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The Depo-Provera Controversy: A Sociological Analysis

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THE DEPO-PROVERA CONTROVERSY: A SOCIOLOGICAL ANALYSIS

by

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This study is a sociological analysis of the Depo-Provera Controversy. The strong programme in the sociology of science was the method employed for examining the social and political dimensions of the decision-making process underlying science and technology as it relates to the approval of Depo-Provera as a contraceptive in the United States. The data were consistent with the social constructionist perspective, rather than the positivistic view of science. In almost every instance, scientific conclusions followed alignment rather than arising from objective, universalistic analysis. Upjohn scientists and family planners concluded that Depo-Provera was safe and advocated its use; feminists and consumer advocates concluded the opposite. This analysis supports the view that science is inherently social and political.

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Pamela A. Hayman

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CHAPTER I

INTRODUCTION

A major goal of contraceptive research is to develop a long-acting, effective means of birth control which is easily reversible, but does not have to be administered daily or at each act of coitus. Depo-Provera, the trade name for injectable depot medroxyprogesterone acetate (DMPA), is such a drug. A synthetic analog of the female sex hormone progesterone, it is injected in doses which prevent contraception for three months. By the 1980s DMPA was used by more than two million women in eighty countries. Almost everything about DMPA - from abstract ethical issues to the interpretation of the medical data - has become controversial.

This thesis is a sociological analysis of the Depo-Provera controversy. Numerous technical controversies have emerged in the last decade creating an interest in the sociological factors influencing technical decision-making. This analysis of the Depo-Provera controversy examines the social and political dimensions of the decision-making process underlying science and technology.

While the Depo-Provera controversy offers many

opportunities for interesting sociological research both cross-culturally and domestically, this thesis specifically examines the controversy in the United States over the approval of Depo-Provera as a contraceptive. This chapter will first examine the two competing views of science. Then, the application of the social constructionist perspective to technical controversies and the Depo-Provera controversy specifically will be discussed.

Competing Views of Science

Two competing views which emerge in examining technical controversies are the positivistic and the social constructionist views of science. These two theoretical approaches differ in their background assumptions and have different implications for the interpretation of the Depo-Provera controversy.

The positivist view of science treats scientific knowledge as epistemologically unique, firmly grounded in the rigorous procedures of the scientific method. Because knowledge is objectified, positivists deny any intrinsic relationship between subject and object. Therefore, true scientific knowledge is not conceptualized as being shaped by or a product of subjective socializing processes - e.g. the social structure, ethics, and culture - but as neutral and value-free.

According to positivists, the scientific method allows scientists to maintain objectivity and to report truths about the physical world with completeness and accuracy. Because scientific knowledge is not socially influenced, it is not subject to the bias and distortion of other areas of knowledge. Therefore, scientific knowledge is not a source for sociological analysis.

Positivists also maintain that there are universalistic ethos within the scientific community which forms a cohesion among scientists - "...general conformity to such normative principles as impartiality, emotional neutrality, and particularly universalism, is seen as necessarily implied by the nature of scientific knowledge" (Mulkay,1979,p.64). Any person who knows and follows proper scientific methods is capable of producing truths. Therefore, the truths expressed are not influenced by the scientist or his/her environment and are thus reproducible by any other scientist (Gilbert,1976,p.285). By removing social processes from the realm of scientific activity, the positivist perspective is ahistorical, influenced by neither time or place.

The social constructionist paradigm focuses on the processes through which the subject, operating within the institutional and social structural milieu,

creates or constructs scientific knowledge. Science is not revealed, but created. It is created out of a cultural context. Like any other institution, science is inherently ideological; so-called facts arise out of elaborations, interpretations, and orientations of basic value positions (Thomas,1982). These elaborations are often referred to as claims.

Spector and Kitsuse (1977) argue that definitions of social problems are a claims-making activity. Members who find particular social situations repugnant, call attention to the situation by attempting to mobilize resources to do something about it - thus, constructing a social problem. Claims-making is a form of interaction in that one side makes demands upon the other side to alleviate the putative condition. Therefore, all participants involved in the claims-making activities are also participants in the process of defining social problems. The primary focus for analysis is to account for the emergence, nature, and maintenance of claims-making and responding activities (Spector & Kitsuse,1977,p.76).

Basic assumptions of the sociology of science are similar to the social constructionist paradigm. Interests are viewed as inspiring the construction of knowledge out of available cultural resources specific to particular times and situations and their overall social and cultural context. The maintenance of knowledge

is related to the objectives and interests of a society by virtue of its historical development.

The strong programme (Bloor,1976) has been one of the most influential methodologies for doing the sociology of science. The purpose is to examine the relationship among knowledge, social interests, and social structure. Bloor defines knowledge as consisting of beliefs which people confidently hold to and live by and is collectively endorsed. The focus of study is on the distribution of beliefs and the factors which influence it.

Bloor (1976) developed a basic framework for examining scientific knowledge as social constructions. He identified four basic tenets of the strong programme: causality, impartiality, symmetry, and reflexivity. First, because the growth of knowledge arises out of the historical development of procedures, competences, and techniques relevant to the objectives of culture, causality is concerned with conditions which bring about beliefs. Second, all knowledge is generated and sustained in light of particular interests and by use of available cultural resources, therefore, both true and false beliefs must be explained (impartiality). Third, the same sort of causes must generate both classes - true and false beliefs. Finally, the same patterns of explanation must be applicable

to sociology itself (reflexivity).

Critics of the social constructionist paradigm argue that social constructionists fall into a "relativity trap". In treating knowledge as by products of social influences, social constructionists invalidate their own research.

Mulkay (1979) suggests that instead of assuming that socially determined ideas are invalid, the definition of valid knowledge must be altered to the idea that all knowledge is socially created. Whether or not a belief is true or false is irrelevant. What is important is the process whereby certain beliefs become "operable truths". That is, beliefs that influence public policy which effects the lives of many people as well as future knowledge.

Social Assessment of Science

The social assessment of science is becoming increasingly popular with the growing number of scientific controversies in the last two decades. Scientific research has been subject to evaluations involving social and ethical criteria. The expertise of scientists is no longer going unchallenged on many public issues, but is becoming the basis of public debate. This new relationship between science and society has brought scientific knowledge away from the technical arena

where scientists with their objective expertise evaluate available knowledge to determine the most effective alternative for meeting an objective - to the political arena where objectivity is challenged and conflicting interests weighed in deciding public policy (Mendelsohn, Nelkin, Weingart,1979; Nelkin,1975; Petersen,1984; Pinch and Bijker,1974).

In the past, few challenged the expert testimonies of scientists, but in the last decade, consumer advocate groups have been organized to challenge the assumptions of "scientific objectivity", the "misuse of expertise", and the political use of scientists in policy decisions with significant public implications (Nelkin,1975). Advocates claim that the technical data that scientists assert to be "objective truths" is ambiguous and subject to different interpretations. At this point, advocates are beginning what Spector and Kitsuse (1977) define as claims-making activities by calling attention to a particular situation and making demands on the other group to alleviate the imputed condition.

In examining scientific controversies within the sociology of science, an attempt is made to analyze how competing social groups impose their ideological positions as definitions of reality by asserting knowledge claims and value claims based on their world view. Therefore, it is necessary to examine the relationship

between interests, alignments, ideology, and claims.

Spector and Kitsuse (1977) define interests as "any real and material advantage or stake that an individual or group claims, or is imputed by others to have, in the outcome of activity" (p.87). An interest group are those persons who claim to have something to gain or lose over the imputed condition. Woolgar (1981,p.370) claims that "interests can be shown to influence rather than determine knowledge production. The research strategy is to reveal interests as a backcloth of attendant circumstances and to imply that this revelation throws into better perspective the knowledge, claim or event." Scientific controversies can be better understood in light of particular interests of claims-making participants and can put into perspective the events and knowledge claims of competing sides in a controversy.

By monopolizing and controlling the distribution of knowledge, scientists have been well placed to legitimize their expertise and to justify excluding the public from scientific decision-making. Increasingly, consumer advocates have been challenging the authority structure's right to control the development of technological products and the decision-making process, as well as the right of professionals to assess the impact of their research on affected individuals.

As the public becomes more aware of the challenges to the "objective truths" of scientists, the political impact of scientific experts decreases. Those challenging the expertise of scientists do not necessarily offer counter-arguments to expert claims, but undermine the power and legitimacy of expert testimony by questioning their data and the validity of their interpretations and by bringing out the ethical concerns that arise out of their ideological stance (Nelkin,1979).

Alignment reflects the special interests and personal values of the actors involved and serves as an avenue for interpreting issues within a controversy consistently. The imputed condition must be broad enough to arouse the concern of a number of interested parties to have any political impact for it is social structural features, as well as the technology itself that influence alignment.

Robbins & Johnston's (1976) study on the role of cognitive and occupational differentiation in scientific controversies is an example of the contribution of special interests and values to alignment. The scientist as a transmitter of expertise rests on the power and objectivity of the scientific method. This should ensure that the same facts would be obtained from any scientist. However, the cognitive and occupational differentiation among scientists has created different

perspectives on issues of public concern. Academic, industrial, and government scientists are unable to reach consensus on many public issues due to differing norms of behavior, different institutional settings, differing modes of advancement, and different peers.

As sides become distinctly polarized in a debate, an ideology is developed unique to each side (Mazur,1981). Ideologies do not necessarily represent a means for determining the truth or falsity of scientific data, but rather may delineate ethical positions, interpretations of data, and risk/benefit assessments supporting and largely shaped by special interests and values. Ideologies consist of value and knowledge claims. According to Spector and Kitsuse (1977) a claim is a demand by one group to another group that a change must occur to eliminate the putative condition. Knowledge claims involve assertions about the scientific findings whereas value claims arise out of the socio-political ideologies shaping the controversy (Petersen & Markle,1981).

When an ideology is challenged, the technical issue becomes a controversy. The ideologies become tactical tools for bringing the controversy into the political arena..."access to knowledge and the resulting ability to question the data used to legitimize decisions is an essential basis of power and influence" (Nelkin,1979,p.15). The competing ideologies are presented

before Congress, the Senate, and other formal channels which legitimize the controversy. It is often extended to the public through news media and popular magazines to stimulate public pressure to influence political decisions for determining whose interests or ideology will become the "operable truth" or public policy.

Controversies as Research Sites

The technical complexity of society has enabled those with specialized competence to exert tremendous power over technical decision making and public policy. Scientific and technical controversies have arisen in large numbers due to the concern about those who have the political clout to reduce the capacity of individuals in shaping policies that affect them and who use traditional scientific rationality to mask political interests (Nelkin,1979).

Numerous sociological analyses have been done of case studies in science and technology from a sociology of science perspective (nuclear power plants, automobile airbags, laetrile, DNA, industrial plants, etc.). Controversies analysed from the social constructionist approach involving female steroids include estrogen therapy (McCrea & Markle,1984) and DES (Hadden,1979).

Controversies have also arisen concerning medical complications of various contraceptive methods. Contro-

versy over the combination and sequential pill developed over studies associating the pill with increased risk of mortality, blood clots, heart attacks, cancer, venereal disease, among other complications. The IUD and Dalkon Shield studies associating them with perforation of the uterus, sterility and pelvic inflammatory disease also led to controversy (Boston Women's Health Book Collective,1979). Judy Norsigian of the National Women's Health Network (NWHN) stated at the 1978 Select Committee on Population hearing (pg.375), that "the sequential Pill and Dalkon Shield are two well-publicized cases where insufficient research has resulted in premature approval of contraceptive methods and large female populations have been exposed unnecessarily to dangers."

Statement of the Problem

This thesis examines the Depo-Provera controversy as a claims-making activity. It describes how interests shape alignment, the rules of evidence, interpretation of the data, and assessment of the risks and benefits and how each side presents their claims in an attempt to bolster their own positions.

The strong programme provides a useful framework for examining claims. Arguments and counter-arguments (beliefs) of the proponent and opponents in the Depo-Provera

debate are examined in relation to their ideology and the structural and institutional context in which they arose (causality). Both classes of beliefs are presented (impartiality) with similar explanations of causality (symmetry).

Documentary research is the methodological approach used. Claims presented in U.S. House of Representative hearings, Senate hearings, FDA Board of Inquiry hearings, newspapers, professional journals, and popular magazines is the basis of analysis. Chapter two describes the historical perspective of the controversy. Chapter three examines alignment, ideology, and interests of the major actors. Chapter four presents the major knowledge and value claims presented by opponents and proponents on the medical and ethical issues. Finally, Chapter five summarizes and discusses how alignment influences the position of the actors in the Depo-Provera controversy and how the social context of the controversy shaped their interpretation of the data.

CHAPTER II

HISTORICAL PERSPECTIVE

The Upjohn Company has invested enormous amounts of time, money, and resources in developing Depo-Provera and in trying to gain the Food and Drug Administration's (FDA) approval for the contraceptive use of the drug. The Upjohn Company and its supporters claim that they have adequate grounds for achieving FDA approval for the domestic marketing of DMPA. Frustrations of proponents have escalated in the last decade due to numerous attacks by Depo-Provera critics which has stifled Upjohn's chances for gaining approval of the drug. This chapter will describe the chronology of events in the history of Depo-Provera as well as Upjohn's attempts at achieving approval of Depo-Provera.

The Progesterone Context

Progesterone is a steroid hormone responsible for changes in the endometrium (mucous membrane lining the inner surface of the uterus) in the second half of the menstrual cycle. It prepares the uterus for implantation of an embryo, for the development of

the placenta after implantation, and it assists in the development of mammary glands (Taber's Medical Dictionary,1977). Increasing the level of progesterone in the body can have a contraceptive effect by preventing sperm from penetrating through a thickened cervical mucous; by preventing ovulation; and by making the endometrium less suitable for implantation (Remington's Pharmaceutical Sciences,1975).

In the early 1950's, Dr. Gregory Pincus discovered the contraceptive effect of progesterone with estrogen and combined them into the oral contraceptive pill (Smith,1978). In 1953, Karl Junkmann at Schering AG in Berlin discovered the long-lasting effects of progesterone in its injectable form. By 1957, Karl Junkmann and his associates produced the first injectable progestin contraceptive - Norethisterone - thus eliminating the daily regimen and estrogenic side-effects of the oral pill (Rosenfield,Maine,Rochat,Shelton,Hatcher,1983).

DMPA Discovery

In 1957, The Upjohn Company developed medroxy-progesterone acetate (DMPA). The Upjohn Company filed an Investigative New Drug Exemption (IND) with the U.S. Food and Drug Administration to begin experimental testing with DMPA. Upjohn then began Phase one - toxicity studies in animals. In 1959 phase two and

Phase three clinical trials began to test the safe dosage level and efficacy of DMPA as a progestational agent. It was approved as a progestational agent for the treatment of endometriosis and threatened abortion in 1960. Further clinical trials on women failed to substantiate DMPA effectiveness in preventing premature labor, but it did have a contraceptive effect in women who took DMPA for premature labor for up to one year (Levine,1979,Zanartu,1968).

If a drug is approved for use, the IND is still effective for the testing of the drug for other indications. Consequently, clinical trials for the contraceptive use of DMPA began in 1963. In 1966, it was reported in the Journal of Reproduction and Fertility, that large doses of DMPA given to women during labor to suppress uterine activity prevented them from conceiving for twelve to twenty-one months post-partum (Coutinho & DeSouzo,1966). Therefore, smaller doses at three month intervals were tested and found to be highly effective (Fraser & Weisberg,1981).

The first field trials for the contraceptive use of Depo-Provera began in 1965. Paul C. Schwallie and J. Robert Assenzo of the Fertility Research and Biostatistic Department of The Upjohn Company conducted a field trial involving thirty-nine private practice physicians and fifteen researchers in family planning

clinics. The study included 3,857 women (Schwallie & Assenzo,1973). At the same time, the McCormick Hospital in Chiangmai, Thailand, under the direction of Edwin B. McDaniel and Tieng Pardthaisong, investigated the drug in its family planning program (McDaniel & Pardthaisong,1973). The field trials sought to determine the optimum dosage levels, safety, efficacy, patient acceptance, and adverse effects of DMPA (Schwallie & Assenzo,1973). It was found that medroxyprogesterone acetate administered as an injectable contraceptive in a dosage of 150 mg at 90 day intervals was well accepted by women. A high percentage of women experienced amenorrhea or irregular menses. The drop out rate from these side-effects were minimal if the women were aware of it before accepting the method (Schwallie & Assenzo,1973).

The Battle for Approval - First Attempt

In 1967, The Upjohn Company believed that they had finally reached the turning point. It was time to submit its Supplemental New Drug Application to the FDA for approval. They felt their discovery was the near ideal contraceptive - a three monthly, injectable contraceptive requiring no daily regimen and independent of coitus. A thirteen year clinical trial began in 1967 at Grady Memorial Hospital in Atlanta, Georgia

and also, a clinical trial at the Los Angeles County, University of Southern California Medical Center began to test the efficacy and potential health risks which could be associated with DMPA (Liang et al.,1983). By 1968, safety tests on rodents, beagles, and monkeys had begun.

On April 27, 1973, the Obstetrics and Gynecology Advisory Committee for the FDA recommended that DMPA be approved as a contraceptive for a limited population of women - those unwilling or unable to use other contraceptable methods - e.g., women who refuse to use other methods, have counterindications to other contraceptives, are mentally ill, are mentally retarded. The FDA announced its approval of DMPA for limited use claiming that there was a significant population of women in need of DMPA and with the available evidence from clinical trials the benefits outweighed the risks for this population.

Because Depo-Provera is a long-acting contraceptive that requires no action by individual women, critics argued that it would be an attractive contraceptive to population controllers and would invite abuse. Senator Edward Kennedy strongly objected to FDA approval as a result of testimonies given at the February 15, 1973 Senate Health Subcommittee Hearing for which he chaired. Testimony was given concerning the use

of DMPA in a rural Tennessee Family Planning Program and a state facility for the mentally retarded where DMPA was used without informed consent. Kennedy purported that approval would "result in widespread use of the drug in institutions for the mentally retarded and health clinics serving the poor and uneducated without proper safeguards" (Maine,1978,p.342).

At this same time, Upjohn reported that its seven year beagle study had revealed malignant breast tumors in two of sixteen treated dogs. No tumors were found in the control group. The cancer findings in the beagle dogs were the beginning of the long difficult approval process for The Upjohn Company. Upjohn's excitement over the near ideal injectable contraceptive began to dwindle as critics sharply criticized The Upjohn Company, its supporters, and the FDA for considering approval of an "unsafe drug" for a healthy population of women (Johnson,1978; NWHN,1978; Wolfe,1978). However, Upjohn continued to argue for the safety of the drug.

The FDA continued to support its position and the final approval notice was prepared for publication in the Federal Register in April,1974. On September 12, 1974, the FDA announced its final approval for the contraceptive use of DMPA to go into effect October 15, 1974 (Rosenfield et al., 1983). The FDA mandated that all potential users must be fully informed of

the possible serious risks associated with DMPA and that "a registry of all physicians administering the injectable drug would be established so that the FDA could notify the physicians in the event that any of the potential carcinogenic risks were confirmed" (Maine,1978,p.342). Letters were sent to physicians across the country notifying them of the pending approval (Rosenfield et al., 1983). Dr. Robert Temple, Acting Director of the Office of New Drug Evaluation (1983,p.31) stated that the 1973 FDA notice "did an unusual thing, it actually called for informed consent which ... has never been done for any other drug."

While the FDA was in the process of finalizing approval of DMPA, the Subcommittee on Intergovernmental Relations of the House Committee on Government Operations held a hearing on Depo-Provera (Levine,1979). A question concerning cervical cancer-in-situ was raised when 1974 statistics from the Grady Memorial Hospital Study revealed a higher than normal rate of cervical cancer-in-situ in DMPA users as compared to the rates reported by the Third National Cancer Institute's Survey (Johnson,1978; Moghissi,1978). On October 2, 1974, Representative L.H. Fountain (D.N.C.), chairman of the subcommittee on Intergovernmental Relations, wrote a letter of protest to Secretary Weinberger of the Department of Health, Education, and Welfare after

hearing testimonies at the Subcommittee Hearings, condemning the FDA approval decision and predicting that "many women may be irreparably injured" as a result of DMPA use (Zwerdling,1974,p.8). He then requested that Weinberger stay approval of the drug (Upjohn,1983b) citing evidence of the cancer-in-situ findings and its prevalence among low socio-economic groups (Levine,1979). Weinberger claimed that Fountain's fears "are significant and demonstrate a justifiable concern over possible cancer-causing agents" (N.Y. Times 9 Oct,1974). Alexander M. Schmidt (1974), former Food and Drug Commissioner, agreed to stay formal Federal approval of the drug and schedule a public hearing (N.Y. Times,9 Oct,1974).

Second Attempt for Approval

By 1975, The Upjohn Company was beginning to gain crucial support from international organizations. The Central Medical Committee of the International Planned Parenthood Federation officially endorsed the use of DMPA in the U.S. and abroad in April,1975; "...injectable contraceptives...represent a most dependable and useful method of family planning" (Senanyake,1978, p.327).

The FDA Advisory Committee on Obstetrics and Gynecology recommended FDA approval of Depo-Provera

on numerous occasions. In 1975, the FDA held a joint meeting with its advisory committees on Obstetrics and Gynecology and on Biometric and Epidemiological Methodology. A subcommittee task force was appointed to evaluate the cervical cancer question. It concluded that there was no increased risk of cervical cancer (Rosenfield,et al,1981). The Obstetrics and Gynecology Committee again recommended FDA approval of Depo-Provera with the same limitations that the FDA had established in 1973 (Rosenfield, et al,1983; Levine,1979; Sun,1982; Ewalt,1982). The FDA did not act on the committee's recommendation, so the advisory committee persisted in its recommendation again on December 15, 1975.

At this time, the FDA had not taken a firm position on Depo-Provera. Schmidt stayed the approval order in 1974 and did not act on the advisory committee's recommendation in 1975, but approval was never denied. So, there was still pressure by proponents and the FDA advisory committee to make a decision. Critics argued that the indecisiveness of the FDA was a stand in favor of DMPA use by the medical community (HRG,1978).

In 1976, the Depo-Provera issue became more controversial when the Health Research Group (HRG) began actively opposing DMPA approval. On December 16, 1976, Sidney M. Wolfe, director of the Health Research Group wrote a letter to the Assistant Secretary of

the Department of Health, Education, and Welfare in protest of DMPA approval (Sun,1982; Upjohn,1983b). Sidney Wolfe, claimed that "any substance, with few exceptions, which conclusively causes cancer in animals should be considered a potential cancer hazard in man" (Sun,1982,p.425).

On August 30, 1977, the FDA requested that Upjohn withdraw its Supplemental New Drug Application (NDA) to avoid a published notice of rejection (Upjohn,1983b). The FDA claimed that new contraceptives were now available, thus eliminating any significant population in need of Depo-Provera given its potential risks (Sun,1982). On September 2, 1977, Upjohn notified the FDA that the NDA would not be withdrawn again asserting the safety and efficacy of the drug (Ewalt,1982). Consequently the FDA denied approval of Depo-Provera again on March 7, 1978 (Rosenfield et al.,1983). On March 21, 1978, Upjohn requested the FDA to issue an opportunity for a hearing. As a result a three day hearing was held before the House Select Committee on Population.

By this time, The Upjohn Company had two other major advocates. Representatives of foreign governments and family planning programs strongly urged the FDA to approve Depo-Provera because the United States Agency for International Development, a major supplier of contraceptives to the Third World, could not export

drugs not licensed for distribution in the United States (Levine,1979). R.T. Ravenholt, Director of AID's Office of Population claims that "the drug would be a useful lead-in to surgical sterilization. An effective global population program is like waging a global war. AID can add Depo-Provera to its fertility control armamentarium" (Bader,1979,p.45).

The World Health Organization (WHO) also advocated for FDA approval of Depo-Provera. In October,1978, the WHO Special Program of Research, Development and Research Training in Human Reproduction concluded "...the available evidence does not indicate a risk of adverse effects associated with Depo-Provera which would preclude the use of this drug as a contraceptive" (Fraser and Weisberg,1981,p.4).

After the 1978 hearings, the FDA refused to reverse the non-approval status of Depo-Provera to The Upjohn Company on five grounds: the potential cancer risk due to the mammary tumors found in beagles; other safer alternative methods; the need for estrogen therapy in women who experience excessive bleeding due to Depo-Provera use, thus eliminating the benefit of a progesterone-only contraceptive; its adverse effects on the fetus - e.g. masculinization of the female fetus; and the inability of post-marketing studies to yield meaningful data concerning cancer risks

(Rosenfield,et,al,1983).

In 1973, the FDA felt that there was a limited population of women in need of the drug. In 1978, the FDA decided that the population of women originally defined as being in need of the drug "appeared to be a population that would have great difficulty providing proper informed consent" (Temple,1983,p.31). Therefore, the number of women who could give informed consent was not a large enough population to warrant approval (Temple,1983).

The FDA's decision not to approve DMPA provoked harsh criticism from proponents. The International Planned Parenthood Federation claimed that the FDA had no scientific basis for non-approval (1978,p.320). The American College of Obstetrics and Gynecology claimed that the FDA decision was ungrounded (1978,p.335). Yet, the FDA decision prompted Yemen, Jordan, Korea, Egypt, and Taiwan to reverse their decision on approving DMPA. Family planners claimed that other countries have reconsidered approval due to possible accusations that they are distributing unsafe drugs. Countries which have continued to approve Depo-Provera have faced such charges (Sun,1982).

Some proponents believe that the FDA chose not to approve Depo-Provera because of increasing pressure from consumer groups over the last ten years. The

fact that the FDA considered approving Depo-Provera at all in light of the adverse findings suggests the political nature of their role. The Delaney Amendment to the Food and Drug Act restricts the sale of any product known to be carcinogenic. In 1973, the FDA had unofficially approved the contraceptive use of Depo-Provera, even after the carcinogenic findings in the beagle. It was already approved for other indications and has been widely used for contraceptive purposes which is a decision left to physicians for any drug with approved indications. The FDA did not stay the order until it received strong pressure from critics concerning the human cancer-in-situ findings. Until 1978, the FDA never issued a non-approval order for the contraceptive use of Depo-Provera and the FDA Obstetrics and Gynecology Advisory Panel made numerous recommendations for FDA approval. Why the New Drug Application ever made it as far as it did can only be speculated.

Third Attempt for Approval

On August 25, 1978, The Upjohn Company requested from the FDA that a hearing be held before a Public Board of Inquiry. On July 26, 1979, Upjohn's request for a Board of Inquiry hearing was published in the Federal Register by the FDA (Upjohn,1983b). Upjohn's

request to have its scientific evidence presented before a Board of Inquiry was only the second request in FDA history (the first request was made by the manufacturer of Aspartame, an artificial sweetner).

While The Upjohn Company was in the process of gaining FDA approval for a Board of Inquiry hearing, its ten-year animal safety tests in rhesus monkeys were completed. Two of the monkeys developed cancer of the endometrium. None of the control group showed this condition. The Upjohn Company and the WHO claimed that monkeys react differently than women to progestogen. The condition under which the cancer arose in the monkeys is not found in women (WHO,1982). The National Women's Health Network (1983,p.59) claimed that "the findings failed to prove that Depo-Provera is not carcinogenic." Robert Temple (1983),of the FDA, claimed that animal studies did not show Depo-Provera to be safe.

Again, foreign governments voiced their concern that the FDA would not approve Depo-Provera. They claimed that the United States could not distribute a drug that was not approved for use in the United States. On September 9, 1980, Congressman Bingham's Subcommittee on International Economic Policy and Trade heard testimony on Depo-Provera. The Agency for International Development created an ad hoc committee

in 1980 to review scientific data pertaining to the exportation of Depo-Provera after numerous foreign governments pressured AID to allot money and supply Depo-Provera calling AID's position righteous and paternalistic. Members of the panel which largely constituted population experts, advised AID to allow Depo-Provera to be exported due to its "outstanding merit". AID did not reverse its position to export the drug or to directly finance it (Sun,1982).

Also, in 1980, Steven Minkin, Health Policy Analyst for the National Women's Health Network, published an article called "Depo-Provera - A Critical Analysis" in Women and Health. This frequently cited article, which was distributed internationally, caused several governments to withdraw or consider withdrawing its use of Depo-Provera in its family planning programs (WHO,1982). Proponents of the drug claim that Minkin's article is "an exceptional example of this biased and nonobjective reporting...which shows how easy it is to be emotive and destructively critical about a drug such as DMPA, and is a classical illustration of the misuse of selected references, unauthenticated data, unjustified extrapolations, and innuendos" (Fraser and Weisberg,1981,p.12; Benangiano,1980; Upjohn,1980; WHO,1982).

On September 11, 1981, the FDA appointed three

medical scientists to the Public Board of Inquiry: Judith Weisz,M.D., Head of the Department of Obstetrics and Gynecology, Hershey Medical Center, Hershey, Pennsylvania; Griff T. Ross,M.D., Associate Dean of Clinical Affairs, University of Texas; and Paul Stolley, Professor, Department of Research Medicine, University of Pennsylvania (Upjohn,1983d). Five days of hearings were held in Washington D.C. from January 10 to January 14, 1983. Issues of concern included an assessment of risks and benefits; the cancer question raised by animal safety tests; the adequacy of the human data; the potential abuse of the drug if approved for general marketing; potential teratogenic effects; the need for estrogen therapy with Depo-Provera use; and the adequacy of labelling and distribution controls if Depo-Provera was approved for limited marketing (Upjohn,1983d).

While the FDA was in the process of reconsidering Upjohn's case before the Public Board of Inquiry, a class action suit against Upjohn on behalf of women purportedly harmed by Depo-Provera was filed by the National Women's Health Network (Green,1983). The National Women's Health Network "has collected 150 case histories of women who claim to have suffered ill effects from taking Depo-Provera" (Time,1983,p.67).

The hearings received much publicity. Major

newspapers and network news broadcasts covered the event. Upjohn representatives appeared on television discussion programs such as the McNeil-Lehrer Report (Upjohn,1983b). "Upjohn officials were generally pleased with a week-long Public Board of Inquiry conducted by the FDA. Gordon W. Duncan of Upjohn stated 'We had a very fair hearing before the panel. It was conducted as a scientific inquiry'"(Upjohn,1983b,p.1 and 6).

The advisory board to the FDA recommended that Depo-Provera not be approved for general marketing in the United States. The Board of Inquiry panel claimed that the "data linking the drug to breast cancer in beagles and uterine cancer in monkeys cannot be dismissed as irrelevant to the human without conclusive evidence to the contrary. Such evidence is not available at the time" (Battle Creek Enquirer,1984,p.A-5; N.Y. Times,1984). The board decided that Depo-Provera does not cause irreversible side-effects such as possible blood embolisms. It discounted the findings concerning an association between DMPA and deformities in fetuses. It also decided that there was insufficient evidence to prove an association of DMPA with osteoporosis (bone disease) or atherosclerosis (hardening of the arteries).

Status of DMPA as of 1985

The Upjohn Company filed a rebuttal when with the FDA Commissioner pertaining to the recommendation of the panel. The Upjohn Company is now waiting for the FDA to make a decision in regard to the new approval status of DMPA.

CHAPTER III

MAJOR ACTORS

Alignment in the Depo-Provera controversy revolves around commonalities in values and interests among various groups and organizations. In Chapter Three, a basic description of the proponents and opponents is presented. The general ideology and specific position on Depo-Provera of each proponent and opponent are presented and related.

Proponents

Major proponents in the Depo-Provera Controversy include The Upjohn Company - the manufacturer of Depo-Provera; The International Planned Parenthood Federation - the largest supplier of Depo-Provera; The World Health Organization - the major technical advisor to governments and international organizations regarding the safety and efficacy of the drug; The Agency for International Development and its subsidiaries involved in the distribution of DMPA; and the medical community which disseminates the drug. A listing of the key spokespersons and their alignments is presented in Table 1.

Table 1

Major Proponents - Key Spokespersons

PERSON	AFFILIATION	POSITION
William N. Hubbard, Jr., M.D.	The Upjohn Company	President
Dr. Gordon W. Duncan	The Upjohn Compnay	Chief Scientific Spokesperson
Jeannie I. Rosoff	Alan Guttmacher Institute	Senior Vice-President
Joyce C. Lashof, M.D.	DHEW	Deputy Assistant Secretary For Health and Population Affairs
Dr. Pramilla Sananyake	IPPF	Deputy Medical Director
Allan Rosenfield, M.D.	Ministry of Health, Thailand	Medical Advisor on Family Planning
Malcolm Potts	IFRP	Executive Director
Dr. Joseph Speidel	AID	Deputy Director Office of Population
Sander Levin	AID	Former Assistant Administrator
S. Bruce Shearer	Population Council	Associate
Sheldon J. Segal	Population Council	Vice President Director
Halvor Gille	UNFPA	Deputy Executive Director
Kamran S. Moghissi, M.D.	American Board of Obstetrics and Gynecology	Diplomat

The Upjohn Company

The Upjohn Company is the manufacturer of Depo-Provera and its major proponent. The Upjohn Company is a worldwide research-based manufacturer and marketer of pharmaceuticals, health services, chemicals, seeds, and agricultural specialities, with corporate headquarters in Kalamazoo, Michigan (Upjohn Company Annual Report, 1984,p.1).

William N. Hubbard, Jr.,M.D., President of the Upjohn Company (1978) claims that in choosing to do contraceptive research, the company is showing its commitment to population control. But, in a capitalist society, industry only exists as long as it makes a profit. Therefore, industry's major commitment is to profitability.

According to Hubbard, impediments to industry's commitment to contraceptive research are increasing. Among the major impediments are a cost/price squeeze which continues to decrease the return on assets at their current value; shortened patent life as a result of the increased time that it takes to gain approval of a new product; product liability as a business risk; the uncertainty of payback for long-term research investments; the economically effective demand for new contraceptive forms; attacks by special interest groups; and the lack of any evident cooperative spirit

by regulatory agencies(Hubbard,1978,p.517-521).

The cost/price squeeze makes it more difficult to obtain a profitable return on investments. There is wide disagreement on the value to place on a finished product.

> Since the maintenance of health and the amelioration or cure of disease is hard to value in commercial terms, there is sharp disagreement about socially acceptable levels of profitability by manufacturers and particularly, originators of medicinals. In general, worldwide there is a strong trend toward shortening the time when patents give advantage to the innovator of new medicinals. Through this means and others, the prices of pharmaceuticals in the last decade have lagged far behind the growth in the overall costs of doing business(Hubbard,1978,p.468).

According to Hubbard, product liability as a business risk has increased dramatically. The definition of liability is radically changing making it virtually impossible to insure against it. "The relatively low level of the public understanding of science, along with a rapidly changing view toward liability for injury, combines to make the general use of a medicinal hazardous from the view of legal liability for damages"(Hubbard,1978,p.470).

The demand for new contraceptive forms combined with the uncertainty of payback is a risk in contraceptive research whether new products with marginal advantages over existing methods is sufficiently in demand is unclear. Market demands are generally the

primary influence for determining whether or not to innovate a new product.

Expenditures for developing a new contraceptive average two million dollars annually for ten years. This means that a potential market would need to generate annual sales of approximately twenty-one million dollars to warrant resource allocation because pharmaceutical products for nonhealthy populations (products not used for preventive purposes) generally require less time, lower costs, and often have a larger market (Hubbard,1978,p.308).

The lack of public confidence in industry in the last decade has further impeded contraceptive development. According to Hubbard, there is an inherent lack of certainty in all scientific observations making it inevitable that unexpected risks and benefits will occur after widespread use of any medicinal. However, while consumer advocates accept advantages, the disadvantages are not tolerated and are rarely weighed against the risks involved in not using the drug. "...the role of the consumer advocate generally is piercingly critical without any attempt whatsoever to recognize the benefits that might offset disadvantages" (1978,p.471). Interestingly, Hubbard's criticism of consumer advocates can be applied to industry, also, with regard to health and safety regulations.

Hubbard believes that for the public to be capable of adequately assessing the risks and benefits of a drug, they need a better understanding of science. The media, as well as consumer advocates and regulatory agencies fail to provide a genuine public understanding. Hubbard claims..."it may well be that the mass media of communications should not be expected to provide the kind of public understanding of science that would be necessary in order for a truly informed public..." (1978,p.472).

Because of the many impediments in doing contraceptive research, choosing to develop and market a contraceptive agent is an important commitment and a major investment. In trying to gain FDA approval of Depo-Provera, Upjohn has faced each major impediment. Upjohn has been applying for approval of Depo-Provera for fifteen years and still has not won FDA approval. The long-term research investment has substantially cut profitability and the long approval process has shortened the profits to be gained on the patent. Attacks by consumer and feminist groups as well as suits brought against Upjohn for adverse effects has been detrimental for obtaining economic gain.

Each year between 1978 and 1981, the Upjohn Company sold about seven million doses of Depo-Provera which

is enough for approximately 1.75 million women. In 1982, sales reached eight million doses which would supply two million women annually. Upjohn manufacturers in Italy and Eastern Europe produce and sell Depo-Provera. Sales are evenly distributed between developed and developing nations (Population Information Program, 1983,p.K-21).

Dr. Gordon W. Duncan, Upjohn's Chief Scientific Spokesperson on Depo-Provera, defined Upjohn's stance on Depo-Provera at the 1983 FDA Board of Inquiry Hearings (1983,p.15):

> Our basic tenant is that Depo-Provera 150 is a highly effective, safe, and acceptable contraceptive....We base this on the nature of the compound itself, the extensive laboratory and clinical data which exists in this compound, the worldwide experience not only for its contraceptive use, but other indicators, the scrutiny which this drug has had by both health and regulatory agencies, the number of critical reviews by members of the medical community and by the continued surveillance that this drug is receiving in clinical trials both by Upjohn and by a number of international organizations.

The tone in which the Upjohn position is presented reinforces the rational, objective, scientific approach which Upjohn continues to display throughout their interpretation of the medical issues. Ethical issues are minimized or considered unfounded. Presentations are made to appear very methodical and objective; therefore, the evidence appears factual and void of values, personal interests or motives.

International Planned Parenthood Federation

The International Planned Parenthood Federation (IPPF) has played an important role in supporting Upjohn's efforts to gain the FDA approval for the contraceptive use of Depo-Provera. IPPF is a federation of ninety-six national family planning organizations in the United States, Canada, Latin America, and the Carribean Islands. The basic philosophy of the IPPF is "the expression of the human rights of couples to have only the children they want and to have them when they want them" (Yearbook of International Associations,1981).

The overall purpose of the organization is the dissemination of information, education, and services for the practice of voluntary family planning programs to governments throughout the world. There are nearly 5,000 family planning clinical settings in the United States of which fifty-five percent are health departments, twenty percent are hospitals, and six percent are planned parenthood affiliates. By fiscal year 1978, funding for family planning programs was estimated to be $384,000,000 (Lashof,1978,p.295).

Because the IPPF places value on the necessary control of unwanted pregnancies many of their claims revolve around this goal. They claim that the consequences

of an unwanted birth is tragic for the child, parents, and society and that teenagers and the poor are the primary target populations. Jeannie I. Rosoff, Senior Vice President of the Alan Guttmacher Institute (a member organization of IPPF) (1978, p.311) claims:

> An estimated three million low and marginal income women, and two million sexually active teenagers in all income groups still do not obtain family planning services either from clinics or private physicians. Unintended fertility continues to exact unacceptably high health, social, economic, and emotional costs from both individuals and society.

Rosoff (1978,p.312) claims that methods currently available are not always medically acceptable and do not necessarily meet personal needs. Because the failure rate and the long-term safety are questionable with the present contraceptives, it is necessary to develop safer and more effective contraceptives. But the present methods have substantially reduced the fertility rate and are therefore important. Developing better contraceptive methods is a major goal, but providing the available methods to those at risk of pregnancy is the primary short term goal.

> We can identify with some precision which groups are particularly at risk of unwanted pregnancy. We can pinpoint where they live. We have developed a pluralistic clinic network capable of rapid growth. We have trained, or can easily train the necessary personnel. All we need is the will (1978,p.312).

In 1975 the IPPF Central Medical Committee

concluded that injectable contraceptives "represent a most dependable and useful method of family planning and that the IPPF should continue to distribute them through Family Planning Associations"(Senanyake,1978, p.327). IPPF is presently the largest distributor of injectables. It has supplied Depo-Provera to developing nations for ten years and since 1975 has supplied almost four million doses (Population Information Program,1983).

According to Allan Rosenfield, M.D., a medical advisor on family planning for the Ministry of Health in Thailand (1978,p.534) "the majority of scientists working in the population field strive for objective conclusions based on as complete a scientific risk/ benefit assessment as possible." Dr. Pramilla Senanyake, Deputy Medical Director of IPPF stated the position of IPPF (1983,p.52):

> It is important to bear in mind that the perfect contraceptive is not yet with us. The international experience of more than 15 years of clinical use of Depo-Provera has demonstrated that the drug represents a safe and effective method of fertility regulation. The approval of Depo-Provera for long-term contraceptive use would, by adding to the range of available, safe contraceptive techniques increase the options open to users and physicians, improving their chances to reach a decision which more closely corresponds with the specific contraceptive needs of the couple in question.

The IPPF position on Depo-Provera exemplifies their value in minimizing the risk of unwanted births. While it is important to continue research on more

safe and effective contraceptives, in the short range, priority must be placed on locating and implementing current methods of those populations at risk. Depo-Provera would reduce the risk of childbirth and abortion by providing another contraceptive alternative to assist individuals and society in meeting their fertility goals (Potts and Paxman,1984).

World Health Organization

The World Health Organization (WHO) is an international organization whose objective is the "attainment by all people of the highest possible level of health." WHO directs and coordinates international health work, assists government in strengthening their health services, and furnishes appropriate technical assistance to conduct and promote research in health (Yearbook of International Organizations,1981).

The World Health Organization has a Special Programme of Research, Development, and Research Training in Human Reproduction. This program focuses primarily on less developed countries. WHO involves U.S. researchers and cooperates with U.S. sponsors in the testing of new products. It aims to develop new contraceptive methods by supporting programs which can develop a product from the initial laboratory stage to the utilization of the product by the "target population"

(Segal,1978).

Funds to support the WHO Special Programme are provided by the governments of Canada, Denmark, Finland, India, Mexico, Norway, Sweden, and the United Kingdom. Its 1978 budget was about $15 million. The programme gives grants and contracts designed by international task forces of scientists to commercial and independent organizations (Segal,1978, p. 588).

The WHO Special Programme developed a Task Force on Long Acting Systemic Agents for the Regulation of Fertility. WHO is the major technical advisor to governments and international organizations regarding the safety and efficacy of the drug. In 1977, WHO spent approximately $1,250,000 on research of injectable contraceptives and $1,500,000 in 1978. Research included: multicentre clinical trials, epidemiological studies, and studies in relation to special problems - e.g. metabolic studies, studies in lactating women; animal models for testing long-acting agents; and the acceptability and service delivery of injectable contraceptives. The WHO Special Programme (WHO,1982,p.199) concluded:

> Based on the extensive epidemiological, biochemical, and clinical data available to date, Depo-Provera (DMPA) appears to be an acceptable method of fertility regulation. Clinical evidence from more than fifteen years of use shows no additional and possibly fewer adverse side-effects than are found with other hormonal methods of contraception. The particular advantages of DMPA as a highly effective, long-lasting, and reversible

contraceptive makes it an important option for women desiring a method of fertility regulation.

United States Agency for International Development

The U.S. Agency for International Development (AID) is an autonomous agency within the U.S. Department of State. Its goal, according to its own literature, is "to improve the health, well being, and economic status of the people of the developing countries and to provide essential international assistance for population and family planning"(Whitnah,1983).

AID substantially supports the International Committee for Contraceptive Research, a program established by the Population Council. It also funds the Program for Applied Research and Fertility at Northwestern University which has a $2 million grant program supporting scientists in the U.S. and abroad with ideas for new methods in fertility regulation (Segal,1978,p.590). The International Fertility Research Program (IFRP) recently renamed the Family Health International at Chapel Hill, N.C. is also funded by AID. IFRP tests and evaluates new contraceptive methods and attempts to hasten the process between development and implementation of contraceptives in family planning programs (Potts,1978,p.228).

AID and its affiliates believe that the widest

range of contraceptive options should be available. Dr. Joseph Speidel, Deputy Director, Office of Population, AID (1983,p.56) claims:

> Assistance for voluntary population and family planning programs is an essential part of U.S. development assistance programs. An important aspect of this program is to provide couples with the widest choice of safe, effective, and acceptable contraceptives so they can freely and voluntarily choose the fertility they desire. AID therefore seeks to foster the availability of the latest scientific and technological knowledge and family planning methods to improve the effectiveness of developing countries family planning programs.

Malcolm Potts, Executive Director of IFRP went one step further. He stated (1978,p.230):

> It should be a firm policy to add to the range of contraceptive methods available all those that it is economically and logistically possible to distribute. Only in this way will the prevalence of contraceptive use be raised, the choice of fertility regulation extended to all individuals and the need for induced abortion (legal or illegal) cut down.

AID is interested in the important role that Depo-Provera could play in both developed and developing nations. AID claims that a significant number of women would employ injectable contraceptives if they were available (Speidel,1983,p.56). Sander Levin, former Assistant Administrator of AID (1978,p.128) said that AID would support FDA approval of the drug or a legislative change in the statute prohibiting AID from purchasing Depo-Provera in the U.S. for export to developing countries.

Malcolm Potts (1983,p.103) stated IFRP's position with an analogy between contraception and transport:

> Just as we need autos and planes, so I think we need IUD's, pills, condoms, and Depo-Provera. I think Depo-Provera is a Volkswagon. I think its a sturdy, predictable method of contraception and likely to be around for a long time. I think it will probably soon be overtaken by some Honda or Chrysler K Car. I think its a little bit rattly and drafty, it certainly has got its drawbacks, but I think it is unfortunate to deny the choice of this contraceptive to American women and I think that it has enhanced the health of women in many parts of the world who have been able to use it. I think that if it were available in this country there would be a measurable number of women who would use the method.

Medical Community

The American Medical Association, the American Academy of Pediatrics and the American Board of Obstetrics and Gynecology all endorsed the approval of Depo-Provera for contraceptive use. This is significant in regard to the Depo-Provera Debate because these organizations largely shape physicians attitude toward a drug. If a physician believes a drug is safe and effective as endorsed by the major medical community, then it is more likely to be used for non-approved use. If a drug is approved for one use by the FDA, a physician can use the drug for a non-approved use if s/he feels that it is in the best interest of the patient (Upjohn, 1980).

The American Medical Association (AMA) disseminates

scientific information to members and the public. It informs members of significant medical and health legislation on state and national levels and represents the profession before congress and governmental agencies. The AMA stated:

> Reviewing the literature on the risks and benefits of depo-medroxyprogesteron (Depo-Provera), we find no reason to deny DMPA approval, provided that studies of its possible side-effects are continued and that women use it only after having made an informed choice between this and other methods of contraception (Rosenfield et al., 1983,p.2922).

The American Academy of Pediatrics (AAP) is interested in the study of children and their diseases, prevention of illness, and promotion of health in childhood (Encyclopedia of Associations,1981). The AAP endorsed Depo-Provera for a limited population on the recommendation of the Committee on Drugs. The Committee on Drugs stated:

> Depo-Provera - or a similar, long-acting contraceptive agent - can be invaluable to a small, well-defined group of adolescents who need effective contraception and are unable to benefit from other methods. They may be at risk of participating in sexual activity unknowingly or unwillingly, or may be sexually active by choice. Some of these adolescents are intellectually impaired and pregnancy is especially unwanted(Committee on Drugs,1980,p.648).

The American Board of Obstetrics and Gynecology has played a major role in testifying at the various hearings. Of the three medical organizations, it is the most affected by the approval or non-approval

of Depo-Provera since it is a potential product to add to the contraceptives available to their clients. Because Depo-Provera must be administered by medical personnel, there should be regular follow-ups, and it requires no time in training the patient to use the method. It is in the economic interests of physicians to promote the drug.

> Scientific and clinical evidence indicated that MPA was both essential and safe for the purpose for which it was initially approved (Moghissi,1978,p.335). Depo-Provera is currently believed to be the only drug which has been extensively evaluated and found to be highly effective, safe and acceptable to those who might otherwise be deprived of the protection they deserve (Moghissi,1978,p.347).

Opponents

The two most active groups opposing the approval of Depo-Provera for contraceptive use are the National Women's Health Network (NWHN) and Ralph Nader's Health Research Group (HRG). These two groups view the controversy as a power struggle with organizations that do not value the interests of the consumer.

The special interests and personal values creating an alignment between the HRG and NWHN are the protection of individuals from the political power of businesses and organizations who will promote products and pass governmental policies which are hazardous to powerless individuals to support their own interests. In the

case of Depo-Provera, they claim that Upjohn, WHO, IPPF, and AID are exposing women and children to serious risks for their own interest in profit and population control. Key spokespersons and their alignment are presented in Table 2.

Health Research Group

Ralph Nader's Health Research Group (HRG) researches areas related to workplace safety, health, drug regulation, food additives, medical device safety, and environmental influences on health. It testifies on behalf of consumers before congress and federal agencies concerning health matters and monitors the enforcement of health and safety legislation. It provides research and consumer action materials and publicizes health findings through the media (Encyclopedia of Associations,1985).

The consumer movement gained momentum in the late 1960's as a result of Ralph Nader's auto safety investigation. At the same time President Kennedy established the rights of consumers to safety, to be informed, to choose, and to be heard which became the core of consumerism. Consumerism "is concerned with protecting consumers from businesses and organizations with whom they are involved in an exchange relationship"(Aaker & Day,1974,p.xvii).

The values central to the consumer advocates

Table 2

Major Opponents - Key Spokespersons

PERSON	AFFILIATION	POSITION
Dr. Sidney Wolfe	HRG	Director
Anita Johnson	HRG	
Ralph Nader	HRG	Founder
Dr. Helen Bequaert Holmes		Biologist-Feminist
Gena Corea		Feminist Author
Stephen Minkin	NWHN	Health Policy Analyst
Michael Gross		Professor/Feminist
Diane Silberstein,Esq.	NWHN	Counsel for NWHN
Judy Norsigian		Co-Author- Our Bodies, Ourselves
Helen Roberts		Feminist Author
Jill Rakusen		Feminist Author Women's Health Issues
Carol Levine	Hastings Center	Medical Ethicist Journalist
Dr. Ruth W. Shearer		Counsultant, Genetic Toxicology

role are: protection against the promotion of hazardous goods which may harm one's health or life (safety); protection against deception and the availability of sufficient information to make an informed choice (to be informed); competition must be adequate to provide the consumers with a choice of satisfactory products (to choose); consumer interests must be represented at regulatory hearings and in governmental policy (to be heard)(Aaker & Day,1974,p.vxiii). Nader (1974,p.24) states:

> "Consumerism" is a term given vogue recently by business spokesmen to describe what they believe is a concerted, disruptive ideology concocted by self-appointed bleeding hearts and politicians who find that it pays off to attack the corporations. But what most troubles the corporations is the consumer movement's relentless documentation that consumers are being manipulated, defrauded and injured not just by marginal businesses or fly-by-night hucksters, but by the U.S. blue-chip business firms whose practices are unchecked by the older regulatory agencies. Since the consumer movement can cite statistics showing that these practices have raised the rate of mortality and disease, it is not difficult to understand the growing corporate concern.

The core values of consumerism are present in the HRG interpretation of the medical and ethical issues. The right to safety is the most prominent in the Depo- Provera Debate. The HRG claims that Upjohn's clinical studies are inadequate making evidence of safety impossible. The adverse findings in the animal studies and in independent clinical research

show that Depo-Provera is too hazardous for use in healthy women.

Because Depo-Provera is being promoted as a contraceptive for those women incapable or unwilling to use other methods of contraception, the right to be informed is purportedly violated since many of these women would be denied necessary information for making an adequate assessment, misinformed, manipulated, and/or coerced into using Depo-Provera as a contraceptive. The right to choose would also be denied since they have already been classified as unwilling or incapable of using other methods.

Finally, the right to be heard might also be denied since women lack power in a patriarchal system, the "target population" for Depo-Provera use is the most disadvantaged and victimized group, and the structure of the medical system with doctors appearing omnipotent and women assumed to be incapable of understanding complex technological explanations is designed to give physicians ultimate authority (Health Policy Advisory Center,1974).

> Even when confronted with what seems to be irrational therapy, most patients feel helpless to question or complain. A new folklore of medicine has emerged, rivaling that of the old witch doctors. Medical technology, from all that the patient has read in the newspapers, is as complex and mystifying as space technology. Physicians appear to be steely-nerved, omnicient medical astronauts. The patient is often undressed, a nameless observer in a process

> which he can never hope to understand. Everything about the American medical system seems calculated to maintain the child-like, dependent, and depersonalized condition of the patient. It is bad enough that modern medicl technology has been infused by its practitioners with all the mystery and unaccountability of primitive shamanism. What is worse is that the patient is given absolutely no means of judging what care he/she should get or evaluating what he has gotten(Health Policy Advisory Center,1974,p.40).

In 1978 the Health Research Group stated its specific position on the approval of Depo-Provera before the Select Committee on Population. While the HRG agreed that it was a highly effective contraceptive, its side-effects and carcinogenic nature made it "too hazardous for use in healthy women" (1978,p.788). It is likely to be approved for those women least likely to "withstand the enthusiasm of a zealous population- control doctor" and if it is approved for this limited population of women, it would be intended for "second class citizens" since it is too hazardous for middle class women (1978,p.788). "FDA's approach is morally repulsive. FDA must stop human exposure to Depo-Provera, a dangerous drug" (HRG,1978,p.788).

National Women's Health Network

The National Women's Health Network is made up of individual consumers, organizations and health centers. It monitors federal health policy as it affects women and acts as a representative in the women's health movement.

Members testify before Congress and federal agencies. They conduct workshops and conferences and sponsor health projects related to women.

Dr. Helen Bequaert Holmes, a biologist and feminist defines some of the major women-centered values operating within the feminist ideology. Respect for the individual and her uniqueness is vital to the feminists interpretation of all issues. Policy-makers claim to have women's best interests in mind in developing contraceptives. But Holmes claims that patriarchal research institutions cannot be excused for not involving women in decision-making. Determining whether or not a contraceptive and its risks are acceptable is a social decision that can be validly made only by the consumer(Holmes,1980).

Feminists claim that the personal is political. A person's past experiences shape present attitudes and biases. Owning and revealing these biases is contrary to the practice of medical science which claims objectivity (Holmes,1980). Patriarchal research institutions base decisions on profitability. Consequently they "foster the goals of racist population controllers" (Gross,1980, p.25). Instead of exposing these values, they present their evidence as "scientific truths" which is contrary to the needs of women.

Feminists also view the political as ethical. People in power determine what is right and wrong, and

it is these ethical stances which determine political policy (Holmes,1980). Feminists claim that male power that monopolizes the church, the state, the medical profession, research institutions, drug companies, and personal relationships must be overcome if women are to gain control of the relevant technology and information that shape their lives to make informed choices and to have adequate alternatives. Women are operating in systems not of their own making due to the broadly unequal distribution of power (Roberts,1981). "If women and consumer advocates, rather than such professionals as physicians, were the primary frame workers of deliberations over Depo-Provera, a different process for analyzing the problems of women's reproductive lives would be in operation" (Corea,1983,p.181).

Another value is the right to autonomy and choice. Any person affected by a policy should have the choice of submitting to it and participate in controlling its use (Holmes,1980). Corea (1983,p.182) states:

> There must be an informed consent procedure in which a woman is truly informed, not just about effectiveness and convenience of contraceptives, but also about safety, side-effects and how they might affect the quality of her life. She might be the best one to judge whether an effect of a contraceptive is major or minor.

A value in the wholeness of the individual includes her psychological, physical, and emotional aspects. In looking at a particular organ or disease it is necessary

to take her body and entire life span into consideration. Safety concerns arise from this value (Holmes,1980). Corea (1983,p.182) stated:

> Women would look not just at the physiological effects of Depo-Provera, but also at what it does to our spirit to be lined up and injected with an animal carcinogen because we are not motivated enough to put a diaphram in as often as certain professionals think we ought to, we would look at how such treatment would contribute to our self image and lack of a sense of our own power.

Wholeness of the community of women is a value to strengthen the bond among all women. In identifying with the situation of minority and disadvantaged women and working to alieviate the inferior position of women in society, feminists improve the power base of women and their quality of life.

The value on wholeness of the human community into the future is a crucial concern for the unborn child and her/his future. It is important that women can control those substances that effect the unborn child and prevent a legacy of disabilities and disease.

The last major value is connectedness and non-hierachism. People and values exist as a circle and not as a rank-order. The resolution of dilemmas require the participation of affected persons. While they value increasing contraceptive options in order to respect individual differences, a dilemma arises when a potential option creates risks to one's entire

body and future generations.

> The conflict is between regulation and free choice. So far the cafeteria has been male-supplied and that its problems might vanish if the cafeteria were to be female supplied. Suppose profit and objectification were replaced by our women-centered values in motivating the development of contraceptives (Holmes,1980,p.15).

In 1967, critics claimed that only $50,000 out of $70,000,000 spent on contraceptive research worldwide were spent on safe barrier methods. They argued that potentially dangerous methods receive major funding because the medical establishment and corporations promote patents, profits, and the development of new technologies (NWHN,1978,p.375). Almost all contraceptive research is sponsored by drug companies, International Planned Parenthood, the federal government, and private organizations such as the Population Council, the Ford Foundation and the Rockefeller Foundation which are made up primarily of males with little or no input from women. It is our position (NWHN,1978,p.379):

> That women should be creating policy on behalf of women, at the very least, and that all users of contraceptives should have a significant voice in determining what kind of research is to be funded. To the extent that birth control is still primarily the responsibility of women, and that women are the ones who bear the major consequences of childbirth, as well as the risks and serious complications of birth control. Women should have a major voice in determining which contraceptive research priorities will best meet their needs.

These women centered values are the framework used

by feminists in interpreting major ethical and medical issues in the Depo-Provera controversy. Respect for the individual is the feminist unit of analysis which significantly alters the risk/benefit assessment from that of the proponents because adverse side-effects and carcinogenesis takes on a much more serious meaning. Jeopordizing the wholeness of the individual - her quality of life - is a greater risk than the benefit of population control.

The feminist view that the personal is political and the political is ethical is the basis for challenging technical data and "scientific facts". They claim that science is not objective but instead is influenced by the biases and interests of those promoting the technology. In the Depo-Provera Debate feminists make claims that the experimental designs and experimental data while being seriously flawed were interpreted by proponents to minimize the risk and maximize the benefits to support their own interests. Corea stated (1980,p.107):

> Experts testifying on contraceptives before the Senate last year occasionally sounded like army generals giving congressmen a briefing on new weapon systems. For example, one witness used such terms as "the vaginal delivery system", "target organ", "subject compliance", "delivery platform", and the "target population". In the Senate hearings, experts discussed Depo-Provera with all its side-effects - minor and major, suspected or unknown - it is difficult to imagine how such a drug could ever be considered as a contraceptive for free citizens. But if we look at Depo-Provera, not as an aid developed to help

> women control their reproductive lives, but as a particularly efficient weapon in a war against female fertility then much confusing information becomes comprehensible.

The values on autonomy and choice and wholeness to the community of women was emphasized in the Depo-Provera Debate by feminists in their claims that the manufacturer, international health organizations, and the medical community were involved in widespread abuse of Depo-Provera among the minority and poor women through bribes to governments and hospitals, threats to women concerning welfare and social security benefits, withholding of information to give an informed consent, denial of contraceptive alternative and forced use without the consent or knowledge of the individual.

Wholeness of the human community of the future is brought out in the Depo-Provera controversy because of Depo-Provera'a claimed teratogenic effects and the transmission of Depo-Provera through breastmilk and the subsequent long term effects. Silberstein (1983,p.64-65) summed up the feminist position on Depo-Provera:

> Depo-Provera may be convenient, but it is in no way a life-saving drug. These facts, along with the ability of other adequate, viable, safe contra- ceptives in this country, clearly demonstrates the risks outweigh any benefits. If the drug is approved and given to women and it turns out to cause cancer or birth defects, the injury to those women and children will be irreversible, and the harm immeasurable. Until competent studies are completed that refute the clearly indicative

> risks, the NWHN strongly believes that Depo-Provera should not be approved for contraception in this country.

Steven Minkin, a Health Policy Analyst with the NWHN and former Chief of the UNICEF Nutrition Program became one of the most controversial spokespersons after publishing his article "Depo-Provera: A Critical Analysis" (1980) commonly cited by critics. Minkin (1980,p.49) claims that much of the information came from "proprietary trade-secret documents not available to the public or the medical community". Minkin (1980,p.65) claims:

> Apparently the health and safety of women and children have a lower priority in AID and other international organizations than does population control. Even after the cancers were discovered in monkeys, the U.S. Agency for Inter- national Development, the International Planned Parenthood Federation and the World Health Organization continued to pressure the FDA. The official position of these agencies on Depo-Provera is not necessarily scientific nor well informed. It clearly reflects the political orientation, male dominance, and perhaps the undue influence of the pharmaceutical industry at the policymaking levels.

Food and Drug Administration

The Food and Drug Administration (FDA) is a regulatory agency established in 1931 "to monitor research performed by industry to assure that the subjects of such research receive adequate protection, and that products offered for marketing are safe and effective for their intended

use" (Kennedy,1978,p.555). The FDA is a part of the Public Health Service of the Department of Health and Human Services. Its authority was created as a result of the Food and Drug Act of 1907, revised in 1938 and 1962.

According to Donald Kennedy, former FDA Commissioner (1978,p.556), the primary responsibilities of the FDA includes developing standards to follow in the testing of products, monitoring research to assure adherence to FDA standards, reviewing research in support of New Drug Applications, monitoring post- marketing studies assessing the safety and efficacy of the drug, and assuring proper labeling to provide useful information to physicians and users. The FDA has many outside advisory groups such as the National Center for Drug and Biologics, U.S. Environmental Protection Agency, National Cancer Institute, and Centers for Disease Control to assist the FDA in its role as a technical agency.

The FDA has often been charged with being politically aligned with industry. FDA officials sometimes move into or come from positions within industry. For example, Mark Novitch, former deputy commissioner of the FDA became Vice-President of the Upjohn Company in March, 1985. The Ethics in Government Act prohibits former FDA representatives, from representing industry in matters they had been directly involved with while with the

FDA. But, according to Upjohn, Novitch's knowledge of the inner workings of the FDA and his contacts is valuable to the company (Woodruff,1985).

The FDA has been documented as being reluctant to ban highly profitable drugs (Hadden,1979). Also, because industry performs the required safety tests, the FDA is dependent on industry for information to perform its regulatory function (Hadden,1979). The FDA is partially kept in check by other branches of government through Senate and U.S. House of Representative subcommittee hearings on issues directly related to the drug or technology before the FDA.

The FDA's concern with contraceptives differ from those of many other drugs because there are a large number of women who use contraceptives, estimated at eight to ten million women using contraceptive drugs as opposed to contraceptive devices. Also, the risk/benefit assessment differs from therapeutic drugs because it is intended for healthy users and the risks extend beyond the user herself to include unwanted pregnancies and effects on the fetus (Kennedy, 1978,p.555). Kennedy (1978,p.566) claims:

> the first concern of FDA is human safety, we must design requirements and take actions to assure that maximum protection is offered to test subjects and users. In our view, FDA requirements are not barriers to progressive research but rather are valuable adjuncts to quality research in the contraceptive field.

According to Doctor Fletcher Campbell, Jr., Associate Chief Counsel for Radiological Health, FDA, safety is not an absolute, but must be compared to the benefits. Tests are important because FDA regulation is based on a judgement of the adequacy of these studies and the findings from these studies. Campbell (1983,p.89) claims that there have not been any tests that adequately show the safety of Depo-Provera. Human studies have been inadequate and animal studies did not show safety. "...I don't think it is because Upjohn has been negligent, I think they can't get safety data because the drug isn't safe". Dr. Robert Temple, Acting Director of the Office of New Drug Evaluation, in the National Center of Drugs and Biologics, of the FDA stated"...data now available do not show that the benefits of Depo-Provera outweigh its potential risks in a defined population, taking into account the alternative modes of contraception that are available"(1983,p.6).

Summary

This chapter examined the fundamental ideology of the proponents and opponents, and how their ideology influenced their specific position on Depo-Provera and their action in regard to the use of the drug. A summary of the position of major actors on Depo-Provera is presented

in Table 3.

The following chapter will examine specifically what tests were required by the FDA in Upjohn's New Drug Application for Depo-Provera approval, how these tests were assessed by the proponents and opponents, and how their ideology shaped their interpretation of the medical and ethical issues.

Table 3

Position of Major Actors on Depo-Provera
Summary

Major Actor	Position
The Upjohn Company	Depo-Provera is a highly effective, safe, and acceptable contraceptive.
International Planned Parenthood Federation	The international experience of more than 15 years of clinical use of Depo-Provera has demonstrated that the drug represents a safe and effective method of fertility regulation.
World Health Organization	Based on the extensive epidemiological, and clinical data available to date, Depo-Provera appears to be an acceptable method of fertility regulation.
U.S. Agency for International Development	It should be a firm policy to add to the range of contraceptive methods available all those that are economically and logistically possible to distribute.
Medical Community	We find no reason to deny DMPA approval provided that studies of its possible side-effects are continued.
Health Research Group	Depo-Provera is too hazardous for use in healthy women. FDA should stop human exposure to Depo-Provera, a dangerous drug.
National Women's Health Network	Until competent studies are completed that refute the clearly indicative risks, Depo-Provera should not be approved for contraception in this country.

CHAPTER IV

INTERPRETATION OF MEDICAL ISSUES

The medical and ethical issues making the approval of Depo-Provera so controversial include: the prioritizing of values for determining an acceptable risk/benefit assessment; the need for the drug and its effectiveness; rules of evidence for interpreting required animal and human tests for new contraceptives established by the Food and Drug Administration; the carcinogenic nature of Depo-Provera; other adverse side-effects in women; and its teratogenic effects. This chapter examines the position of proponents and critics, on each of these major issues.

General Assessment of Risks and Benefits

Assessment of the risks and benefits of all drugs necessarily requires subjective evaluation by those persons determining the safety of the drug "...in deciding that the risks outweigh the benefits or vice-versa, one is crossing from evidence of risks to value judgements of safety" (Corea,1983,p.178). Prioritization of values and interests operate in deciding what constitutes acceptable

risks and in evaluating scientific evidence - e.g. assessing the validity of studies measuring adverse effects, determining appropriate rules for interpreting evidence.

Robert Temple, Acting Director of the Office of New Drug Evaluation in the National Center of Drug and Biologics of the FDA (1983,p.15) claims that the legal requirements for evidence of safety of a drug are two-fold. First, "the drug must have been tested by all tests reasonably applicable. Obviously, it is a matter of judgement as to what constitutes a reasonable, applicable test." Second, the drug must show through the applicable tests to be safe for its intended use "...safe for its intended use means that the risks of treatment are outweighed by its benefits when the drug is used as labeled." (Temple, 1983,p.15).

Legal requirements are broadly defined giving the evaluator sufficient room for interpretation. Who decides what constitutes a reasonable, applicable test? Safety means that the "risks of treatment outweigh the benefits" according to Temple. Who decides acceptable risks? Risks to whom? Who benefits? These are all issues that have contributed to the controversial nature of the Depo-Provera debate. The following section examines what criteria proponents and critics use in assessing he risks and benefits of Depo-Provera.

Proponents and Critics Criteria for Assessment of Risk

Proponents evaluate the benefits that Depo-Provera contributes to population control and assess the risks accordingly. If the benefits are great, the risks to the individual are minimized in their evaluation of the issues. In the Depo-Provera controversy, the proponents believe that the benefits heavily outweigh the risks. Potential risks to the individual from Depo-Provera use are less significant when weighed against unwanted pregnancy, unwanted births, and world overpopulation. (Hubbard,1978; Potts and Paxman,1984; Moghissi,1978; Potts,1978; Wilson,1976; Senanyake,1983).

Critics assess risks in relation to the benefits that Depo-Provera offers for the individual. Benefits to society are less significant if the risks to the individual are great. Critics claim that the risks outweigh the benefits. "Depo-Provera's main advantage is its convenience which hardly outweighs the increased risk of cancer, heavy bleeding, permanent sterility, and other serious and irreversible side-effects" (Rhodes, 1983,p.120; Johnson & Wolfe,1983,p.40). Because contraceptives are used by healthy women, potentially fatal risks must be considered very seriously (Johnson,1978, p.783).

Childbirth Mortality Argument

Proponents defend their criteria for evaluating risks by arguing that the mortality rate associated with childbirth for low-income women is a much greater risk than the risks associated with Depo-Provera. According to Malcolm Potts of Family Planning International and John M. Paxman of the Pathfinder Fund (1984), seventy percent of births in the world today are not attended by a trained physician which is an "obscene social injustice" as well as a serious health hazard. "To deny individuals access to contraceptives such as Depo-Provera, and thereby eliminate the possibility of choosing not to give birth is to compound not to relieve that injustice and frustrate the right to reproductive freedom" (Potts and Paxman,1984, p.18). Malcolm Potts (1978,p.238) claims that the risks of childbirth and infant mortality are as high in some parts of the United States as in developing nations. Potts and Paxman (1984,p.13) stated, "an appreciation of the fact that practically every choice in life has a quantifiable risk of death associated with it is ethically helpful and the risks and benefits can then be fit into perspective, however limited".

Proponents rationale that the risks of Depo-Provera use are less than the risk of childbirth mortality is ignoring structural causes contributing to childbirth

mortality according to critics. Giving weight to the childbirth mortality argument in support of contraceptive use promotes the self-interests of the opponents, but does not improve the general quality of life or enhance the wholeness of the individual woman. Corea (1983,p.182) claims:

> To the degree that it is possible, programs should focus on the totality of a woman's life. Doing less is ignoring such problems as the low status of women and lack of a power base for the indigent. Birth control services alone will do little, if anything to raise the standard and quality of life for women and their families. It is not the failure to accept contraception, which is responsible for the high rate of death and sickness among poor women at childbirth, rather it is among other factors - the poor health and nutritional status of women, the low wages, 59 cents on a man's dollar, which can help to keep her poor and ill-fed and the absence of appropriate prenatal and other health services.

Discrediting the Opponent's Position

After proponents and opponents present their assessment of the risks and benefits based on their own interests and values, they attempt to discredit the position of their adversary by claiming that their opponent's assessment is bias as a result of emotionalism or manipulation of data. Proponents claim that critics lack a necessary understanding of science (Hubbard,1978,p.470) in which to interpret data accurately and present their case in a highly emotional fashion making an objective assessment of risks and benefits difficult. William N. Hubbard,

President of the Upjohn Company (1978,p.513) claimed, "the discussion tends to be pitched at a level of extremism...In this highly charged atmosphere, the likelihood of a most objective appraisal of the definable risks and benefits is very sharply reduced."

Opponents claim that doctors, patients, and family planners were not able to assess the risks of Depo-Provera because Upjohn did not make all of the information available to the public. Minkin (1980,p.51) claimed, "During the last twelve years many incriminating findings from animal test data were not made public. As a result, Upjohn was well placed to manipulate the flow of information regarding the alleged benefits and risks of the drug." Proponents refute Minkin's accusation by declaring that "the suggestion that the scientific and medical community seems to be poorly informed about DMPA and its effects, both in the human and in experimental animals, is hard to reconcile with the fact that there have been hundreds of publications reporting on almost every conceivable aspect" of DMPA (Benangiano and Fraser,1981,p.497; Upjohn, 1980).

Opponents claim that under the law, the burden of proof is on Upjohn to demonstrate the safety of Depo-Provera. According to Diane Silberstein, Counsel for the National Women's Health Network (1983,p.58), "Upjohn has failed to meet the burden of proof. The findings

of safety must be based on reliable, scientific evidence. Upjohn has not offered a single, credible study to support its allegations that Depo-Provera is a safe drug".

FDA Position on Safety

Robert Temple of the Food and Drug Administration (1983,p.6) concluded:

> Data not available do not show that the benefits of Depo-Provera outweigh its potential and known risks in a defined population, taking into account the alternative modes of contraception that are available (p.6)...If there were no adequate means of contraception available, the concerns might well be resolved in favor of approving Depo-Provera, with labeling, describing the known and potential risks. There are adequate means available for virtually all people, however, and that has affected our conclusion (p.12).

Effectiveness and Need

Proponents describe the effectiveness and need for Depo-Provera with a positivistic approach - factual and value-free. They discuss the properties of Depo-Provera, its mechanism of action, and delivery methods. Little or not reference is made to ethical concerns because ethical issues are not inherent within Depo-Provera itself and therefore should not be made a major issue.

Opponents approach the effectiveness and need issue by discussing the implications of its highly effective nature from an ethical standpoint. Critics view ethical concerns as vital to the debate because they are inseparable

from the technology itself when it is applied to the individual.

Effectiveness

Proponents claim that Depo-Provera is among the most effective contraceptives available. A 150 mg injection every 90 days has an efficacy rate of 99.7% (Upjohn,1983; Kirton & Cornett,1974; Duncan,1983; Hubbard,1978; Nash,1975). It is unique in that it contains no estrogen, thus eliminating estrogen side-effects and its long duration of action is a positive attribute for many women (Duncan,1983, p.20). Inhibition of the cyclic ovarian function is caused by the slow absorption of DMPA into the system and continues until DMPA is undetectable which generally occurs seven to nine months after DMPA administration (Ortiz,et al,1977,p.32).

Critics agree that Depo-Provera is a highly effective contraceptive agent. In fact, its highly effective nature can act as a detriment since it is active in the bloodstream for three to five months. In situations where women had adverse side-effects or became pregnant, they would have no recourse for which to alleviate the effects (Levine,1979).

Depo-Provera's effectiveness and its injectable nature, takes the control from the woman and gives it to the physician. Rakusen (1981:78) claims:

> The speed with which Depo-Provera can be given is unashamedly regarded by population controllers as Depo-Provera's big bonuses. This together with Depo-Provera'a beauty as a contraceptive that women can't control for themselves, leads to family planning workers favoring Depo-Provera above other methods, particularly if they are being paid incentives for recruits to their program.

Need

Proponents claim that there is a significant population of women in the United States who would desire or who would need Depo-Provera as a contraceptive. Duncan (1983,p.17) estimated that over eleven million women around the world have used Depo-Provera as a contraceptive and between two and four million women are presently using Depo-Provera. The Upjohn Company (1983) claims that five to nine percent of women in the U.S. using reversible contraceptives would elect to use Depo-Provera. Duncan (1983) claims that these estimates were obtained with full disclosure of the risks and benefits.

Many physicians believe that Depo-Provera is the best contraceptive for a select population and that "no safe, effective, and acceptable alternative is available" (Moghissi,1978,p.342). Potential users identified by proponents for whom Depo-Provers is especially suitable include drug addicts; mentally defective women "for whom pregnancy is obviously undesirable"; mentally ill patients; patients with sickle cell anemia; patients

with blood dyscroasia for whom amenorrhea is beneficial; women in later reproductive years when thromboembolic complications of pills increase; women with counter indications to estrogen, and women who are unable or unwilling to use other methods (Hubbard,1978,p.270; Moghissi,1978,p.342; Wilson,1980). Teenagers are also identified as potential users. "Were full FDA approval of DMPA gained, some physicians would use this medication fairly extensively for teenagers" (Hubbard,1978,p.271). Senanyake (1983,p.48) claims that Depo-Provera would be perfectly acceptable to women whose partners are hostile to the idea of family planning. Senanyake (1983, p.48) claims:

> A woman in any of these situations could be deprived of being prescribed the most reliable contraceptive method suited to her needs and will be faced with a choice of sterilization for herself or her partner or accepting the low effectiveness of the IUD, or increasing risks associated with the pill. This is surely a supreme irony given that she is currently denied access to Depo-Provera allegedly for her own protection.

Critics claim that while Depo-Provera could be an acceptable option for some women after making an informed risk/benefit assessment, the availability of the drug for these women would encourage abuse of the drug by the medical community on individuals who otherwise would not have chosen to use the drug because of the risks. Wolfe (1983) claimed that there are no groups of women for whom the benefits outweigh the risks.

The FDA was going to approve Depo-Provera for a limited population of women - those women unwilling or unable to accept the responsibility for other methods of contraceptives - i.e. poor, mentally retarded. "Subjecting these groups of women to an increased risk of cancer and other serious side-effects judged to be unacceptable for other women creates a double standard of safety which is morally offensive and unacceptable" (Wolfe,1983, p.54). These women are least likely to be able to weigh the risks and benefits. If the double standard were appropriate, which it is not, it would be impossible to locate and evaluate those women who are incapable or unwilling to accept responsibility for other methods of contraception. The burden would be placed on physicians to identify this population, encouraging physicians to make certain subjective evaluations which invites widespread abuse (Wolfe,1983,p.57). This violates women's right to give informed consent and to choose for themselves how they will control their reproductive lives.

According to critics, because the FDA had not taken a strong stand against Depo-Provera use widespread abuse has taken place. Gena Corea (1980,p.180) claims:

> A long acting injectable is considered desirable for 'a certain population' because its use requires a minimum of intelligence and initiative in recipients. Like the eugenicist, their ideological forefathers, many population controllers tend to view the poor as ignorant and irresponsible. The great advantage of Depo-Provera to population control advocates

> is that they can inject the women, send them on their way, and not have to see them again for three months. The program is designed without a provision for follow-up.

Critics argue that while the FDA made it mandatory to obtain informed consent for the contraceptive use of Depo-Provera for clinical testing, Depo-Provera is used outside of clinical testing without informed consent. Family planners and physicians have used the forms to maintain power by not providing adequate information of the risks; intimidating the client with an atmosphere of authority; and demanding a signature during an emotionally or physically painful situation (Holmes,1980). Depo-Provera was prescribed 40,000 times in the United States in 1975 (Johnson,1978), largely due to the inability of the FDA to monitor non-approved use of the drug (Levine, 1979). Marcia Greenberger (1973,p.74) claims that there is no general FDA regulation against unapproved use of the drug. The following are examples of purported abuse.

The U.S. National Welfare Rights Organization asserted that many cases have been reported where women - especially blacks and minorities were threatened by the loss of their social security money into accepting Depo-Provera (Rakusen,1981).

At the George Washington University Family Planning Clinic in Washington, D.C. it is claimed that a candidate for Depo-Provera was a "teenager who cannot, will not,

be relied upon to take pills and does not want an IUD. She got her 150 mg injection and no informational leaflet" (Zwerdling,1974,p.8).

Richard Brookman, M.D., of the Children's Hospital Medical Center in Cincinnati claimed that "like most adolescents, young women with sickle cell anemia (generally black) have great difficulty employing mechanical devices consistently, correctly, effectively". Levine (1979) claims that Brookman's social argument is not grounds for supporting the drug and invites abuse.

The New York Times (12 Oct 1973, 6 July 1973) stated that Depo-Provera was used in a case involving two girls in Alabama who were surgically sterilized without their consent or the consent of their parents. Medical personnel from the Montegomery Family Planning Program injected the girls with Depo-Provera prior to the sterilization procedures. Other involuntary sterilizations occurred that same year, in the same clinic - ten were black, five were minors, and seven were retarded. As a result, the use of Depo-Provera was halted.

Nathan Kase, M.D., Chairman of the Department of Obstetrics and Gynecology, Yale University School testified at the 1973 Congressional hearing that Depo-Provera was used in the practice of medicine (not as an experimental drug) at the Family Planning Clinic of the Cumberland County Health Department, Tennessee. Patients were

not given any information about risks, consequently, informed consent was not given. Physical check-ups were not consistently given before, during, or after Depo-Provera use. At least one patient felt she was coerced into using the drug (Kase,1973,p.61).

Marcia Greenberger, Center for Law and Social Policy, Washington, D.C. (1973) testified that Arlington Hospital and School in Tennessee for the mentally retarded has been prescribing Depo-Provera since 1969 to 250 patients for contraception and to prevent menstruation. Dr. Edward Mogan (1973), a physician for Arlington claimed that he thought it was approved because it was easy to obtain. Many private physicians were prescribing it for contraception, and Memphis and Shelby County Public Health Departments were using it as a supplement to the pill without informed consent or follow-up.

James S. Brown, M.D. (1973), Superintendent of Arlington Hospital and School testified that while Depo-Provera was not specifically licensed for contraceptive use, it would safely control menstruation and contraception. He stated that Mexia State Hospital and School in Mexia, Texas gave recommendations based on extensive use at Mexia.

Senator Kennedy, at the 1973 Congressional hearing, asked Leonard Brooks, M.D., New Women's Clinic, Washington, D.C. whether physicians should be able to prescribe

a drug not approved for those purposes by the FDA. Brooks (1973,p.80) stated:

> You as a male are faced with birth, but as a middle-aged male you have not been victimized in your productive life. It is not an issue to you anymore and you are not a woman. Depo-Provera is something all my colleagues are closely familiar with, and if you are sensitive to the suffering of people, how else can we help our people? Harry Truman said, "The buck passing stops here" and with the doctor it stops with me, and if I have the capability to uplift a person's life in some small measure, I will do it with the agent at hand. There is no alternative.

Robert Hutcheson, Tennessee State Health Official said they had to prescribe a drug for a non-approved purpose because "we didn't have any FDA approved contraceptive drug to offer them" (NY Times,22 Feb 1973,1:1).

Sheila M. Rothman, Research Associate at the Center for Policy Research wrote in the New York Times (22 Feb 1975,p.27:1) that:

> abuses are not limited to a few southern states and are not the fault of a handful of overenthusiastic doctors. Rather, family planning officials in many states freely prescribe Depo-Provera as a contraceptive drug even though the FDA had prohibited such use of it because permanent sterilization was one of its adverse side-effects.

Critics claim that these case studies are examples of abuse of a non-approved drug aimed at the poor, minorities, teenagers, and mentally retarded women - the powerless - by a patriarchal system which uses its authority and expertise to force their interests on a population of people least capable of protecting their own rights.

Not only were their rights to safety, to be informed, to choose, and to be heard violated, but their respect and wholeness as individuals was totally disregarded by paternalistic physicians claiming to be working in the woman's best interests. Levine (1979,p.10) states:

> The purpose of this drug is not to prevent disease, but to prevent pregnancy. Is that goal so crucial to the lives of those patients for whom Depo-Provera might be recommended that the risks ought to be discounted. Those who are arguing that contraception is paramount are not the women themselves, but those who claim to speak for them - family planners, medical professionals, program administrators. Depo-Provera is now more attractive to these people since sterilization is more closely regulated under DHEW's new guidelines. The proposed limited approval for women who cannot or will not use contraception strongly suggests that it is intended for poor women or second class citizens even though Upjohn vehemently denies it. One can feel in these words the frustration of the medical professionals and family planners in dealing with women who will not or cannot do what is considered by others to be in their best interest!

Jill Rakusen (1981,p.100) believes that while under many circumstances Depo-Provera is abused by professionals on those populations proponents defined as the "target population", she claims that the situation is more complicated because some of the women who do want to use Depo-Provera are those women whose partner is forcibly against any use of contraceptives.

> This is the case particularly with some Roman Catholic and Asian families. Men have been known to throw pills away, forcibly to remove IUD's, and beat their wives for using contraception, and it is understandable that women faced with this kind of problem might welcome an injectable contraceptive. Depo-Provera could be seen as the least oppressive

> alternative, although it does not change their situation and maintains the status quo. But the banning of Depo-Provera could be seen to be yet another cross to bear.

Opponents would not be so adament about denying approval of Depo-Provera if women could be guaranteed their full rights to informed consent and choice, but due to the nature of the drug and some structural features of society i.e. patriarchy - critics believe widespread abuse is inevitable. While some women may see Depo-Provera as a positive option, many who would be victimized by the system would not. Therefore, critics claim the risks outweigh the benefits for all women.

FDA Position on Need

In 1973, the FDA decided to approve Depo-Provera for a limited population. The patient population was described in the Federal Register, October 10, 1973 (p.27940):

> the drug product is intended for the patient who accepts the possibility that she may not be able to become pregnant after discontinuing the drug, and who refuses or is unable to accept responsibility demanded by other contraceptive methods, or is incapable or unwilling to tolerate the side-effects of conventional oral contraceptives, or is one in whom other methods of contraception are contradicated or have repeatedly failed.

In 1978, the FDA reversed its position claiming that there was not an adequate population of women for whom Depo-Provera was needed in light of presently available contraceptive methods (Kennedy,1978). Many of the women

defined as needing the drug in 1973 are no longer considered an appropriate population because of their inability to give informed consent (Temple,1983).

Rules of Evidence

How the proponents and critics define the rules of evidence is crucial to their assessment of the medical issues. Consequently, the rules are defined to maximize their interests and support their position. The following issues have been critical to the debate: What is the relevancy of adverse effects in animals in their applicability to humans? Do the reproductive systems of animals react similarly to humans when certain drugs or hormones such as progesterone are administered into the body? What is the conclusiveness of the human studies which have found no adverse effects in humans? Are they methodologically sound? Are the populations studied adequate in size and representation? Are there control groups? Is there adequate follow-up time to obtain accurate cancer findings? Because the rules of evidence have been unresolved between proponents and critics, each side has a very different definition of the medical issues.

Relevancy of Animal Data

The data on laboratory animals has been a major

source of controversy in the debate. The data have acted as a detriment to proponents because of the adverse findings in animals. Consequently, proponents attempt to de-emphasize the animal data by claiming that it is inappropriate, instead emphasizing the relevancy of human studies. Critics focus on the animal studies because they strongly support their position against Depo-Provera.

Animal studies are important for several reasons. First, they may suggest adverse effects without placing any risks on human subjects. Second, large doses can be given to animals to increase the speed in which possible adverse effects can be identified. Third, there are fewer external risk factors to complicate the study, allowing for a more controlled study (Population Information Program,1983,p.K31).

Numerous investigators have questioned the suitability of the beagle as a predictor of carcinogenesis in humans. Proponents concluded that dogs are not an appropriate animal model for the evaluation of carcinogenic risks associated with progestogens (Duncan,1983,p.102; Upjohn,1980, p.29; WHO,1978,p.777; Hill and Dumas,1974,p.74; El Etreby et al.,1979,p.237). The beagle appears to be highly susceptible to breast nodules due to an increased level of growth hormone when stimulated with progestogens. Proponents claim that this does not occur in women.

Beagles may have a reservoir of microscopic lesions which grow in response to progestogens. They also develop pyometra (type of uterine infection) and acromegaly (an abnormal growth condition). Again, proponents claim that these effects are not found in women (Population Information Program, 1983,p.K-32; Upjohn,1980,p.29; WHO,1978,p.777).

Critics claim that the beagle is an appropriate animal model for evaluating carcinogenic risk. Shearer (1983) claims that Upjohn's rejection of the positive carcinogenic findings in beagles is invalid. He claims:

> The three international panels of experts in Upjohn's submission which concluded that the beagle bitch is not an appropriate model for carcinogenicity testing of progesterone derivatives were not impartial panels of concerned scientists. They represent organizations which have been responsible for wide-spread use of Depo-Provera. If they admitted the demonstrated hazard of carcinogensis, their organizations would be admitting their responsibility for future massive cancer (1983,p.98).

Shearer (1983,p.97) disqualifies Upjohn's assessment on three grounds: First, Upjohn claims that the reproductive endoctrinology differs in dogs and humans. Shearer claims this is the case among any different species and therefore is irrelevant. Second, Upjohn claims that progestogens have a unique effect on the growth response of the mammary glands in beagles. Shearer claims, "Hyperplasia (excessive proliferation of normal cells in the normal tissue arrangement) can be distinguished

from neoplasia (a new and abnormal formation of tissue) by appropriate genetic tests to determine multiple or single cell origin of the nodule. Upjohn's claim that most dog mammary nodules represent hyperplasia rather than neoplasia should be supported by genetic data" (Shearer,1983,p.97). Finally, Upjohn claims that mammary tumorigenesis is related to the increase in growth hormone. Shearer claims that a cause and effect relationship has not been demonstrated, only that these two effects exist. For Upjohn to make such a claim would require data from the "administration of growth hormone to dogs using bioassay methodology" (Shearer,1983,p.97).

According to Minkin (1983,p.148), Upjohn rejected the significance of the cancer findings in beagles because it resulted from very high doses of the drug. Minkin claimed that "it is widely accepted that high doses of suspected carcinogens are necessary to increase tumor incidence to a level that can be detected in a limited number of animals". A chemical may cause cancer at a significant rate in the general population, but go undetected in a test population due to the low number of subjects. So, it is necessary to increase the dosage to increase the sensitivity in order for the response to be at a detectable level. Johnson (1978,p.391) argued that "Industry did not object to the validity of such dog studies as long as they yielded negative results,

but protested only when some of their products caused tumors in these studies".

FDA Position

Robert Temple, National Center of Drugs and Biologics of the FDA (1983,p.9) concluded:

> I have heard no persuasive argument, only assertions that the beagle is too sensitive, and that the monkey tumors may have arisen from a special endometrial structure, obviously, these are highly conjectural matters, ones on which people with comparable and high level experience could disagree. One only knows that a model is too sensitive as a result of comparing its results with the results of human exposure, and we don't have those data or analysis to deal with. It would be difficult to conclude that there can be said to be strong evidence that the dog data are meaningless.

Conclusiveness of Human Studies

Human studies assessing the adverse effects of Depo-Provera use in women have shown variable, but often minimal findings. Consequently, proponents have attempted to draw attention away from the animal studies by focusing on the fifteen years of epidemiological research. Opponents have attempted to undermine the significance of human studies by focusing on their methodological problems and ambiguous interpretations.

Epidemiological studies are inherently difficult and may not always produce conclusive results. Problems that arise in implementing epidemiological studies include

the many genetic and behavioral factors which influence the onset of reproductive cancer - e.g. the age at first birth influences the risk of breast cancer; for many forms of cancer years elapse between exposure to the drug and detection of the cancer or adverse effect; for rare cancers, it is difficult to locate enough cases for an adequate epidemiological analysis; long term studies of all cancers is difficult and expensive to conduct (Population Information Program,1983,p.K32).

Proponents claim that based on the extensive clinical trials and the detailed evaluation by the medical community of the volumes of literature on Depo-Provera that adequate human data has been obtained to assess the safety of the drug (Duncan,1983,p.99). According to The Upjohn Company, if there were serious adverse effects they would be detected by the clinical studies or by the voluntary reporting system.

> As far as major risk is concerned, or risks associated with relatively rare events, I think we have adequate studies in place and we would have been alerted to those either by the voluntary reporting systems or by the carefully designed and controlled clinical studies (Duncan,1983,p.36).

Extensive experience with Depo-Provera, along with the evaluations by authorities in the medical and scientific community, reinforce the safe nature of the drug. There has been an aggregate of over three million women - months of experience with the drug and it has received

greater evaluation by the medical and scientific community than any other steroid contraceptive in the world. "None of these studies that are reporting literature show Depo-Provera to be lacking in efficacy or to be responsible for serious untoward effects, morbidity or mortality when extensively used" (Duncan,1983,p.16). The following organizations have also recommended that Depo-Provera be approved for contraceptive use: the Committee on the Safety of Medicine in the United Kingdom, the WHO, the IPPF, the American College of OBGYN, the Royal College of OBGYN, the National Board of Health and Welfare in Sweden, and the Special Advisory Committee on Reproductive Physiology in Canada.

Proponents claim that the animal tests and clinical trials done in the United States thus far only determine whether it is responsible to administer the drug to a larger population. Absolute safety cannot be proven unless the drug is widely used over a significant period of time. Proponents contend that Depo-Provera has been proven to be safe in clinical trials thus far, therefore it would be a responsible decision to approve the drug for general use with sufficient post-marketing surveillance and follow-up.

Critics claim that deficiencies in the quality of research on Depo-Provera makes it difficult to draw conclusive evidence pertaining to its safety and adverse

side-effects in women. Among the methodological problems in the research are inadequate population size, no control groups, lack of follow-up, and sloppy and inconsistent interpretations of the data (Johnson,1978; Holmes,1983; Rhodes,1983; Wolfe,1983; Rakusen,1980).

There have been approximately eleven million women exposed to Depo-Provera, yet published reports reveal studies of small populations in the 10s, 100s, and rarely 1000s (Holmes,1983). Reports have been written in terms of number of women - years which has no long term value. Interpretations become meaningless because exposure time and follow-up per individual is undefined (Shearer,1983, p.99).

The Health Research Group claimed that many questions about safety may have been answered if Upjohn had conducted their studies with control groups. The Grady Memorial Hospital Study is one of the larger studies done on Depo-Provera, yet Upjohn did not set up a control group, so there was no comparison to determine whether the rates for adverse effects were normal or elevated. When the National Cancer Survey (NCS) was used as a control and showed an increase rate of cervical cancer, the NCS was determined by proponents to be an inappropriate control because it was claimed to have underreported the real incidence of cervical cancer among non-users. Without adequate controls it is not possible to assess

safety (HRG,1978,p.783-785).

Lack of follow-up or poor follow-up has been a serious problem with the Upjohn studies. Studies cited by proponents claim that bleeding problems significantly decrease after the first year. They do not report that the bleeding problems decrease because women who experience prolonged or severe bleeding generally discontinue the drug and therefore are not included in the analysis after one year. This self-selection bias, when not accounted for due to poor follow-up results in inaccurate reporting of adverse findings (Wolfe,1983,p.43). Reports have never associated DMPA with death. Depo-Provera has been reported to be associated with no mortalities. Yet, with the large percentage of women at loss for follow-up, it cannot be determined if the mortality rate is zero until it is established that these women are still living (Holmes,1983,p.188).

Another flaw in many of the Upjohn studies, according to the critics, is the lack of internal controls - i.e., what other drugs they were taking. When little information is compiled on patients, it is difficult to ascertain what the cause and effect relationship is between Depo-Provera and the adverse side-effects. Upjohn did not collect data on which patients were given estrogen with Depo-Provera making it impossible to separate the estrogen and/or progestin effects (HRG,1978,p.788).

In many studies there was a voluntary reporting system of side-effects. If the patient did not offer the information without prompting, it was not recorded (Holmes,1983,p.190). Rhoades (1983,p.123) stated that the physicians associated with research-oriented university hospitals that he is in contact with would report at best 10 to 20% of the side-effects simply because they are too busy. Holmes (1983,p.188-189) claims that women may be unlikely to return or voluntarily offer information about side-effects after experiencing bleeding problems, splitting headaches, or loss of libido because:

> the user may be ashamed to describe any of these to a stranger, expecially to one of a different social class or race. She may be fearful of having her symptoms exacerbated if she is talked into a second injection. Even a normally assertive woman may be intimidated by the power of the so called medical mystique. It stands to reason that the timid or medically unsophisticated woman would simply avoid the clinic rather than risk disapproval (Holmes,1983,p.189).

Therefore, according to critics, an accurate assessment of adverse side-effects is not plausible with a voluntary reporting system.

Finally, critics claim that the sloppy and inconsistent interpretations by Upjohn of the data make conclusive evidence about side-effects impossible. The HRG (1978,p.788) stated:

> The variability of the figures reported by Upjohn to the FDA at different times concerning the same studies and subgroups of studies, also calls into question the quality of the studies conducted by

Upjohn. The quality of the data suggests that Upjohn and its investigator-doctors looked upon these studies as cattle counts rather than medical studies.

FDA Position

Robert Temple (1983,p.10-11) of the FDA stated:

> The plain fact is, as Upjohn has not even attempted to refute, that there really are no credible epidemiological studies of Depo-Provera. Absent such studies, what does it mean to say that Depo-Provera has no risk of increasing mortality? I think the answer is that it means nothing at all...It seems to me that it is reasonable to ask for data on the effects of Depo-Provera, and not rely on speculation ...It certainly seems that before general use of Depo-Provera could be recommended, epidemiological studies adequate to characterize the risks of its use should be carried out.

Carcinogenesis

The issue of carcinogenesis is the most serious potential side-effect of Depo-Provera and the issue that has stimulated the most controversy between proponents and critics. Controversy has revolved around the cancer findings in the beagle dogs and monkeys and methodological problems in the human studies.

Beagle Studies

Two beagle studies were conducted under contract with The Upjohn Company. The first beagle study began in 1968. By 1972, 18 out of 20 dogs died in the Depo-Provera group. Only one dog died in the control group. The

Upjohn Company believed that the high mortality rate in the Depo-Provera group was due to the over-sensitivity of the beagle to progesterone. Consequently, another beagle study was carried out to evaluate Depo-Provera and progesterone treatment in the beagle.

First Beagle Study

FDA guidelines require a seven year evaluation of dogs treated with ten times (10X) and twenty-five times (25X) the intended human dosage. The International Research and Development Corporation of Mattawan, Michigan conducted a seven year animal safety study in beagles. By three and one-half years, all of the high dose group had died mostly from pyometra (an accumulation of pus in the uterus) (Frank,1978). Proponents claim pyometra rarely occurs in women. Minkin (1980,p.54), a critic, claims that pyometra is found in women in malignant states of the uterus and is the best recognized form of chronic endometritis. To control for this effect, treated animals of both groups were hysterectomized by the sixty-sixth week (Frank,1978). At the end of the study, a dose-related effect in the occurrence of benign breast tumors was found. Also, two dogs in the 25X group were found to have cancer of the breast (Upjohn, 1983,p.27;Frank,1978,p.596).

Dawson Study

Another beagle study sponsored by the Upjohn Company was conducted by the Dawson Research Corporation of Orlando, Florida to evaluate Depo-Provera and progesterone treatment in the beagle. The progesterone groups receiving the 10X and 25X doses were added to evaluate the sensitivity of the beagle to progesterone and to separate the progesterone and Depo-Provera effects. The progesterone group received weekly instead of 90 day doses so that the blood levels of progesterone would more closely approximate that of Depo-Provera since the absorption rates of the progesterones differed (Upjohn,1983,p.28;Frank,1978,p.610).

In the Dawson Study Upjohn removed the uteri of the beagles before injecting them with Depo-Provera because they were trying to measure its effect in the breast not the uterus according to Upjohn. Critics argued, "Why the FDA would agree to the routine removal of a large part of the reproductive tract in contraceptive studies need to be further explained" (Minkin,1980). Corea (1980,p.111) objected to the hysterectomies in canines because it is the uterine cancer that caused considerable concern since 1971 and needs more careful observation. Even with the hysterectomies thirty percent of the high dose group were dead within three years. WHO (Frank,1978,p.610; Frank,et al,1979) concluded "this

study has demonstrated that progesterone and Depo-Provera produce tumors in the beagle. The relevance of this finding to the safety assessment is disputed".

Corea (1980,p.112), a critic, claimed that instead of looking seriously at the carcinogenic effect in beagles, Upjohn diverted attention by "getting into esoteric discussions about beagle responses to progesterones and so on". According to Johnson (1978,p.392), beagles do not get tumors from all progestins which raises questions about Upjohn's claim that beagles are overly sensitive to progestins. Some synthetic progestins like DMPA cause cancer in beagles, others like norethindrone (an injectable contraceptive) does not.

As a result of these studies, according to critics, several oral progestins were removed from the market including Upjohn's Provest containing MPA; Lilly's C-Quens oral contraceptive containing chlormadinone acetate; experimental use of the Syntex mini-pill, a Mead-Johnson contraceptive; and Merck's ethynerone. Upjohn discontinued many of their human clinical studies with Depo-Provera (Johnson,1978, p.390).

FDA Position on Beagle Studies

The FDA claimed that the animal tests did not prove Depo-Provera to be a safe drug. Adrian Gross, Senior

Scientific Adviser of the Environmental Protection Agency (1983,p.76) claimed that the Dawson study was one of the best studies she had ever encountered. She concluded that "as far as the percentage of animals that responded with malignancies of the breast, mammary tumors, the progesterone by itself was not really as marked as Depo-Provera...Neoplasia is by no means the only health problem indicated by these studies". Norris (1983,p.112), witness for the FDA, criticized the Upjohn studies because the animals that died were inadequately studied. "If you check out the survivors, and only look at the survivors, you would conclude that the process was not malignant, but if you look at the ones dying, it may be a different matter."

Monkey Study

FDA guidelines also require a ten-year study in monkeys with dose levels of 10X and 50X the proposed human dose and administered through the intended site (injection). The 10-year study in rhesus monkeys was conducted by the International Research and Development Corporation in Mattawan, Michigan. Monkeys received doses at 1X, 10X, and 50X the human dose of Depo-Provera. Seven monkeys were substituted during the study because three died and four were TB suspects. Hyperplastic mammary nodules were found in all but the 50X group.

Two monkeys at the 50X dose developed endometrial carcinoma and one metastasized to the lung. Three other monkeys developed benign tumors - two in the 50X group and one in the control group. Findings of endometrial carcinoma were unexpected since Depo-Provera is approved for and has been extensively used as a palliative treatment of human endometrial carcinoma. WHO (1982,p.202) claimed that the tumors in the endometrium may have arose from a "cell type not found in women". In conclusion, proponents claim that the rhesus monkey has shown a very minimal adverse response to Depo-Provera at 1X, 10X, 50X the human dose for ten years (Frank,1978,p.604).

Critics claim that while the monkey study was not statistically significant in regard to cancer finding, the fact that two of sixteen monkeys developed cancer strongly suggests that the results would be statistically significant if a proper size sample - at least fifty - were used. "Thorough testing and definitive results are particularly important because this drug is intended to be given to healthy women. As it is designed and carried out, the monkey study not only fails to prove that Depo-Provera is not carcinogenic, but strongly suggests that the drug does cause cancer in monkeys" (Silberstein,1983,p.59).

FDA Position on the Monkey Study

Dr. Gisela Dallenbach-Hellweg, of the Women's Clinic, of the city of Mannheim (1983,p.143) is a human pathologist who testified at the Board of Inquiry hearings on behalf of the FDA. She claimed that "the carcinomas in the monkeys did not arise in the endometrium, but rather in the endocervical mucosa". She claimed that variables such as socio-economic status have no relevance for the origin of adenocarcinoma of the endocervix. Hellweg claimed that "a long acting unopposed gestagenic stimulation in a young healthy female...would cause a hyperproliferation of the endocervical mucosa which would be a precursor of a carcinoma. In my opinion, DMPA is contraindicated in young, healthy females" (1983,p.150).

Dr. Solomon Sobel, Director, Division of Metabolism and Endoctrine Drug Products, Office of New Drug Evaluation, National Center for Drugs and Biologics also testified on behalf of the FDA. Sobel (1983,p.25) claimed "there was a clear dose-related response, frequency of carcinomas was much higher than seen with any oral contraceptive tested".

Robert Temple (1983,p.7-8) explained three approaches that Upjohn could use to present evidence to persuade the FDA that the animal data does not constitute a risk or that the benefits outweigh the carcinogenic risk. Upjohn could discredit the dog and monkey models to

show that the animal data is irrelevant; Upjohn could carry out large, well-designed human studies to show that there is no carcinogenic risk in humans; or Upjohn could show that the benefits to a select population are so great that the cancer risk is overshadowed. "It is our view that Upjohn, and its consultants have not made any of the showings" (1983,p.8).

Clinical Studies

Clinical studies have been carried out in the United States and in other developed and developing nations. It is difficult to conclusively determine the association between DMPA and cancer because it may take decades to establish. According to Potts (1978,p.236), "it is possible that the lifetime of use of a pharmacologically active contraceptive will be less than that required for the final analysis of all the risks and benefits associated with its use."

Dr. Ory, Deputy Director of the Division of Reproductive Health, Center for Disease Control and his associates conducted a large clinical study of 11,500 women at Grady Memorial Hospital in Atlanta, Georgia from 1967 to 1979. They claimed that no evidence of an increased risk of breast, uterine, and ovarian cancer was found (Ory,1983,p.66; Greenspan, et al, 1980,p.563; Liang, et al, 1983,p.2909). Ory (1983) and Greenspan (1980)

claimed that because of the short exposure to DMPA, the lack of detail about DMPA users, and the short follow-up, the results had to be interpreted cautiously. While a weak carcinogenic response cannot be determined from from the Grady Study, it is reasonable to assume that a strong association is unlikely (Ory,1983).

Critics claim that in the Grady Memorial Study, rates of cervical cancer in-situ (early cervical cancer) were three to nine times greater than the rates in the general population as measured by the Third National Cancer Survey (3NCS). The 3NCS was used because Upjohn did not conduct the study with a control group. Because the Grady Memorial group reported gross excesses as compared to the 3NCS, the 3NCS was rejected as a comparison group due to the claim by proponents that it underreported the real incidence of cervical cancer in women.

The HRG found a different comparison group. The Memphis, Tennessee Study by Erickson, et al was the best comparison group for blacks. These women were repeatedly screened by pap smears after having the first smear diagnosed as normal. In comparison to the black control group, black Depo-Provera users were found to have a 2.67 fold excess of cervical cancer. A British Columbia study (Fidler,et al,1968) was a more appropriate comparison group for whites. A 4.4 fold excess of cervical cancer was found. These comparisons met the objections

that the 3NCS raised (Johnson,1978,p.392). Hoover of the National Cancer Institute (1978,p.790) stated:

> I believe the analyses presented by the HRG were quite responsible and made the maximum use out of the small amount of human information that was available. My conclusion from these analyses was that the data presented certainly did not support the view that Depo-Provera was "safe" with respect to the subsequent risk of cancer of the uterine cervix.

Critics claim that uterine cancer is one of the major types of cancer in women. It generally occurs after fifty years of age so at least twenty years or more of follow-up would be necessary to evaluate the impact of this drug on women (Minkin,1983,p.150; Shearer, 1983,p.99). Studies only looking for cancer in specific organs may be invalid since organs most sensitive to a particular carcinogen may vary between species. While Depo-Provera may reduce endometrial hyperplasia, it may cause cancer in the endocervix where it is being found to occur in some women (Shearer,1983,p.101).

The increase in risk may be particularly applicable to women at high risk for cervical neoplasia - e.g. demographic or sexual variables. These are the women most likely to be given Depo-Provera which should increase concern (Hoover,1978,p.791).

Ongoing - Clinical Studies

WHO is conducting a case control study in nine

countries. The study is examining women who are presently or who have used injectables in the past both with and without cancer of the reproductive organs. Preliminary data from three centers in Thailand where DMPA has been used for more then twenty years detected no relationship between DMPA and cervical cancer. WHO claims that the preliminary data had a ninety percent chance of detecting a risk as low as 1.6 times greater for DMPA users as compared to non- users. No association between DMPA and breast cancer was also found in the preliminary data (Population Information Program,1983,p.K-33; Shelton,1983,p.71; McDaniel and Pardthaisong,1973,p.83).

Upjohn is sponsoring a large scale retrospective study in New Zealand. However, Upjohn (1983,p.15) claims that retrospective studies are extremely difficult because patients often switch contraceptive methods making it difficult to establish a link and follow-up is also difficult because patients move, switch clinics, or stop using contraceptives. Attempts to find these patients can be an invasion of privacy. The New Zealand study will have 12,000 patients in which one-fourth will use DMPA. DMPA users will be compared to users of other contraceptive methods for safety, efficacy and rates of cervical cancer. Upjohn claims that the New Zealand study is more feasible because it is easier to obtain personal histories on the users in New Zealand.

Protective Effect of DMPA in Cancer Patients

Some medical professionals claim that DMPA has a protective effect against breast and endometrial cancer. Some physicians use DMPA to treat recurrent fibrocystic disease of the breast (Rosenfield,1978,p.535). Oral MPA has been found to lead to partial remission of breast cancer in about one-third of the cases. DMPA has also been found to be an effective treatment for endometrial cancer which it was approved for by the FDA. DMPA has been found to cause a complete or partial remission in 18 to 57% of metastatic cancer patients.

FDA Position on Human Studies

Robert Hoover, Acting Chief of the Environmental Epidemiology Branch, the National Cancer Institute (1983,p.187) testified on behalf of the FDA. He claimed, "The existing epidemiologic studies of Depo-Provera are inadequate and do not establish the safety of the drug in terms of carcinogenicity."

Other Side Effects

Proponents and critics interpret the research findings differently in regard to side-effects. Proponents conclude there are few adverse side-effects. Of the adverse side-effects associated with Depo-Provera, most women

find them tolerable. Critics argue that there are serious adverse side-effects associated with Depo-Provera. They claim that proponents minimize their significance while in fact they can ruin the quality of life for women. Major side-effects (excluding carcinogenesis, teratogenic, and reproductive side-effects) include menstrual disturbances, estrogen therapy, cardiovascular disease, diabetes, inhibition of bone growth and "subjective" side-effects - e.g., headaches, loss of libido, depression.

Proponents argue that some critics have seriously misinterpreted the scientific evidence in support of their own political philosophy (Ewalt,1982). Upjohn (1980,p.3) claims that "a detailed knowledge of the endocrinology of reproduction in both humans and animals is essential for the proper interpretation of events observed when DMPA is administered."

Menstrual Disturbances

Menstrual disturbances is the major side-effect associated with Depo-Provera use. There is a wide variation in bleeding patterns among individual women and the patterns are completely unpredictable. Over seventy percent of users never have one "normal" cycle while using Depo-Provera and during any one injection interval only seven percent of the users claim to have a "normal" cycle (Fraser & Weisberg,1981,p.6). After three months

approximately one-third of the women experience amenorrhea and another one-third experience prolonged bleeding or spotting (more than seven days a month). After one year, over fifty percent experience amenorrhea and after two years, seventy to seventy-five percent have amenorrhea (Moghissi,1978,p.344; Smith,1978,p.224; WHO,1978,p.396).

Estrogen Therapy

Proponents claim that heavy bleeding is uncommon. Where DMPA is widely used, curretage is necessary in less than one case in one thousand (Fraser & Weisberg, 1981,p.6). Cyclical supplementation with oral estrogens have been used to regulate bleeding patterns. Recently, estrogen therapy has been determined to have little value and has not been recommended for the treatment of bleeding anomalies (Duncan,1983,p.31). Upjohn claims:

> it does not recommend the administration of estrogens to control irregular bleeding or spotting associated with use of Depo-Provera. The proposed package insert mentions the possibility that irregular bleeding or amenorrhea might occur but does not suggest any means of treatment (Hubbard,1978,p.286).

Malcolm Potts (1983,p.102) claims that the use of estrogen therapy has declined and therefore has basically become a non-issue in the FDA's consideration of Depo-Provera for approval.

Proponents claim that most women with irregular bleeding or amenorrhea are willing to tolerate this

side-effect if they are informed of it before Depo-Provera administration (Smith, 1978,p.224). About four to seven percent discontinue use due to menstrual irregularities (Hubbard,1978,p.288).

According to critics, many investigators have found it necessary to use estrogen therapy to get the bleeding in control. One investigator used estrogen routinely, another found it necessary for one-third of his patients. Many of its claimed benefits no longer exist when estrogen is administered. Wolfe (1983,p.42) claims that bleeding is serious enough in some cases to cause hospitalization. In one study 63% (52) of women administered Depo-Provera postpartum bled constantly for ninety days compared to two out of fifty-two in the control group. While Upjohn claims that heavy bleeding tappers off the first year and many women then experience amenorrhea, there are no reliable studies that demonstrate the claim. Heavy bleeding is not only dangerous, it is also extremely inconvenient for women using the drug. Rhodes (1983,p.123) claims:

> It has been suggested that the effect of Depo-Provera could be reversed by treating someone with estrogens. I can find no reliable study which proves that this would work and quite frankly, I think that treating a woman as a test-tube and trying to trade her back to normality by use of estrogens against progestins is itself wrought with hazard and I can see no guarantee that it would work.

Cardiovascular Disease

Proponents claim that there have not been conclusive findings in regard to Depo-Provera's effect on lipid metabolism. Some researchers claim that there is a significant reduction in levels of high density lipoprotein (HDL) cholesterol which is suspected of increasing the risk of cardiovascular disease (Population Information Program,1983,p.K-28; Kremer et al,1980,p.350). Other researchers claim that if Depo-Provera does effect HDL, it is less than other available progestins and equivalent with oral contraceptives (Carlson,1983,p.110; Dhall, et al,1977,p.156; Fraser & Weisberg,1981,p.9).

Critics claim there is animal and human evidence to suggest that Depo-Provera may increase the risk of cardiovascular disease. Wolfe (1983,p.49) claims that decreased levels of HDL and other lipoproteins is associated with an increased risk of atherosclerosis (hardening of the arteries) and heart attack. Women using Depo-Provera in one controlled retrospective study found a significantly lower level of HDL in their blood. Upjohn's beagle studies - IRDC and the Dawson Study showed an extremely high incidence of pulmonary thrombosis (Holmes,1983,p.192).

Dr. John C. LaRosa, Director of the Lipid Research Clinic at George Washington University Medical Center and Bruce Stodel, Medical Officer in the Contraceptive Evaluation Branch of the Center for Population Research

at NICHHD were witnesses for the FDA at the 1983 Board of Inquiry hearings (1983,p.42) claimed:

> Lipids are important because of their relationship to atherosclerotic disease...I would avoid prescribing a drug which lowered HDL levels...Although the evidence is limited in quantity and quality, the available evidence concerning the effects of DMPA on lipid levels demonstrated that at least DMPA may be associated with a substantial decline in HDL cholesterol levels. This effect should be investigated before Depo-Provera is made available generally for contraceptive use.

Diabetes

While the development of clinical diabetes as a result of Depo-Provera use is rare, there is a definite diabetogenic effect (Fraser & Weisberg,1981,p.9; Tuttle and Turkington,1974,p.690). The Upjohn Company (1980,p.17) concluded:

> The development of clinical diabetes has been rare enough that it has not become a problem in the extensive use of the method to date. However, as with the orals, screening for diabetes is advisable prior to initiation of treatment.

Lowered Resistance to Infection

Proponents claim that there is no clinical evidence that Depo-Provera is an immunosuppressant. Even when Depo-Provera has been used for cancer treatment at very high doses over a prolonged period of time, there is not evidence of a lowered resistance to infection

(Benangiano & Fraser,1981,p.511; Upjohn,1980,p.12).

Critics claim that Depo-Provera appears to lower host resistance to infection. According to Minkin (1980), animals given Depo-Provera died much sooner than unexposed animals. Corea (1980,p.113) claims that "lowered resistance to infection may be the most devastating effect of Depo-Provera." Proponents argue that the use of Depo-Provera is partly designed to lower the maternal mortality rate. But by increasing the susceptibility of childbearing women to fatal disease, Depo-Provera may, in fact, be raising the death rate among these women.

Inhibition of Bone Growth

Proponents claim that DMPA has no effect or possibly a positive effect on bone metabolism. Depo-Provera has increased the ability of bones to incorporate calcium (Upjohn,1980). Critics claim Depo-Provera inhibited bone growth in monkeys. Curvature of the spine was found in one monkey in the 1X group, two monkeys in the 10X group, and six monkeys in the 50X group. None of the control monkeys developed curvature of the spine (Minkin,1980,p.53).

"Subjective" Side Effects

Proponents claim that subjective side-effects such as headaches, depression, fatigue, dizziness, loss of

libido, nausea, nervousness, brease discomfort, changes in skin pigmentation, limb pain, etc. are difficult to measure and are largely dependent on personal reports. The high incidence of reported side-effects with contraceptive placebos reinforces the difficulty in assessing the relationship between Depo-Provera and subjective side-effects (Fraser & Weisberg,1981,p.7; Nash,1975).

Weight gain has been regularly observed in DMPA users (Fraser & Weisberg,1981; Moghissi,1978; Amatayakul, et al,1980; Spellacy,et al,1972; Population Information Program,1983; Smith,1978). Women tend to gain from 1.4 to nine pounds in the first year. Some gain substantially more weight. About twenty-five percent lose weight (Moghissi,1978,p.340; Fraser & Weisberg,1981,p.7). Proponents claim that this is a positive side-effect for some underweight and malnourished women. It rarely leads to discontinuation of use (Fraser & Weisberg,1981,p.7).

Critics claim that side-effects such as depression, headaches, loss of libido, weight gain/loss as labeled by proponents as "minor" or subjective are trivialized as not important, while in realtiy, these "minor" side-effects can ruin the quality of a person's life. Headaches can make a person dysfunctional and is often reported as the reason for discontinuing Depo-Provera (Holmes,1983, p.190).

Effects on Reproduction

Reproductive concerns related to Depo-Provera have revolved around the issue of return of fertility. Proponents argue that return of fertility is similar to other forms of contraceptives, while critics argue that it may cause infertility or sterility. Proponents claim that infertility is not a side-effect of Depo-Provera. For fertility to return, it is necessary for blood levels of the drug to diminish in order for pituitary hormones to begin releasing a mature egg. The average rate of return is three to nine months following the last injection and by eighteen months it is similar to all other contraceptive users (Upjohn,1983; Schwallie and Assenzo,1981; Nash,1975; Senanyake,1978; McDaniel & Pardthaisong,1973; Duncan,1983). Return of fertility appears to be unrelated to the number of injections, so there is not a cumulative effect (Moghissi,1978; Smith,1978). Duncan (1983,p.112) stated, "we at present, do not feel concern over the return of fertility for women using Depo-Provera. We do not preclude its use in women who are considering subsequent pregnancies."

Critics claim that early warnings for Depo-Provera use made by Upjohn and family planners (on package insert) is that Depo-Provera should not be used by women who have not completed their families. Some programs still

adher to this stipulation because return of fertility has not been established. On the average, fertility takes three months longer to return with Depo-Provera than with the Pill. Fertility does not return to all women by twenty-four months. Contrary to proponents argument, critics claim that there appears to be an accumulative effect in relation to its effect on menstruation, because menstruation is slower to return with more prolonged use of the drug (Scutchfield et al.,1971).

Teratogenic Effects

Concern over teratogenic effects is related to the effects of Depo-Provera in utero, to the breastfed infant, and the longterm effects on children exposed to Depo-Provera.

Effects In-Utero

Proponents claim that "there has been no evidence that Depo-Provera used for contraception increases the incidence of congenital anomalies" (Upjohn,1980,p.18; Schwallie,1981; Wilson & Brent,1981; Duncan,1983; Senanyake,1977). Upjohn (1980) goes on to say that there have been rare instances where Depo-Provera was given accidently to pregnant women and masculinization of the female fetus (clitoral enlargement) was found. This masculinizing effect was also documented by Burnstein and Wasserman (1964). Both claim that the fetus returned

to normal after six months. Moghissi (1978,p.346) claims that "clitoral enlargement, a minor abnormality has been described, but no major anomaly has been observed."

Cardiovascular malformations have been found in infants exposed to progestogens in-utero. Heinonen et al (1977) claim that progestogens may disturb the normal cardiovascular development of the fetus. Shapiro (1978) claims that teratogenic effects are difficult to conclude from the studies because sample sizes are small, procedural problems in data collection, and the combination of estrogens and progesterones in many of the studies. Upjohn claims that there was not a significant increase in heart defects, limb deformities, or gonad dysgenesis (Hubbard,1978,p.293). However, the Upjohn Company package insert for Depo-Provera states:

> There is an increased risk of birth defects such as heart or limb defects, if progesterone and progesterone -like drugs are taken during the first four months of pregnancy. One study found that babies born to women who had taken sex hormones (such as progesterone-like drugs) during the first three months of pregnancy were four to five times more likely to have abnormalities of the arms or legs than if their mothers had not taken such drugs.

As for DMPA effect on psychological adjustment, Upjohn cites one study in which "progestin exposed children were characterized by the tests as more independent, sensitive, self-assured, individualistic, and self-sufficient." The second study concluded that "the girls exposed in-utero to Depo-Provera were slightly more

likely to prefer feminine clothes styles and slightly less likely to rate themselves as tomboys." (Upjohn,1980, p.23).

According to the HRG (1978,p.787), progestins have been associated with a syndrome of human birth defects labeled VACTERYL - vertebral, anal, cardiac, tracheoesophageal, renal, and limb in humans and limb reduction defects in males. Malformation of the head and heart have been found in animal studies. MPA has been shown to cause masculinization of female babies and heart and head deformities. Silberstein (1983,p.62) stated, "Upjohn is certainly aware of the teratogenic effects by virtue of the suits brought against it by users of MPA who have given birth to infants with birth defects. Depo-Provera has been shown to have deleterious effects on the fetus."

FDA Position On In-Utero Effects

Allan S. Goldman, M.D., Teratologist and Senior Physician at the Children's Hospital of Philadelphia testified on behalf of the FDA at the 1983 Board of Inquiry hearings. He claimed:

> Depo-Provera is a human teratogen... Progesterone produces skeletal malformations and Depo-Provera causes cleft plate in rabbits, genital defects in males. In its most severe form, it can require a sex change operation at birth. The risk of teratogenicity from Depo-Provera is significantly greater from that of other progestins in that it

is long-acting. The off-spring would be exposed to an active level throughout pregnancy (1983,p.212-17).

Effects on the Breast-Fed Infant

Three issues have been raised in regard to infants who are breastfed by women treated with Depo-Provera: Depo-Provera's effect on lactation, its effect on the child's immunological system, and its effect on the child's later sexual development. According to proponents, Depo-Provera has been found to have no adverse effect on lactation and may increase milk volume and duration (Upjohn,1980;Karim,et al,1971;Population Information Program,983; Nash,1975). The IPPF went so far as to say that Depo-Provera is particularly suitable for nursing mothers (Senanyake,1978,p.327). Critics claim not only has Depo-Provera been given to lactating women in a "cavalier fashion", it has even been promoted by manufacturers because it has been shown in some studies to increase the quantity of breast milk (1983,p.163-164).

Critics argue that Depo-Provera may have toxic effects on breast-fed infants. "The newborns capacity to metabolize and eliminate drugs is poorly developed. The toxicity of Depo-Provera in the breastmilk is enhanced by its high concentration, long action, and multiple administration and because it is stored in the fat tissue" (Minkin,1980,p.63).

Children of mothers who postpartum used Depo-Provera had a 75% higher rate of infectious disease as measured by clinic visits than the children of non-users (Holmes,1983,p.193). Also, one study showed that post-partum mothers using Depo-Provera showed a greater degree of undernutrition as compared to users of IUD's and non-chemical methods (Richwald,1983,p.84). Minkin (1980,p.63) states "to continue carelessly administering Depo-Provera to millions of lactating women would be callous and cruel."

Proponents argue that a long-term study was conducted in Chile and in Thailand to measure the effect of Depo-Provera on children exposed during lactation. Variables included height, body weight, diseases, hospitalizations, examination of body systems, as well as psycho-motor development. No significant differences were found to indicate adverse effects (Assenzo,1983,pg.114-116). Other studies (Zanartu,et al,1976; Karim,et al,1971) also found no adverse effects (Upjohn,1980).

Upjohn (1980) claims that the accusation by critics that Depo-Provera has an immunosuppressive effect on infants is unfounded. Upjohn claims that the progesterone level in newborns is much higher in its natural presence in the placenta than could be transmitted through breast-milk. Also, infants who are breastfed receive colostrum through breastmilk to help protect against infections

until their own immunological system is more competent. Generally Depo-Provera treatment is delayed for six weeks to establish lactation and to insure the transmission of colostrum. Studies have shown that Depo-Provera does not cause an "appreciable difference" on the immunologic powers of breast milk.

Critics claim that it is necessary to do long-term follow-up on children exposed to Depo-Provera. Because Depo-Provera blocks various functions of the mother's hypothalamus, it may effect the child's similarly. Some of these adverse effects would not be apparent until puberty - e.g. menstrual cycle disturbances, premature or late puberty, acromegaly, low fertility, reproductive tract neoplasias, and lower resistance to infection (Holmes,1983,p.192).

According to proponents, in order for Depo-Provera to produce modification of sexual behavior and sterility, it would have to be administered during the critical period for development of hypothalamic control of reproductive function. In humans, this occurs before birth while the fetus is in the uterus - not after birth as critics claim. Therefore, the effect of Depo-Provera through lactation on later sexual development appears unfounded (Upjohn,1980,p.18).

Critics argument that Depo-Provera can be dangerous to the growth and sexual development of children is

"totally speculative" and "unsupported by any facts" (Upjohn,1980,p.20). Proponents claim that Depo-Provera has not been used long enough to have conclusive evidence of its effect on children during puberty. Proponents claim no adverse effects have been observed in ongoing clinical studies of breastfed children whose mothers received Depo-Provera for contraception.

Summary

The proponents and critics in the Depo-Provera controversy have conflicting claims on all major medical and ethical issues. These conflicting claims are the result of different interpretations of the rules of evidence, and consequently, the differential emphasis on either the animal data or human data. Table 4 describes the differing positions of proponents and critics on major medical issues.

Table 4

Position of Proponents and Critics on Major Medical Issues
Summary

Risk/Benefit Assessment

Potential risks to individuals from Depo-Provera use is less significant when weighed against unwanted pregnancy, unwanted births and world overpopulation (Hubbard,1978).

Depo-Provera's main advantage is its convenience which hardly outweighs the increased risk of cancer, heavy bleeding, and other serious side-effects (Rhodes,1983).

Need

Five to nine percent of women in the U.S. using reversible contraceptives would elect to use Depo-Provera (Upjohn,1983).

There are no groups of women for whom the benefits outweigh the risks (Wolfe,1983).

Rules of Evidence

Dogs are not an appropriate animal model for the evaluation of carcinogenic risk associated with progestogens (Upjohn, 1980).

Beagle is an appropriate animal model for evaluating carcinogenic risk (Shearer,1983).

Adequate human data has been obtained to assess the safety of Depo-Provera (Duncan,1983).

Deficiencies in the quality of human studies on Depo-Provera make it difficult to draw conclusions about the safety of Depo-Provera (Johnson,1978).

Carcinogenesis

No evidence of an increased risk of breast, uterine, or ovarian cancer was found (Ory,1983).

The data does not support the view that Depo-Provera was "safe" with the subsequent risk of cancer of the uterine cervix (Hoover,1978).

Side-Effects

Of the adverse side-effects associated with Depo-Provera, most women find them tolerable.

Side-effects such as depression, headaches, loss of libido, weight gain are trivialized by proponents while in reality they can ruin the quality of a person's life.

Effects on Reproduction

We at present, do not feel concern over the return of fertility for women using Depo-Provera. We do not preclude its use in women who are considering subsequent pregnancies (Duncan,1983)..

Fertility does not return to all women by twenty-four months. Menstruation is slower to return with more prolonged use of the drug (Scutchfield,et al,1971).

Teratogenic Effects

There has been no evidence that Depo-Provera used for contraception increases the incidence of congenital anomalies (Upjohn,1980).

DMPA has been shown to cause masculinization of female babies and head and heart deformities. Depo-Provera has been shown to have deleterious effects on the fetus (Silberstein,1983).

CHAPTER V

DISCUSSION AND CONCLUSION

This thesis examined the Depo-Provera controversy as a specific case study within the sociology of science. This chapter will discuss the limitations of the study, the idea of parallel and intersecting arguments in alignment, the social context giving rise to alignment, and further research on Depo-Provera which could make a contribution to sociological scholarship.

Limitations

Limitations of the study include methodological issues in documentary research; the scope of the thesis; and explanation of the FDA's role in the controversy. Methodological issues which may arise in documentary research include missing or incomplete data, the validity of conclusions expressed by actors within groups, systematic bias among editors of historical data, and the non-reactive nature of documents. (Webb, Campbell, Schwartz, and Sechrest, 1966).

Missing or incomplete data are a significant problem when documents are the only source of data employed

in a sociological analysis. The researcher may or may not be aware that data are missing for completing a historical analysis of an issue. For example, in developing the historical perspective of the Depo-Provera controversy, the details of Upjohn's initial animal and human testing in relation to its New Drug Application were incomplete in the documents. The missing data were not acknowledged until personal communication with an Upjohn representative occurred. Sometimes the author is aware that data is not available. For example, details on some of the early animal and clinical tests sponsored by Upjohn were not found. Also, critics sometimes claimed that Upjohn gave information to the FDA not accessible to the public. The validity of this statement is unknown, but important information for completing historical accounts is often unrecorded in public documents.

The consensus on conclusions expressed by actors within groups is another source of discrepency in alignment research. Determining positions and interpretations of issues by alignment necessarily requires that the researcher makes the assumption that major actors in the debate are reflecting the position of the side they are aligned with. Discrepencies are likely to be reduced when interpretations are compared with other actors with the same alignment and with the basic ideology of the aligning side. An example is the interpretations

of Steven Minkin. Overall, critics referenced Minkin in their interpretation of the issues and recognized him as an important aligner, but some of his arguments were inconsistent with other critics - e.g. Minkin (1980) argued that Upjohn deliberately held back necessary information for assessing the risks of Depo-Provera. Other critics praised Upjohn's disclosure of information.

Systematic bias among editors of historical data is common to all written and verbal data. Bias occurs from the values of the author, the perspective from which the author is writing, the knowledge available to the author, and the bias of the author's sources. Inconsistencies are often found among data due to these potential sources of bias. While biased information is generally not a concern in alignment research since it reflects the interests or values of each side, it does create some problems for attempting to record the chronology of events in a debate. In documents pertaining to the Depo-Provera controversy, there were discrepencies between reports stating that Depo-Provera was officially approved in 1973 and other reports stating that that Depo-Provera had never been officially approved. Comparative evaluations of resources written by authors with varying qualifications allow the researcher to draw inferences on the accuracy of the data.

Generally, the non-reactive nature of documents

is a positive attribute of documents but, in alignment studies, human subjects could offer valuable insights not available through documents. While interviews would not uncover hidden motives, they could greatly enhance documentary research in technical controversies by clarifying interests and issues. Interviews were not included in this study due to necessary constraints on the research, but will provide an important contribution to phase two of the study.

The Depo-Provera controversy involves issues of national and international significance appropriate for sociological analysis. It was necessary to restrict the parameters of this thesis to the controversy within the United States concerning alignment for and against the approval of Depo-Provera.

Finally, the role of government in technical controversies is always obscure. Some view the government as playing an active role in decision-making - e.g. radical theorists argue that government policy-making is often a response to the demands of socially powerful groups (Gibbons,1979). Pluralists claim that government policy-making can be attributed to a diffuse and pluralistic pattern of conflicting interest groups (Lipset & Raab,1978). Others view government as playing a passive role. Right-Wing conservatists believe that government intervention in the affairs of business is bad. If

business were left alone, it would regulate itself (Lipset & Raab,1978). This author contends that the government plays an active role in scientific controversies. Due to the political nature of its position, hidden interests and motives are not extractable from documents to clarify their stance.

Parallel and Intersecting Arguments

The strong programme provided a methodological framework for examining the relationship among alignment, interests, ideology, and claims. Alignment is created partially from a particular technology itself, but largely from the structural asymmetry between opposing sides attempting to bolster their own interest. Structural asymmetry results from the individual focus of critics and social focus of proponents. It gives rise to conflicting assumptions, beliefs, and claims. The underlying interests, motives, and beliefs which were extractable from documents were analyzed to explain claims presented by both sides.

Critics of the strong programme (Lauden,1982) argue that causality cannot be attributed to "truths" because they are explanatory within themselves. Therefore, the same causal agents cannot be assumed, a priori, to be involved in rational and irrational beliefs. The analysis of the Depo-Provera controversy offered an alternative definition to Lauden. The complexity

of human behavior involves complicated ethical issues to which there are no single correct answers. Truth is relative depending on the unit of analysis, the defined rules of evidence, and acceptable risks in light of the benefits.

I propose that the ideology defined by each side is composed of parallel arguments - consisting of value claims - and intersecting arguments - consisting of knowledge claims. Parallel arguments involve claims based on interests, values, and beliefs. Parallel arguments establish the unit of analysis of each side's ideology. Opponents in a debate could only reach agreement on parallel arguments by altering their belief system to that of their opponents. For example, proponents in the Depo-Provera controversy value population control, their assumptions arising out of their belief system revolve around the idea that population control can reduce poverty, starvation, unwanted children and consequently, improve the quality of life in general. Their value claims revolve around these assumptions - e.g. Depo-Provera provides an effective means for reducing world overpopulation. Therefore, their unit of analysis is society.

Critics value the protection of individual rights. Assumptions arising out of their belief system are based on the idea that freedom of choice, informed consent,

and reproductive freedom are necessary rights of individuals. Their value claims revolve around these assumptions - e.g. Depo-Provera, because of its long-term injectable nature takes the control away from the individual which potentially violates their right to choice and reproductive freedom. Therefore, their unit of analysis is the individual.

Parallel arguments are based on parallel truths. That is, both positions are true based on a particular belief system and unit of analysis. One either accepts or rejects the position based on their own belief system, but their is not opportunity to negotiate interpretations of evidence at this level.

Intersecting arguments are based on interpretation of scientific evidence evolving out of particular definitions of the rules of evidence. To the extent that definitions of rules of evidence are negotiable, proponents and critics could possibly reach consensus on intersecting arguments. Intersecting arguments have a single meeting point where proponents and critics cross paths in their analysis which does not exist in parallel arguments. For example, in the Depo-Provera controversy, proponents argue Depo-Provera has not been shown to be carcinogenic because animal models are overly sensitive to progestogen, therefore not suitable for carcinogenic testing. Also, human studies have not revealed any cancer findings.

Critics argue Depo-Provera has been shown to be a potential carcinogen because animal models have revealed carcinomas and proponents have not proven that animal models are overly-sensitive to progestogen. Also human findings are too methodologically problematic to draw any conclusions.

The points of intersection in this argument are the suitability of the animal models for carcinogenic testing and the conclusiveness of human studies. To the extent that one side can produce evidence to change the other side's definition of the rules of evidence, proponents and critics could achieve consensus on intersecting arguments. If definitions of the rules of evidence are based on conflicting unproven theories - e.g., linear vs. threshold dose-response curve (Epstein,1978), intersecting arguments take on the characteristics of parallel arguments because they are based on beliefs as opposed to evidence. Rules of evidence in the Depo-Provera controversy are not of this nature. Rules of evidence which have created conflicting knowledge claims are the suitability of animal models for revealing adverse effects in humans and the adequacy of human studies.

It is my suspicion that because the intersecting arguments in the Depo-Provera controversy were negotiable, and because The Upjohn Company still failed to conduct adequate human and animal studies, this suggests that

Depo-Provera is an unsafe drug. Upjohn could have conducted further animal tests to measure the sensitivity of beagles to progestogens. Instead, they asserted this claim on speculation. The one study they did conduct with progesterone - The Dawson Beagle Study - found that Depo-Provera had stronger adverse effects than progesterone. Upjohn could also have reduced the significance of the beagle studies by conducting adequate epidemiological studies with control groups, proper follow-up, sufficient background information on patients, and adequate interview procedures for probing subjects to gain adequate information regarding potential adverse side-effects. Depo-Provera has been approved in over 80 countries and used for over 15 years, so Upjohn has had adequate time and an adequate patient population in which to conduct the studies.

If Upjohn did conduct sufficient studies, and agreement was reached that Depo-Provera increases individual risk to cancer, critics would continue to support their position against Depo-Provera and proponents might continue to support their position in favor of Depo-Provera depending on how they weigh the benefits to population control in light of the risk of cancer.

However, if Upjohn conducted adequate tests and both sides agreed that Depo-Provera did not show serious adverse effects in humans, it is more probable that critics would have supported Depo-Provera. While the

potential abuse to women who would not choose to use Depo-Provera would still be a risk, the risk is weaker in a risk/benefit assessment when there are no serious adverse effects and the benefit to women of having this option available for reproductive freedom is strengthened.

Therefore, because Upjohn had the opportunity to reverse alignment of critics through adequate studies, I suspect that the FDA could not continue to support Upjohn's position on Depo-Provera. With increasing public reaction to the adverse findings and the failure of Upjohn to conduct adequate studies to clarify the rules of evidence, the FDA could not continue to support Upjohn without making a blatant statement through its actions of its political ties to industry. When ideologies in a controversy have the characteristics of parallel arguments, then the FDA has the freedom to favor either position it chooses, but this was not the case in the Depo-Provera controversy.

Regardless of which position is accepted as "truth", both positions can be explained with regard to the defined unit of analysis, prioritization of values and interests, definition of the rules of evidence, and definition of acceptable risks in light of the benefits. Therefore, the position that gains the largest consensus or the consensus of those with the political power to determine policy, in effect, becomes the "operable truth".

Social Context Of Alignment

Scientists have been given an elevated status in society because of their claimed access to truths not accessible to the general public. These "truths" have been a source of power in the political process involving public policy-making.

> However much human values are involved in the scientific process or are affected by the results of scientific research, there is an essential element in science that is cold, objective, and non-humane. At the center of the scientific method is a free-commitment to a standard of truth. Having committed ourselves to the scientific standard of truth, we have thus far been forced, not by our own choosing, away from the rhapsodic sensibility. To change science to incorporate other modes of knowledge would be abandoning our commitment. To do so would be to lose all of science, and break off our search for its ultimate laws (Weinberg,1977,p.57).

In general, proponents in technical debates take this conservative position. There are a number of assumptions implied in Weinberg's statement which applies to proponents position in technical debates. First, a scientist's free commitment to a standard of truth implies that this inside tract to finding "truths" places the scientist in the position of expert as the "truths" are revealed to him/her. S/he has access to knowledge not available to the general public. Second, the elitist position that the scientist has acquired through his/her differential access to knowledge, has made him/her a necessary tool in the formulation of policies regarding

technology. "The greater complexity and the more extensive ramifications that technology brings about in society creates the need for experts ... to formulate policies adequate to the complexity of social issues" (Mesthene,1977,p.177). Finally, the exclusive position that scientists have placed themselves in has given them a paternalistic role in determining what is in the best interests of society.

For example, Weinberg (1977) argues that social problems exist because many people behave individually in an unacceptable way - e.g. "have too many babies". Consequently, he says social scientists are forced to invent methods to persuade these individuals to behave rationally by foregoing immediate pleasure or personal gain for the good of society. Weinberg argues solutions would be much simpler if we transfer our social problems into technological problems. Technological problems require few individual decisions in creating new technologies to remove the condition creating the problem.

A specific example, is the Intrauterine Device (IUD). Weinberg claims that the IUD is one of the most important technological inventions because it requires minimal individual motivation, it is easier to persuade women to accept the IUD once, than to take a pill daily. "The IUD so reduces the social component of the problem as to make an impossibly difficult social problem much

less hopeless" (Weinberg,1977,p.25).

In examining the Depo-Provera controversy, Weinberg's logic largely describes the social context and position of the proponents in the debate. Until the last decade, the expertise of scientists was seldom questioned. This differential access to knowledge was a source of power for legitimizing interests into policy. In the Depo-Provera controversy, proponents argued that critics lacked necessary scientific understanding to make accurate interpretations of data, thus trying to disqualify their opposing arguments.

Depo-Provera provides an optimal technical solution to a serious social problem - over-population. Like Weinberg's argument about the IUD, proponents argued that Depo-Provera requires little individual motivation, and therefore, does not require as drastic a social change in women's attitude and behavior toward reducing the number of children they have.

Organizations such as the IPPF, WHO, and AID believed it would be especially useful in Third World countries because it requires little individual motivation, it is quick and easy to administer, it is effective, and injectable drugs are highly respected by the people in Third World countries. In the U.S., they believed it would be especially useful in mental institutions for controlling menstruation and pregnancy and for women

unwilling to accept the daily regimen of the pill or the application of barrier methods.

So, alignment in the Depo-Provera controversy, as in many other technical controversies is influenced by the structural feature of the situation - e.g., over-population and the institution of science. This social context shapes data analysis by reducing the significance of the risks to the individual, if, in the overall assessment of the technology, the benefits to society are great - e.g., reduce over-population.

Also, proponents of technology argue that technology creates new possibilities for human choice. What effects the technology has on society and whose interests it serves are not inherent in the technology itself, but are a result of human intervention. Proponents defend the technology in relation to what the technology itself has to offer "...it is not their business to foresee and anticipate what humans do with it" (Mesthene,1977)

The logic of Weinberg's (1977) argument is precisely what opponents in the Depo-Provera controversy - consumer advocates and feminists - attack. First, opponents argue that scientific "truths" are based on ambiguous data, and open to counter-interpretations. Second, they claim that the scientist's differential access to knowledge is self-serving and generally fails to represent the interests of the individual. Finally,

the paternalistic role that scientists have played, has often disregarded the rights of the poor, minorities, women, and other populations denied access to information necessary to make an informed choice - e.g., mentally handicapped, mentally ill.

Weinberg's conceptualization of the value of changing social problems into technical problems, expressed through his rationalization of the benefits of the IUD and proponents' argument in favor of Depo-Provera, exemplifies proponents' defined paternalistic role - e.g., few individual decisions, minimal individual motivation, and persuades individuals to use the technology to reduce the social component of the problem. This runs contrary to opponents' focus on individual rights.

Opposition to scientists' power position in society grew out of the feminist and consumer movement. Feminists and consumer advocates claim that the patriarchal social structure decides for the individual what is in his/her best interest even when it is contrary to his/her needs. Consequently, feminists and consumer advocates are demanding greater accountability and public participation in policy decisions affecting them (Nelkin,1979). John McDermott (1977,p.97), author of "Technology: The Opiate of the Intellectuals" argues:

> technology refers to systems of rationalized control over large groups of men, events, and machines by small groups of technically skilled men operating

> through organizational hierarchy. The elevation of trained talent into key decision-making slots is... attractive to those in power since they are in a position to reap technology's benefits while avoiding the costs.

Like McDermott, opponents argue that proponents favor technology that serves their own interest. The "disinterested character of the technical decision-maker" biases him/her to finding technical solutions regardless of the consequences to the individual (McDermott,1977). By claiming to be value neutral and to have objective truths, proponents have been in a position to justify their interests at the expense of the individual. Critics argue that proponents are not value-free and objective, but like themselves, are supporting certain values and interests. Belita Cowan wrote a spoof on what the world of contraception would look like if women were the manufacturers, distributors, and researchers in birth control with the same objective, value-free expertise as is presently operating.

> The intrapenal device is a device pushed into the scrotum in much the same way as the intra-uterine device is inserted in the uterus. Occasional perforation is unimportant since the male has few nerve endings in this area. Trials taken place on whales were eminently satisfactory to the female whale since it didn't interfere with her rutting pleasure. Of trials on human males, only relatively small numbers have developed scrotal infection, swelling of the tissue, cancer of the testicles or depression. Other symptoms were merely indications that the man's body had not yet adjusted to the device (Roberts,1981,p.12).

Cowan's spoof reveals some of the underlying assumptions

in contraceptive research. Corea (1980,p.109) states "It is doubtful that a male contraceptive that entailed such a 'side-effect' as loss of libido and/or orgasm would be acceptable to men. Neither is it appropriate for women." Critics claim that side-effects trivialized by proponents can ruin the quality of a person's life (Holmes,1983,p.190). Therefore, feminists and consumer advocates are asserting that those affected by the technology should play a major role in its development, assessment, and implementation.

A major criticism of alignment studies is their deterministic character. While alignment for or against a particular technology is predictable, there are non-deterministic variables operating. For example, not all women are against the approval of Depo-Provera. Some women value the belief in family planning greater than potential abuses that women may incur from administration of the drug, therefore aligning with proponents. Scientists did not align united either. In general, industrial scientists were in favor of approval, government scientists were opposed, and academic and private research scientists contributed to both positions.

There are also more deterministic features of alignment. Alignment for or against a particular technology is a means to protect certain rewards and to assert the importance of personal or group values or interests.

For example, IPPF and WHO aligned against Nestle's rigorous marketing practices of infant formula in Third World countries partially due to the contraceptive effect of breast feeding post-partum which contributes to population control. The IPPF and WHO align in favor of Depo-Provera because it contributes to population control.

Feminists and consumer groups aligned with the IPPF and WHO in the infant formula controversy because of the claimed unscrupulous marketing practices of Nestles which violated the rights of individuals and women. In the Depo-Provera controversy feminists and consumer groups aligned against the IPPF and WHO because Depo-Provera approval could act to violate individual rights. This exemplifies the structural contributions to alignment. Groups can align together on one type of technology and align against each other on another type of technology. Therefore, alignment can be inherently structural, independent of the technology itself.

However, alignment is more complicated. With technology such as contraceptives, alignment is not independent of the technology itself, but is dependent on the characteristics of the specific technology. In general, feminists and consumer groups are in favor of contraceptives because they provide individuals with reproductive freedom. They favor a variety of contraceptive options so that women/men can find a method which best suits their individual

needs. For example, barrier methods such as the contraceptive sponge and the diaphram are options that individuals elect to use, they require individual motivation, and they are relatively safe. The pill has been more controversial because of the adverse side-effects that have been associated with it. While safety and the risk of not making an informed choice are sources of dissension among feminists and consumer advocates, some still support its availability as an option since its use is controlled by the individual i.e., taking the pill daily. The pill, then, is an example of a technology that may divide group alignment depending on how individual members weigh the benefits against the risks.

Depo-Provera falls into another category of contraceptives. Feminists and consumer advocates claim that Depo-Provera is neither safe nor does the control reside with the individual. When informed choice is taken away from the individual - e.g., use among the mentally ill, mentally handicapped, poor, "promiscuous" teenagers, it is not providing a contraceptive option to women. When the method is also unsafe, marketing the drug is completely unethical.

Further Research

The Depo-Provera controversy provides the opportunity for numerous types of sociological analyses. Potential

research includes cross-cultural studies, the role of occupational differentiation in the controversy, Depo-Provera marketing in Third World countries as possible corporate crime, and further direct analysis of alignment through interviews with major actors in the debate.

There are at least three types of cross-cultural studies applicable to the Depo-Provera controversy. First, examination of the differential development of the Depo-Provera controversy in the U.S. as compared to other industrialized nations such as Great Britain, Australia, New Zealand, Federal Republic of Germany, Netherlands, and Spain. An exemplar for such research would be the McCrea and Markle (1984) study of the estrogen replacement controversy in the USA and United Kingdom. They examined how claims among physicians, feminists, consumers, regulatory bodies, researchers, and the pharmaceutical industry differed between these two English speaking nations in assessing risks and benefits.

Second, a comparison of the factors affecting risk benefit assessments between the regulatory bodies in the United States compared to regulatory bodies in Third World countries would be useful. The Upjohn Company has been accused of dumping a substandard product in Third World countries. Proponents argue that this position is elitist and interventionist because disease rates, cultural differences, and geographical considerations

affect the risk-benefit ratio for any product.

A third cross-cultural study would focus on the U.S. Agency for International Development's role in exporting drugs not approved in the country of origin. Some governments of other nations are arguing that the failure of AID to distribute Depo-Provera in their family planning programs is paternalistic by presupposing that U.S. standards apply throughout the world.

An examination of the role of occupational differences within science as it relates to the Depo-Provera controversy would be a significant contribution to the sociology of science. Robbins and Johnston (1976) in their research on the role of cognitive and occupational differentiation in scientific controversies offer a possible framework. They argue that conflicting expertise is a dangerous challenge to the status of science and the credibility of scientists. Scientists working in academic, governmental, and industrial settings operate with different norms of behavior, different peers, and different modes of advancement. Consequently, their perspective on public issues may vary dramatically. This is the case in the Depo-Provera controversy. Government scientists opposed Depo-Provera approval, industrial scientists favored approval, and academic scientists were somewhat divided. In-depth interviews with scientists in each of these fields assessing the risks and benefits of Depo-Provera could be of interest for clarifying the norms and interests

operating in these specialized areas.

A corporate crime perspective to the Depo-Provera debate is another potential expansion of research. Michalowski and Kramer (1984) examined corporate crime in the multinational context. Regulatory laws in many countries, especially Third World countries, are often more lenient than regulatory law in the United States. Consequently, corporate actions which are illegal in the U.S. are permissible in other countries. An interesting question that Michalowski and Kramer raise is whether or not actions legal in other countries can be analyzed as criminal or deviant behavior when they are sufficiently injurious to be prohibited in the country-of-origin. Critics in the Depo-Provera debate argue that women in Third World countries have been the victims of mass experimentation with a dangerous drug. Whether or not this constitutes corporate crime would be an interesting analysis.

Finally, one of the limitations of this study on Depo-Provera is the difficulty in extracting motives and interests of major actors from documents in gaining further clarification of significant arguments. In-depth interviews with major actors in the controversy would expand the sociological contribution that the present study has to offer to the sociology of science.

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