The Odyssey of Depo-Provera: Contraceptives, Carcinogenic Drugs, and Risk-Management Analyses

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INTRODUCTION

Depo-Provera has been a scientific and political battleground for over twenty years. At stake have been the reproductive health of women, the marketing of a long-acting contraceptive by a multinational corporation, and international family planning and population control. Seventy nations have approved its use as a female contraceptive, but the U.S. Food and Drug Administration (FDA) has not, because the drug is a suspected carcinogen. FDA’s decision means marketing of Depo-Provera as a contraceptive is forbidden in the United States and in U.S. foreign aid programs. FDA’s decision also means the drug is less likely to be used in Third World family planning programs.

Depo-Provera’s administrative odyssey provides an opportunity to examine government regulation of the contemporary pharmaceutical revolution in contraception and FDA’s technology transfer function, i.e., determining whether a contraceptive drug is safe and effective for general use. Depo-Provera’s odyssey also provides the opportunity to examine three questions about the risk-management process the Agency uses to perform its technological transfer function. Why did FDA have to rely on ambiguous and uncertain scientific research about a drug’s carcinogenic risk? How did FDA weave together uncertain scientific facts with political and social values to make drug risk-management decisions? How politically and scientifically accountable was FDA in making its carcinogenic risk-management decisions about a contraceptive drug? In sum, Depo-Provera’s odyssey provides the opportunity to further our understanding of the politics of regulatory science.

The conventional view of the risk-management process provides a beginning point for answering these questions. The risk-management process, according to this view, is based on a two-stage model.¹ Risk assessment, the first stage, “is the
use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials or situations. 

Risk acceptability, the second stage, "is the process of . . . integrating the results of risk assessment . . . with social, economic, and political concerns to reach its decision." 3 The conventional view allows us to identify the risk-assessment and -acceptability elements of the Agency's decision, but it cannot explain the controversy over both the assessment and acceptability of the drug's risk because this viewpoint assumes a separation of fact and value. An alternative view holds that the strict separation of facts and values cannot be maintained in practice because the scientific basis of risk assessment is often incomplete and, therefore, policies based on that information become the subject of social, economic, and political debate "for their science alone, even if the critics really oppose the policies for quite different reasons." 4

To see how this happened in the Depo-Provera debate will involve an examination of the major elements of the drug approval process through which Depo-Provera has journeyed. Part I will examine Depo-Provera's premarket testing experience. Part II will explore FDA's Depo-Provera decisions: the role of advisory committees in the 1974 approval of limited marketing and the risk management basis for the 1978 disapproval of general marketing. Part III will examine the review of the disapproval decision by a panel of scientific experts as a public board of inquiry. This article will contend that Depo-Provera's administrative odyssey has felt the interplay of science and politics at each stage of FDA's drug risk-management process. Consequently, the article will focus on the scientific and political aspects of the debate, i.e., the scientific basis of FDA's risk assessments, the Agency's policy judgments about the drug's risk acceptability, and the scientific and political scrutiny of FDA's new drug decisions.

I. PREMARKET TESTING OF DEPO-PROVERA

Depo-Provera is a drug, manufactured by The Upjohn Co., whose active ingredient is medroxyprogesterone acetate (MPA). FDA first approved the drug in 1959 to treat amenorrhea, 5 irregular uterine bleeding, and threatened and habitual abortion. The following year it was approved to treat endometriosis. 6 Later FDA withdrew its approval for use of the drug in preventing miscarriage and endometriosis. 7 In 1972, FDA also approved Depo-Provera as "[adjunctive therapy and

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2 Id.
3 Id.
6 Endometriosis is a growth of endometrial tissue outside the uterus. Id. at 259.
7 FDA withdrew its approval in 1974 because the drug was not effective for these indications, nor was it safe for miscarriage. See 37 Fed. Reg. 15,033 (1972), 38 Fed. Reg. 27,949 (1973), and 39 Fed. Reg. 5221 (1974).
palliative treatment of inoperable, recurrent, and metastatic endometrial carcinoma and renal carcinoma. 9 Depo-Provera, injected intramuscularly in a 150 mg. dose, can also prevent contraception for at least three months by suppressing the hormones which induce ovulation. 9

The Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act) and its 1962 amendments require drugs be proven safe and effective. 10 Depo-Provera’s effectiveness is not in question. A single injection of the drug can stop ovulation for three months and is 99.8% effective in preventing pregnancy. 11 Safety is the issue. Scientific methods exist for determining drug safety, but their ability to determine a drug’s carcinogenic risk is limited by the animal and human experiments used in FDA’s premarket drug testing program. Premarket testing of drugs is based on experimental designs which are feasible prior to marketing. Small-scale and short-term animal studies assess the drug’s therapeutic potential and safety for human testing. Animal studies, conducted for two or more years, assess long-term human risk. Human clinical trials involving very small numbers of persons, which are used to confirm the animal findings on short-term toxicity, are followed by clinical trials, involving several thousand persons to assess a drug’s efficacy and short-term risks. Yet the evidence these tests provide has limited value in assessing carcinogenic risk of drugs because the latency of this risk may be twenty years or more.

Depo-Provera’s premarket screening process began with Upjohn’s initial screening which used animal tests to determine the drug’s therapeutic applications. In 1963, the company submitted to FDA a Notice of Claimed Investigational Exemption for a New Drug (IND) in order to conduct human clinical trials to determine the drug’s safety and efficacy as a female contraceptive. 12 The studies began in 1965. Two years later, Upjohn requested marketing approval by submitting a New Drug Application (NDA).

Upjohn’s NDA testing included two long-term animal toxicity studies initiated in 1968: a seven-year study of thirty-six beagle dogs and a ten-year study of fifty-two rhesus monkeys. The results, in 1975, from the dog study revealed malignant breast tumors in two animals and led FDA in 1978 to disapprove Upjohn’s NDA for Depo-Provera as an injectable contraceptive. 13 The results of the monkey study in 1979, which revealed endometrial cancer in two animals, and the results of the second study of 140 beagle dogs, which revealed breast cancer in twenty-four animals, cast further doubt on the drug’s safety. 14 These studies did not re-
solve the issue of the drug’s carcinogenicity, but have become part of the debate because of the scientific controversy over two major issues: whether the animals were appropriate models on which to test the drug’s human carcinogenicity and whether the high doses the animals received during the experiments were appropriate in light of the lower doses administered as a contraceptive to human females.

Upjohn also sponsored human clinical studies to establish Depo-Provera’s efficacy, appropriate dose level, and “physiological consequences and side effects following short-term use, e.g., weight gain, prolonged amenorrhea or bleeding, return of ovulation, and psychological side effects.”15 These studies were not designed to collect data on the drug’s long-term effects, but they incidentally revealed a risk of cancer as early as 1971 when researchers found women exposed to Depo-Provera had a higher-than-normal rate of cervical cancer. It was not until after FDA disapproved the drug in 1978 that any plans were made to collect data systematically.

Currently, there are over forty human studies of Depo-Provera designed for other purposes and “a few attempts at epidemiological studies” indicate a risk of breast and endometrial cancer. However, the studies contain major research flaws: small samples which do not include enough long-term users, lack of comparable control groups, failure to determine a subject’s cancer risk, limited follow-ups to determine long-range cancer risk, and incomplete record keeping.16 These studies have become part of the debate, but not because of scientific controversy over the data. Proponents of Depo-Provera agree the human data are probably inadequate but make the argument the quantity of the data can substitute for its quality. “The human studies individually may be inconclusive and questionable,” Upjohn has said, but “[t]hey are, in their totality, reassuring and sufficient to provide a basis for a regulatory decision.”17

II. FDA DEPO-PROVERA DECISIONS

Agencies make regulatory decisions which depend heavily upon an assessment of scientific evidence and a determination of what level of risk is acceptable. Depo-Provera’s animal and human tests have not provided FDA’s Center for Drugs and Biologics with a scientifically unambiguous body of information about the drug’s carcinogenicity. Yet FDA has a legislative mandate and bureaucratic jurisdiction to decide whether the drug is safe for human use. How did the Agency, in the face of this uncertain scientific information, decide first to grant Depo-Provera partial approval in 1974, and then, four years later, to reverse itself and disapprove the drug’s use for contraception? FDA’s actions will be examined in terms of two major features of its new drug approval risk-management deci-

16 Id. at 85. For a complete listing of the animal and human research studies, see id. at 70–79 and 109–14.
17 Id. at 85–87.
sionmaking process: the advisory committee’s review and recommendation and the Agency’s decision, based on its assessment of the drug’s risk and its determination of the risk’s acceptability.

The 1974 Decision: The Advisory Committee Role

FDA’s approval of an NDA is a license to a pharmaceutical company to market a drug. In making its decision, the Agency relies on advisory committees, because it is “faced with difficult scientific issue[s] without any simple testing method to determine risk.” 18 The committees provide the Agency with expertise not available in-house and the scientific community, the drug industry, and consumers with the opportunity to participate in NDA approval decisions. 19

When FDA announced its intention on October 9, 1973 to give Depo-Provera approval for limited contraceptive use, the order stated the Agency had relied on its Advisory Committee on Obstetrics and Gynecology’s recommendation that Depo-Provera’s risks outweighed its benefits for those women who found other methods of contraception unacceptable or difficult, or were mentally retarded and institutionalized. The order also stated FDA concurred in the advisory committee’s recommendation the NDA be conditioned on cautionary measures to assure proper use, including a distribution restriction “to maintain a registry of physicians who have utilized the drug for contraception” and an informed consent requirement the drug package include an informational leaflet and a detailed brochure to explain to the patient the drug’s use and risks. 20

This textbook use of an advisory committee became the subject of congressional hearings on FDA’s greatly increased use of advisory committees in NDA review. 21 When the House Subcommittee on Intergovernmental Relations, chaired by Representative L. H. Fountain (D-N.C.) reviewed the circumstances surrounding the Obstetrics and Gynecology Advisory Committee’s affirmative recommendation of Depo-Provera’s limited use, it found FDA had not relied upon the committee’s scientific expertise.

At the April 30, 1974 hearing, Representative Fountain’s questions to Dr. J. Richard Crout, Director of FDA’s Bureau of Drugs, and his examination of Agency documents, revealed that FDA medical officers, after a review of the Upjohn data in 1971 and 1972, had recommended discontinuance of further clinical IND use because preliminary results from the beagle dog studies suggested the potential for human mammary carcinoma and human studies revealed cervical cancer rates in excess of national incidence. 22 The FDA medical officers’

18 Id. at 82.
21 Use of Advisory Committees by the Food and Drug Admin.: Hearings Before the Subcomm. on Intergovernmental Relations of the House Comm. on Governmental Relations, 93rd Cong., 2d Sess. 2 (1977).
22 See id. at 356 and 358–63. The principal source for research findings of excessive cervical cancer rates in clinical studies was Powell & Seymour, Effects of Depo-Medroprogesterone Acetate as a Contraceptive Agent, 110 AM. J. OBSTET. & GYNECOL. 36 (1971).
report stated: "Sixteen subjects [out of 3856] have developed Grade III pap smears while on therapy. Biopsy showed carcinoma in situ in all subjects and all subsequently underwent hysterectomy."23 The transcript of the February 22, 1973 meeting of the Obstetrics and Gynecology Advisory Committee revealed "the cancer in situ figures were not discussed at any time during the committee's consideration of the safety of Depo-Provera."24

What particularly troubled Representative Fountain was that FDA officials said nothing at the advisory committee meeting even though they had known about the substantial variance in the analysis of data by their medical officers and by Upjohn. FDA officials had also known both analyses confirmed rates of cervical cancer which exceeded the national incidence of risk.25 Thus he concluded the committee was "in the unenviable position of having to decide about the safety of the drug without the full data before it."26

FDA was apparently undeterred by this congressional scrutiny, because it issued a final patient label rule on September 6, 1974 in anticipation of Depo-Provera's limited approval.27 At this point, Congressman Fountain intervened. In a letter of protest to then-Department of Health, Education, and Welfare (HEW) Secretary Caspar Weinberger on October 2, 1974, he requested the Agency revoke the rule because "there were many serious and, as yet, unresolved questions concerning the drug's safety including the drug's role in causing cancer."28 FDA Commissioner Alexander Schmidt, citing the need for public confidence in drug safety, subsequently stayed approval of the drug pending further advisory committee review of the scientific evidence.29

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23 Advisory Committee Hearings, supra note 21, at 361. Cancer in situ is cervical cancer and a Grade IV pap smear is "strongly suggestive of malignancy." Id. at 368 (quoting G. Papanicolaou, ATLAS OF EXFOLIATIVE CYTOLOGY).
24 Id. at 369.
25 Id. at 374–75.
26 Id. at 375. The most concise statement of the House subcommittee's findings on FDA's Advisory Committee on Obstetrics and Gynecology was stated in a question by Rep. Fountain to Dr. Crout:

If the evidence or data presented to the committee by Upjohn was not complete, as the participants at the committee meeting indicated during the closed session; if the significance for humans of cancer and tumor results in beagles is not known, as is revealed in the verbatim transcripts and in the FDA's October 10, 1973 Federal Register notice; if the facts, nature, and significance of the cases of cancer in situ were not presented to the committee or in any way discussed, as is apparent from the verbatim transcript; if there is not enough experience, because of the high discontinuation rate and other factors, to determine the extent of infertility caused by the drug, as indicated by the consultants; and if the problem of not being able to get rid of the drug once an adverse reaction occurs could not be resolved, as the transcript reveals at page 72, was the committee ready to make a benefits–risk determination?

Dr. Crout, to Mr. Fountain's utter amazement, answered: "Yes." Id. at 380.
29 Id.
The 1978 Disapproval Decision

FDA's next review began when the Advisory Committee on Obstetrics and Gynecology held a joint meeting in April 1975 with the Advisory Committee on Biometric and Epidemiological Medicine, examined the scientific evidence, and appointed a subcommittee task force. The subcommittee held an open meeting in September 1975 and later recommended limited approval. The Advisory Committee on Obstetrics and Gynecology discussed the subcommittee recommendation at its December 1975 meeting and, in spite of the just released beagle dog study which provided evidence of breast cancer, approved Depo-Provera for the same two limited groups of women and made the approval subject to the same conditions. This time FDA, after a lengthy Agency internal review, rejected the committee's recommendation and advised Upjohn by letter on March 7, 1978 that its NDA for the general marketing of Depo-Provera for contraceptive use had been disapproved. By formal notice on June 22, 1978, the Agency cited six grounds for disapproval and gave Upjohn notice of the opportunity for a hearing. An explanation of the Agency's action begins with an examination of the Food, Drug, and Cosmetic Act's risk-assessment criteria.

Risk Management Analysis

The FD&C Act requires foods and drugs to be tested for their safety. The statute sets two risk-assessment criteria. Food additives, food colorings, and animal drugs are evaluated on the basis of the Delaney Clause's single risk criteria: if they are carcinogenic in animals, they will not be approved regardless of their benefit. Foodstuffs contaminated with pesticide residues are evaluated using a risk-benefit analysis. The statute does not, however, specify a risk-assessment criteria for human drugs, but instead provides that FDA will approve or disapprove a drug on the basis of any one or more of sixteen standards for the drug's safety, effectiveness, manufacture, and labeling. The statute also recognizes the Agency's need for flexibility in applying these standards and in exercising "its scientific judgment to determine the kind and quality of data and information ... required to meet them." FDA, therefore, has broad statutory discretion to establish a human drug risk-assessment and -acceptability standards.

Risk-Assessment Criteria

FDA's disapproval of the limited and general marketing of Depo-Provera in 1978 was formally based on two statutory grounds for refusal to approve an

30 Depo-Provera Hearings, supra note 12, at 304.
31 Id.
36 21 C.F.R. § 314.105(c).
NDA: insufficient information to determine whether the drug was a safe contraceptive and test results which did not show it was safe.\textsuperscript{37} The disapproval decision was not, however, based on a published regulation which sets forth the Agency's criteria, nor is it clear what criteria FDA applied to disapprove the drug in 1978. There are three possibilities, the first two of which—no-risk analysis and risk-risk analysis—give no attention to the drug’s benefits, nor to weighing its benefits and risks.\textsuperscript{38}

First, the disapproval was based on an unwritten single risk factor criteria for assessing animal test results. As Dr. Victor Berliner of FDA's Bureau of Drugs stated: "an old toxicological principal is to spread the risk over species, at least two, preferably more, and to go by the least favorable results in any one of the species, as the leading deciding factor for evaluating toxicity or risk from a drug to the human."\textsuperscript{39} Depo-Provera was tested on three animal species: mice, rats, and dogs. The drug was not approved for human use as a contraceptive using this criteria because the beagle dog developed breast cancer. In this regard, the notice stated: "No other contraceptives that have such safety data are approved for marketing."\textsuperscript{40} FDA Commissioner Donald Kennedy repeated this criteria for the House Select Committee on Population. "No other contraceptive approved for marketing," Kennedy said, "has shown a similar carcinogenic potential in the beagle assay."\textsuperscript{41}

Second, disapproval was based on multiple-risk criteria and a risk-risk analysis. The notice cited three potential risks: breast carcinoma suggested by the beagle dog study, increased congenital malformations from the drug's failure, and the risk from estrogen therapy to control irregular bleeding caused by Depo-Provera use.\textsuperscript{42} The notice also cited risk-risk analysis data. Risk-risk analysis involves weighing the health risks of nonapproval against the health risk of approval, in order to determine whether disapproval would deprive the public of any countervailing health benefits.\textsuperscript{43} The notice stated Depo-Provera was disapproved because there were available "many safe and effective alternative methods of contraception and sterilization which have decreased the need for a long-term, potentially high risk injectable contraceptive."\textsuperscript{44}

Third, the disapproval decision was based on a risk-benefit analysis criteria. If the Agency's notice is read in conjunction with its 1973 and 1974 patient labeling regulation, it is clear the Agency gave attention to the drug's risks and benefits.

\textsuperscript{37} 43 Fed. Reg. at 28,556 (citing 21 C.F.R. § 314.125(b)(3),(4)).
\textsuperscript{39} Depo-Provera Hearings, supra note 12, at 58.
\textsuperscript{40} 43 Fed. Reg. at 28,556.
\textsuperscript{41} Depo-Provera Hearings, supra note 12, at 308.
\textsuperscript{42} 43 Fed. Reg. at 28,556.
\textsuperscript{44} 43 Fed. Reg. at 28,556.
FDA was satisfied when it proposed its 1973 regulation that the studies had proven Depo-Provera’s high contraceptive effectiveness. FDA acknowledged the beagle dog studies revealed the drug’s potential for malignant breast tumors and the human clinical trials demonstrated the drug’s potential for “prolonged and possibly permanent infertility . . . [along with] less significant adverse reactions.” Nevertheless, the Agency concluded Depo-Provera’s benefits outweighed its risks for the institutionalized mentally retarded, as long as the drug was provided with a required patient leaflet and brochure explaining the risks associated with its use and requiring the patient’s, a parent’s, or a guardian’s informed consent prior to administration of the drug. When FDA issued its patient label regulation in 1974, it disposed of congressional concerns about the risk of cervical cancer and reaffirmed its belief the drug’s benefits outweighed its risks for the same limited groups of women subject to the same requirements set out in the proposed rule to assure proper use.

In 1978, FDA stated it was disapproving Depo-Provera, in part, because it found there was “no significant patient population meeting the criteria proposed in 1974 for use of the drug and for whom the benefits of the drug outweighed the risks.” Thus, FDA concluded the drug “no longer has the positive risk–benefit ratio that it thought existed in 1974.”

This risk–benefit analysis applies only to the FDA refusal to give Depo-Provera partial approval in 1978. Yet this disapproval of the drug’s limited use did not, in fact, depend on risk analysis considerations at all, but on a risk-acceptability ground—the absence of a significant patient population—which will be discussed below. Does this risk–benefit analysis apply to the general marketing disapproval? The disapproval notice provides no evidence Depo-Provera had the same benefits for general marketing that it had for limited marketing, but that those benefits had been outweighed by the risk(s) identified under the no-risk or risk–risk analyses.

FDA might have given less weight to Depo-Provera’s risks under any of these three criteria if it had been impressed with a related risk-assessment factor, i.e., Upjohn’s proposed postmarketing survey. FDA had required Upjohn to submit a proposed postmarketing study as part of its NDA because the premarketing research had limited value in assessing the drug’s long-term carcinogenic risk. FDA denied Upjohn approval to market Depo-Provera, in part, because of “serious reservations about the ability of Upjohn’s proposed post-marketing study for breast and cervical carcinoma to yield meaningful data.” Upjohn’s proposed study, FDA concluded, “would require a much larger patient population than

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48 Id.
49 The Food, Drug, and Cosmetic Act does not authorize FDA to conduct postapproval drug monitoring and control of physician practices, but the Agency has increasingly taken potential postapproval problems into consideration in deciding whether to approve an NDA.
50 43 Fed. Reg. at 28,556.
proposed . . . [and] Upjohn would have difficulty finding enough patients . . . to complete them in time."

Risk-Acceptability Judgments

After FDA reached a negative risk assessment by relying upon one or more of the three possible criteria, it then had to confront the question: are the risks identified by the animal and human studies of Depo-Provera’s use acceptable in light of the drug’s demonstrated benefits? Risk acceptability, the second stage of the risk-management process, requires an agency to integrate “the results of risk assessment . . . with social, economic, and political concerns to reach its decision.” How did FDA determine Depo-Provera’s use was an unacceptable risk?

FDA’s disapproval notice states it had three social and political concerns about Depo-Provera which, along with its risk assessment, led it to conclude the drug was an unacceptable contraceptive. Depo-Provera was disapproved for the limited population identified in 1974 because there was “no significant population in need of the drug.”

Depo-Provera was also disapproved for general marketing for three other non-scientific reasons. First, the need for the drug, FDA claimed, had been decreased by the “availability . . . of many safe and effective alternative methods of contraception and sterilization which have become increasingly popular in recent years.” Second, FDA claimed the labeling requirements would have limited value in controlling physician prescription practices and in assuring patient consent. In 1974, FDA had proposed to approve Depo-Provera’s limited contraceptive use subject to leaflet and brochure requirements. By 1978, it doubted the value of such “cautionary measures” because there was “strong evidence Depo-Provera is being used for non-labeled indications.” Approval, FDA argued, would only increase the likelihood “Depo-Provera will be put to non-approved uses for which the benefits do not exceed the risks.” Third, FDA claimed approval would increase a woman’s risk of cancer because “physicians would be likely simultaneously to prescribe estrogens to patients in an attempt to control irregular uterine bleeding” caused by Depo-Provera use.

Political Consequences

FDA’s disapproval of Depo-Provera was a limited risk-management decision. Disapproval did not alter the drug’s IND status nor prohibit physicians on their
own authority from prescribing it for contraceptive use; 59 the disapproval only prohibited the drug's domestic marketing and export "based upon the agency's analysis of risk–benefit considerations in the United States." 60 Disapproval did not affect Depo-Provera's manufacture and sale by Upjohn's Belgian and Canadian subsidiaries to seventy foreign nations, who have approved the drug's contraceptive use, and to international population organizations, including the World Health Organization (WHO) and International Planned Parenthood Federation (IPPF) which dispense it in their Third World population control programs. 61 Depo-Provera, with sales of $25 million, is used by 1.25 million women worldwide.

FDA disapproval did, however, have an impact on Depo-Provera's contraceptive use overseas even though the Agency did not take into consideration, as its disapproval notice states, two risk-acceptability factors—the lesser availability of alternative methods of contraception and the lower quality of health care—that would probably have resulted in a different risk-management decision in other countries. 62 First, disapproval limited the drug's use in U.S. foreign aid programs. The U.S. Agency for International Development policy prohibits the Agency from exporting or directly financing the overseas purchase of nonapproved drugs. 63 Second, disapproval raised doubts, especially in developing nations that rely on FDA's risk-management decisions, about the drug's safety. FDA disapproval eventually led five countries to reverse their approvals to avoid charges of distributing an unsafe drug. 64

59 FDA's decision about an NDA does not affect a drug's use on an investigational basis, nor does it affect the discretion physicians have to prescribe an approved drug for an unapproved use. In fact, Depo-Provera is prescribed as a contraceptive especially in low-income areas and among black, Hispanic, and Indian women. See Congress Questions Indian Health Service Use of Depo-Provera, PMA NEWSLETTER, July 20, 1971, at 2–3.

Depo-Provera is also used experimentally to treat male sexual disorders and has been criticized on medical and legal grounds. See Comment, Sexual Offenders and the Use of Depo-Provera, 22 SAN DIEGO L. REV. 565 (1985); Demsky, The Use of Depo-Provera in the Treatment of Sex Offenders, 5 J. LEGAL MED. 295 (1984); and Comment, The Use of Depo-Provera for Treating Male Sex Offenders: A Review of the Constitutional and Medical Issues, 16 TOLEDO L. REV. 181 (1984).

Depo-Provera's use as a probation condition for convicted rapists, often characterized as chemical castration, has also met with an unfavorable judicial reception. In the most widely publicized case, People v. Gauntlett, 134 Mich. App. 737, 352 N.W.2d 310, modified, 419 Mich. 909, 353 N.W.2d 463 (1984), the Michigan Supreme Court overturned a probation condition requiring weekly injections of Depo-Provera to an Upjohn heir convicted of statutory rape. See Green, Depo-Provera, Castration, and the Probation of Rape Offenders: Statutory and Constitutional Issues, 12 U. DAYTON L. REV. 1 (1986).


61 Depo-Provera is also available internationally for contraceptive use; drugs with IND approval may be exported with a certification which limits their use to that foreign country.


63 The Agency for International Development (AID) does, however, continue to support the purchase of Depo-Provera, because Agency policy does not prohibit indirect financing of the United Nations Fund for Population Activities (UNFPA), the International Fertility Research Program, and the Family Planning International Assistance which supply contraceptives, including Depo-Provera, to developing nations.

64 The countries are Egypt, Jordan, Korea, Taiwan, and Yemen.
The House Select Committee on Population hearings provided the first forum to critique the scientific basis for FDA’s risk assessment and the international consequences of its risk-acceptability judgment. In three days of hearings, August 10–12, 1978, the committee provided the representatives of WHO and IPPF, along with those from the International Fertility Program and the Population Council, with the opportunity to testify that FDA’s action made a needed contraceptive less available to women in developing nations and that pending legislation, the Drug Regulation Reform Act of 1978, would improve the situation by permitting the export of nonapproved drugs.65

The House committee also took the opportunity to criticize the basis for the Agency’s scientific assessment and its determination of domestic patient need. Chairman James Scheuer (D-N.Y.) questioned FDA’s use of the animal test data in making national and international policy, because there was no scientific consensus on the use of the beagle dog to test for the possibility of human cancer.66 Representative Paul N. (Pete) McCloskey, Jr. (R-Cal.) argued FDA’s disapproval of Depo-Provera on the grounds there was no significant patient population in need of the drug went “beyond [its] scientific and pharmacological expertise . . . [and] beyond FDA safety questions.”67 When FDA officials told him their conclusion had not been based on any scientific studies, but on letters, phone conversations, and the absence of “clamor for approval,”68 he replied: “Public clamor—I would hope that an agency like the FDA, in order to preserve its scientific integrity, would not be reacting to public clamor.”69 This criticism was the extent of congressional oversight. As a consequence, the only immediate recourse available to Upjohn was internal Agency review.70

III. PUBLIC BOARD OF INQUIRY REVIEW

Upjohn had the right to challenge FDA’s disapproval of Depo-Provera in a full evidentiary public hearing before an administrative law judge.71 The company

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65 Depo-Provera Hearings, supra note 12. For a general discussion of the congressional hearing, see Maine, Depo: The Debate Continues, 10 FAMILY PLANNING PERSP. 342 (1978).
66 Depo-Provera Hearings, supra note 12, at 64.
67 Id. at 69.
68 Id. at 70.
69 Id.
70 After the failure of drug reform legislation, AID was also prevailed upon to make an exception to its policy which prohibits the Agency from exporting or directly financing the purchase overseas of FDA nonapproved drugs. AID convened a research panel—the AID Ad Hoc Consultative Panel—which found the research had not demonstrated Depo-Provera’s carcinogenicity. The beagle and monkey studies were inconclusive, as were the human data from the study of 86,000 Thai women. At the same time, the AID panel found the drug had substantial benefits for women in developing countries including its long-lasting effectiveness, its advantage for women who breastfeed, and its ease of administration. Balancing Depo-Provera’s risks and benefits, the AID panel, like the WHO and IPPF committees, recommended approval, but the Agency has yet to alter its policy.

made the request on July 24, 1978, but waived that right two weeks after the congressional hearings and requested instead a review procedure which has been invoked only once before in FDA's history: a hearing before a public board of inquiry.72

A board of inquiry is a highly specialized administrative creation whose purpose is "to review medical, scientific, and technical issues."73 FDA regulations indicate a board of inquiry serves in a consultative capacity, but it is not an advisory committee: "A Board functions as an administrative law tribunal."74 Its proceedings are not, however, a legal trial, but "a scientific inquiry"75 conducted as an informal hearing.76 Its findings and conclusions have the legal status of an initial Agency decision.77 This analysis of the public board of inquiry's review of FDA's decision on Depo-Provera will focus on three subjects: its mandate, its hearings, and its risk-management recommendation.

Board of Inquiry: Its Members and Its Mandate

FDA Commissioner Donald Kennedy accepted Upjohn's request for a public board of inquiry on October 24, 1978 and also approved an Upjohn request to delay the hearing until the company could analyze the data from the recently completed rhesus monkey study. Upjohn notified FDA on April 25, 1979 that its review was complete. Then on July 27, 1979, the Commissioner ordered a hearing before the public board of inquiry.78 Two years intervened before the board members were appointed.79 Commissioner Arthur Hull Hayes finally appointed three eminent scientists in September 1981: Judith Weisz as chairperson and Griff T. Ross and Paul Stolley as members.80

The public board of inquiry was charged with reviewing FDA's drug risk-management decision. The board's mandate did not, however, involve a mirror-image review of the scientific evidence and the risk-acceptability grounds of FDA's decision. The scientific risk-assessment issues the board was ordered to address included two grounds which had served as the basis for FDA disapproval—Depo-Provera's risk of breast cancer suggested by the beagle dog study and the drug's teratogenic effect—along with two new issues involving the drug's carcinogenic risk. The animal data now included the second beagle dog study and the rhesus monkey study where the issue was "whether the data . . . indicate a potential risk of . . . endometrial cancer in humans."81 The human clinical data

72 The first public board of inquiry had been established to review the FDA's approval of aspartame. 44 Fed. Reg. 31,716 (1979).
73 21 C.F.R. § 13.30(a).
74 Id. § 13.10(e).
75 Id. § 13.30(a).
76 Id. § 13.30(d).
77 Id. § 13.40.
79 The choice of public board of inquiry members is governed by 21 C.F.R. § 13.10(c).
80 Dr. Judith Weisz, Head, Div. of Reproductive Biology, Dep't of Obstetrics and Gynecology, Hershey Medical Center, Penn. State Univ.; Dr. Griff T. Ross, Assoc. Dean, Clinical Affairs, Univ. of Tex. at Houston; and Dr. Paul Stolley, Prof. of Medicine and Research Medicine, School of Medicine, Univ. of Penn.
issue was also included at Upjohn's request, because the pharmaceutical company believed the data "would successfully refute the risk of cancer suggested by the animal data."82

The board was ordered to address four risk-acceptability issues, two of which had served as grounds for disapproval: whether general marketing was likely to increase Depo-Provera's use for nonlabeled conditions and unrelated indications and whether estrogen therapy was likely to be prescribed for Depo-Provera's side effects.83 The board was also ordered to address two new risk-acceptability issues in making recommendations about limited and general marketing. A recommendation for limited marketing was required to consider "whether there are conditions of labeling and distribution controls which would permit [safe and limited] marketing."84

The board's recommendation for general marketing approval was to be based on a risk-risk analysis of Depo-Provera when compared with drugs FDA approved for contraceptive use.85 In making a recommendation for either limited or general marketing approval, the board was required to restrict its risk-management analysis to the United States.86 In sum, the order of July 27, 1979 required the public board of inquiry to hear testimony assessing the drug risk and determining its acceptability for contraceptive use and then to address both scientific and policy issues in making a risk-management recommendation.

Board of Inquiry Hearing

The public board of inquiry heard five days of testimony on January 10–14, 1983 from all major participants in the Depo-Provera debate: the pharmaceutical industry; medical organizations; population control, consumers', and women's groups; and government agencies including FDA.87 Their testimony was not restricted to the information which served as the basis for the FDA disapproval action, but included a wider range of scientific evidence and alternative analyses.

82 Id.

83 Id. One risk-acceptability ground which had served as basis for disapproval was, however, curiously absent: whether Upjohn's proposed postmarketing study for breast and cervical cancer could yield meaningful data. 43 Fed. Reg. 28,555 (1978).

84 44 Fed. Reg. at 44,275. Limited approval, unlike the 1978 disapproval action, would not depend upon one risk-acceptability factor, but upon the existence of a significant domestic population in need of the drug. 43 Fed. Reg. at 28,556.


87 J. WEISZ, G. ROSS & P. STOLLEY, supra note 15, at 4. Among those organizations represented at the hearing, in addition to Upjohn and FDA's Center for Drugs and Biologics, were the World Health Organization (WHO), the International Planned Parenthood Federation (IPPF), the U.S. Agency for Int'l Dev., the Women's Nat'l Health Network, the Health Research Group, the Inst. for the Study of Medical Ethics, and the American College of Obstetrics and Gynecology.

of that evidence. The two foci of the testimony were the assessments and acceptability of the drug's risk.

The scientific information now included the rhesus monkey study and the beagle dog study. Upjohn argued the test results should be minimized because the beagle dog was an inappropriate test model. The dog metabolized progestins differently from humans and was prone to mammary tumors. The monkey studies, it argued, should also be discounted because endometrial cancer developed spontaneously from a cell type which had no human counterpart. The scientific information also included human test data which had not directly served as a basis for FDA disapproval in 1978. Upjohn agreed the data from over forty studies might be questionable on scientific grounds, but argued they were "in totality, reassuring and sufficient to provide the basis for a regulatory decision." Moreover, the preliminary data from a WHO nine-nation study did not implicate Depo-Provera as the cause of human cancer.

The testimony on risk acceptability focused primarily on the international implications of Depo-Provera's nonapproved status. WHO and IPPF representatives argued that FDA's decision had had a significant impact on decisions developing nations had made about Depo-Provera's use; but the Agency's risk-acceptability judgment had not been based on considerations relevant to those nations. They claimed the drug was a desirable contraceptive for women in the Third World where fertility and maternal mortality rates were extremely high, other methods of contraception were less available and desirable, and the health care system was less advanced and less extensive. The drug was preferable for women who breast-feed, because, unlike oral contraceptives, it did not suppress lactation. The drug was also preferable because it did not require storage under difficult conditions, nor did its administration require a clinic setting—it could be given, even in remote areas, by trained nonprofessionals.

Board of Inquiry Report

The public board of inquiry members took over a year to examine the research data and analyses, and to write their report; a 207-page document issued on October 17, 1984. The board considered its "primary task to be to evaluate the scientific validity of the information available." Since their report had the legal

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88 The alternative post-1978 Depo-Provera analyses include the following: INT'L PLANNED PARENTHOOD FEDERATION, STATEMENT OF THE INTERNATIONAL MEDICAL ADVISORY PANEL ON DEPO-PROVERA (1980); WORLD HEALTH ORGANIZATION, SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION, STATEMENT ON SAFETY OF THE LONG-ACTING INJECTABLE CONTRACEPTIVE DEPO-PROVERA (1978); and U.S. AGENCY FOR INT'L DEV., REPORT OF THE AD-HOC PANEL ON DEPO MEDROXYPROGESTERONE ACETATE (1980).


89 J. WEISZ, G. ROSS & P. STOLLEY, supra note 15, at 82.

90 Id. at 5-6.

91 Id. at 5.
status of an initial decision, the board "attempted to determine how much of this information qualified as facts [as distinguished from assumptions and hypotheses] on which definitive conclusions could be based." The board then reordered the seven questions it had been required to address to evaluate the distinction between scientific assessment of risk and policy judgments about risk acceptability. "We have reordered the sequence," the report stated, "so that the scientific evidence available for assessing the risks . . . required to arrive at a regulatory decision, is presented first and evaluated before considering the regulatory decision itself." Thus, the board first gave detailed consideration to Questions 2, 3, and 5 which concerned Depo-Provera's carcinogenic and teratogenic potential, and then briefly discussed Questions 1, 4, 6, and 7 which involved judgments about the drug's marketing.

Risk-Assessment Analysis

The board of inquiry's review of the scientific evidence began with the issue raised by Question 2: whether the beagle dog study and rhesus monkey study data indicated a potential risk of breast or endometrial cancer in humans from Depo-Provera. The board's examination of this research focused on three sub-issues, i.e., whether the malignancies were drug-related, whether there was a dose–response relationship, and whether the animals' progestogen response was applicable to humans. The board found the first beagle dog study was unable to address these issues because it was poorly designed and executed. However, the second study, well designed and executed, provided "evidence that the mammary carcinomas in the dogs were drug-related . . . There was also [a] good indication of dose–response relationship: malignancies developed both more frequently and earlier with increasing doses of DMPA."

The monkey data was more problematic. The development of malignancies in the rhesus monkey, unlike the beagle dog, were unanticipated. Dr. Weisz established an expert committee of six pathologists to review the monkey research. The pathologists presented their report at a second hearing on August 12, 1983. They unanimously concluded "progestogens can elicit a malignant transformation in the uterus of monkeys." The board was, however, unable to determine whether there was a dose–response relationship because "the study was poorly designed and executed, the number of controls and animals receiving lower doses

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94 Id. at 7.
95 Id.
of DMPA was much too small and the pathological examinations too inadequate."

The board then examined in detail, and dismissed Upjohn's argument, whether the beagle dog and rhesus monkey were inappropriate models for testing the long-term effects of progestogens on human females. Since Depo-Provera had "exhibited the characteristics of a potential carcinogen [in the animal studies] according to generally accepted criteria," the board was unwilling "to dismiss the findings as irrelevant to the human . . . [because there was no] conclusive evidence of fundamental differences among the species in the basic mechanisms of action of the hormone or in the response of target cells." Little research supported Upjohn's argument that the beagle responds differently to progestogens than a woman. No research supported Upjohn's argument that monkeys possessed a special cell type that made them more prone to endometrial cancer.

The board then turned to the issue raised by Question 3: whether the human data submitted by Upjohn could successfully refute the risk of human cancer from Depo-Provera suggested by the animal data. In general, the board found the human data inadequate, because it was not based on studies which addressed the issue of cancer, was not derived from epidemiological studies, and if they were, suffered from major research design and execution limitations. The board's critique of the human studies was organized in terms of the research findings on breast, cervical, and endometrial cancer.

The breast cancer data first came from an IND study of 11,631 women, but the board found the data of limited value because it was "pooled" from over eighty different research centers. As a consequence, it was "not possible to assess the significance of five cases of breast cancer in a mixed population of subjects." A major problem with the studies involving the incidence of breast cancer was that they were descriptive clinical reports which were not designed to provide epidemiological data. Whether retrospective or prospective studies, they included too few long-term users, too short a period of follow-up, a lack of information about the subject's medical history, inadequate or inappropriate controls, and a lack of documentation. The board concluded: "If the same standards are applied equally to all studies, we are left essentially without information on the effect that the use of DMPA as a contraceptive may have on the incidence of breast cancer."

Cervical cancer from Depo-Provera use had gained political attention when Representative Fountain relied on the findings from an IND research study to gain a stay of FDA's proposed limited approval of the drug in 1974. The board was critical of this study not only because "the cervical abnormalities were diagnosed only a short time after the initiation of drug use," but also because the study was poorly designed and executed. "The data were collected from sub-

98 J. Weisz, G. Ross & P. Stolley, supra note 15, at 32.
99 Id. at 174.
100 Id. at 88.
101 Id. at 89.
102 Id. at 102.
jects at various centers, both in and outside the United States representing different populations with unknown background incidence of cervical cancer.''

The board also found no other appropriately designed epidemiological study of Depo-Provera addressed the issue of cervical cancer until after FDA's disapproval action in 1978. The World Health Organization initiated a study in 1979, but it had not been completed by the time the board issued its report. Thus, the board concluded: "Until reports from the above studies are published, the early suggestions that the drug may increase the incidence of cervical neoplasia cannot be dismissed."

Endometrial cancer evidence was based primarily on endometrial biopsies. The early biopsies, the board found, were not designed to study endometrial cancer. Studies conducted after the discovery of endometrial cancer in the rhesus monkey were flawed because the number of subjects in the three biopsy studies was too small and the two retrospective epidemiological studies had a serious lack of information on the subjects. In the Thai study, the subjects were identified from hospital records; the Mexican study diagnoses were obtained from death certificates. Thus, the board concluded: "There are no data available that could serve as a basis for deciding whether the use of DMPA as a contraceptive has an effect on the incidence of [human] endometrial cancer."

After an exhaustive survey of this scientific data on breast, cervical, and endometrial cancer, the board of inquiry rejected Upjohn's argument that the quantity of this data could substitute for its quality, and voluntary reporting could substitute for specific studies. What was needed, but what had only begun after FDA's 1978 disapproval action, were appropriately designed studies which would "collect data in a systematic manner from humans on the consequences of long-term use of Depo-Provera."

Risk-Acceptability Judgments

When the board of inquiry examined the four risk-acceptability issues, its treatment was brief and its analysis almost exclusively scientific. The board dismissed the estrogen therapy issue, Question 6, in one page with the conclusion estrogen use was unlikely because "there appears to be a consensus . . . that estrogen is ineffective in either treating or arresting uterine bleeding caused by DMPA." The board then reformulated the risk-acceptability issues and in ten pages discussed them jointly with its recommendations on limited and general marketing.

Depo-Provera's general marketing approval depended upon its benefits outweighing its risks in comparison with other FDA-approved contraceptive drugs, but the board was unable to weigh the benefits and risks and was, therefore,

104 Id. at 103.
105 Id. at 106.
106 Id. at 100.
107 Id. at 84–85.
108 Id.
109 Id. at 145.
unable to conduct a risk–risk analysis. The drug's benefits, it said, were clear and its short-term side effects had been well documented. "Neither the short-term side effects of the drug, nor its teratogenic potential should constitute a reason for not proposing to use DMPA." 110

What troubled the board was its inability to assess the drug's long-term carcinogenic effects. "The available evidence presented fails to provide an adequate, scientifically justifiable basis for concluding whether the use of DMPA as a contraceptive...does or does not pose any long-term risks." 111 In the absence of this evidence, the board was unable to recommend general marketing approval because there was "no valid basis for comparing the risks of DMPA with those of other contraceptives." 112 This conclusion allowed the board to avoid as "largely irrelevant" the issue of the drug's potential for increased unapproved use under general marketing conditions. 113 The board did, however, reject obiter the view a drug's possible nonapproved uses should influence an NDA decision because "[i]t...is FDA policy not to regulate the physician's practice of medicine in prescribing approved drugs for unapproved indications." 114

Depo-Provera's limited marketing approval, per Question 7, depended upon whether there was adequate control of its distribution to patients with special needs. The board acknowledged this patient population existed, but disagreed over limited approval. Dr. Ross recommended approval, if feasible, for the mentally retarded and for drug addicts, 115 but Drs. Weisz and Stolley were unwilling to recommend limited approval for two reasons. First, they did not "think it desirable that FDA set up broad categories of indications...since...the drug is likely to be appropriate only for selected patients within each category." 116 They preferred instead to have the decision about Depo-Provera's use made on "an individual basis and with informed consent," because it would avoid the need for limited marketing approval. 117 "DMPA is currently approved...for use for other indications." 118 Second, they did not believe FDA had any effective mechanisms to limit the drug's distribution only to patients with special needs or to collect information from them in a systematic manner about its use. 119 These two risk-acceptability judgments, unlike those made about general marketing, were neither well argued nor scientifically well documented by the two members. The first was merely based on a preference for an alternative procedure through an NDA loophole, while the second was briefly stated in conclusory language without any supporting scientific evidence.

110 Id. at 162.
111 Id. at 160.
112 Id. at 165.
113 Id. at 166.
114 Id. at 167.
115 Id. at 170, 181.
116 Id. at 169.
117 Id.
118 Id. at 169–70.
119 Id. at 170.
Risk-Management Recommendation

The public board of inquiry recommended Depo-Provera should not be approved for general marketing. The action was based on the following finding of scientific fact: the "[D]ata available on the long-term risks of DMPA are insufficient and inadequate to provide a basis for a decision whether the benefits of the drug as a contraceptive outweigh its disadvantages under conditions of general marketing in the USA."  

This factual finding led the board to reach a conclusion of law identical to FDA's 1978 disapproval action: Upjohn's NDA for Depo-Provera for contraceptive use "does not contain reports of investigations adequate to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling . . . [which when] combined with other information about the drug, does not provide [a] sufficient basis from which FDA can determine that DMPA is safe for general marketing."  

As noted earlier, this finding of fact and conclusion of law have the status of an initial Agency decision. 

The board of inquiry did not, however, reach any factual findings or legal conclusions about limited marketing. Thus, the board's recommendation provided substantial scientific support for FDA's decision to deny Depo-Provera general marketing approval.

CONCLUSIONS

Depo-Provera's administrative odyssey confronted the interplay of science and politics at each of the major stages in FDA's drug risk-management process: premarket testing, Agency decisionmaking, and external review. FDA's premarket testing of Depo-Provera assured the Agency would have to rely on uncertain scientific research because these studies are designed to assess the drug's efficacy and short-term risks, but not the long-term risk of cancer. When FDA relied on animal and human studies to decide whether to grant Depo-Provera marketing approval, criticism of the scientific basis of this research became a central element in the political controversy over Depo-Provera, not for its science alone, but because of the manner in which the Agency's risk-acceptability judgment integrated its assessment of the drug's carcinogenic risk with its social, economic, and political interests in regulating domestic contraceptive use.

The FDA risk-management decisions on Depo-Provera were based on its broad statutory discretion. In 1974, the Bureau of Drugs assessed the drug's risk and its acceptability for limited marketing and then turned to the Advisory Committee on Obstetrics and Gynecology, not for the panel's recommendation, but for its stamp of approval. In 1974 and 1978, FDA's decisions about limited and general marketing were not based on any criteria set out in Agency regulations to assess the

120 Id. at 172.
121 Id. at 179.
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The drug’s carcinogenic risks. The Agency’s determination of the acceptability of the drug’s risk was also not based on any scientific studies and arguably went beyond the Agency’s scientific expertise and statutory mandate. This administrative discretion has, however, had its political limits. The 1974 approval decision was criticized on risk-assessment grounds and subsequently stayed by the intervention of a consumer-oriented congressman. The 1978 disapproval decision met with minor criticism for its assessment of risk and domestic acceptability and with an unsuccessful attempt to moderate its international consequences through reform of the drug export laws. FDA’s exercise of its regulatory discretion also has had its scientific and legal limits.

FDA’s 1978 disapproval decision was subject to internal Agency review before an administrative law judge, but Upjohn opted instead for review by a public board of inquiry, a panel of scientific experts whose risk-management recommendation has the status of an initial Agency decision. The board of inquiry was ordered to consider both risk-assessment and risk-acceptability issues. However, the board confined its analysis to a scientific assessment of the animal and human research, briefly discussed the marketing issues from a scientific perspective, and reminded the Agency, *obiter*, that risk-acceptability judgments based on a concern with physician prescribing practices were beyond its province. In sum, the board of inquiry’s report has settled, for now, on a scientific basis, FDA’s refusal to grant Depo-Provera general marketing approval, but not its refusal of limited approval for a well-defined patient population.

What is the likelihood FDA will reconsider its refusal to approve Depo-Provera? FDA is willing to certify the drug’s safety and approve an amended NDA for general marketing *if* Upjohn demonstrates the animal test results are not relevant or that better designed human studies show the drug is not carcinogenic. FDA is also willing to grant Depo-Provera limited approval *if* a well-defined patient population exists for which the carcinogenic risks suggested by the animal and human studies are overcome by unusually great benefits. No new animal experiments are being considered, but human studies are being conducted by the Centers for Disease Control, the International Fertility Research Program, Upjohn, and the World Health Organization which may provide evidence sufficient to ameliorate the conclusions of the beagle and monkey studies. Upjohn’s is a well-designed epidemiological study of New Zealand women who use Depo-Provera. The WHO’s is a $1 million, nine-nation case control study of potential cancer risk from various contraceptives, including Depo-Provera. If the evidence from these studies is favorable, FDA will, once again, have to make a risk-management decision, the core of which will be its new assessment of Depo-Provera’s carcinogenic risk.