoose, March 16, 1999.

⁸⁹⁷personal communication, Ms. Van Hoose, March 16, 1999.