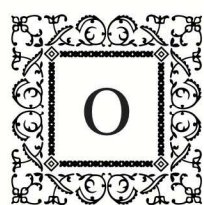


# Women's Trials: The Approval of the First Oral Contraceptive Pill in the United States and Great Britain

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ON 23 June 2000 the United States celebrated the fortieth anniversary of the approval of Enovid, the first oral contraceptive.<sup>1</sup> From the time of the first clinical trials to the present, nearly 200 million women have swallowed various formulations of the contraceptive pill, making it one of the most widely consumed class of drugs in the world. By the end of the twentieth century oral contraceptives had become a feature of everyday life, with more than 70 million women reaching for their pill packet on a daily basis around the globe.<sup>2</sup> Widely regarded as a revolutionary drug in its early years, the pill might retrospectively be considered the first “designer” or “lifestyle” drug of the twentieth century. As with many drug firsts, many lessons can be learned from its development and use. Indeed, as we argue in this essay, the pill played a significant role in reshaping pharmacology, social perceptions of

1. Recent publications cite 8 or 9 May 1960 as the date of approval. From the FDA's perspective, this is incorrect. The announcement that Enovid was “approvable” may have been made first on this date, but on this date the official record lists the application as merely “conditionally approved” pending a final submission of some revised product labeling. “The Pill at 40,” *FDA Consumer*, 2000, 34, no. 4, 36.

2. G. Guillebaud, “Introduction,” in J. Guillebaud, *The Pill* (New York: Oxford University Press, 1980, repr. 1991).

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until the thalidomide disaster of the early 1960s, when the Committee on the Safety of Drugs was set up to review the safety of drugs before and after marketing.<sup>19</sup>

Britain and the United States thus had very limited testing requirements when the first pill was initially approved, and Enovid underwent governmental premarket review only in the United States. The 1938 Food, Drug and Cosmetic Act specified that a drug is not defined by its ability or lack of ability to treat a disease, but rather as any product "affecting the structure or function of the body."<sup>20</sup> This language had been incorporated into the 1938 law for the explicit purpose of giving the FDA jurisdiction over products such as obesity drugs (obesity was not considered a disease), nose straighteners, and especially contraceptive devices such as pessaries and condoms, which, like oral contraceptives, had both therapeutic and contraceptive applications. Therefore, by definition, Enovid was a product that clearly fell under the jurisdiction of the FDA.<sup>21</sup>

#### FIRST APPROVAL OF ENOVID/ENAVID

G. D. Searle and Company made the first American application for the approval of Enovid to the FDA in 1957. The company sought approval for the use of Enovid in cases of menstrual irregularities, including amenorrhea, dysmenorrhea, and menorrhagia, as well as endometriosis (a painful proliferation of uterine tissue outside the uterus) and infertility (Fig. 3). In cases of infertility, it had been shown that women who were given the drug for several months—to "rest" their ovaries—often went on to conceive, a phenomenon often referred to as the "Rock Rebound" effect.<sup>22</sup> Although the original submission addressed only gynecological disorders, it was well known

19. Background on British drug regulation is found in J. Abrahams, *Science, Politics, and the Pharmaceutical Industry: Controversy and Bias in Drug Regulation* (New York: UCL Press, 1995), chapter 2; E. Stieb, "Drug control in Britain, 1850–1914," and T. D. Whittet, "Drug control in Britain: From World War I to the Medicines Bill of 1968," in J. Blake, ed., *Safeguarding the Public: Historical Aspects of Medicinal Drug Control* (Baltimore, Md.: Johns Hopkins University Press, 1970).

20. 1938 Food, Drug, and Cosmetic Act, 21 U.S. Code of Federal Regulations, section 321 (g)(1)(C).

21. D. Cavers, "The Food, Drug, and Cosmetic Act of 1938: Its legislative history and substantive provisions," *Law Contemp. Prob.*, 1939, 6, 31.

22. The term "Rock Rebound" was coined by the obstetrician-gynecologist John Rock, one of Pincus's collaborators. J. Rock, G. Pincus, and C. R. Garcia, "Effects of certain 19-nor steroids on the normal human menstrual cycle," *Science*, 1956, 124, 891–93.

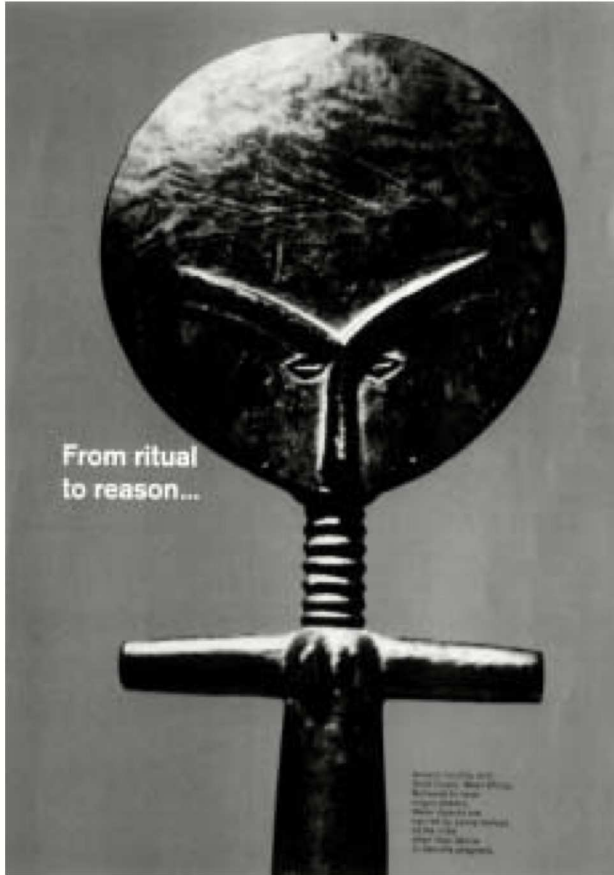


Fig. 3. Early advertisement for Enovid as a menstrual regulator: “Ashanti fertility doll. Gold Coast, West Africa. Believed to have magic powers, these objects are carried by young women of the tribe when they desire to become pregnant.”

among many scientists that this particular formulation could prevent ovulation and therefore could be used as a contraceptive. Publications worldwide had reported Pincus’s work and had speculated on the pill’s clinical prospects.<sup>23</sup>

23. See, for instance, “No magic pill for birth control”, *Science Digest*, March 1956, 39/51; “None for the women,” *Newsweek*, 2 April 1956, 82; “Sell birth control pill 19—nor Steroids,” *Science Newsletter*, 17 November 1956, 309; “Family planning,” *Time*, 12 August 1957, 67.



Nonetheless, Searle made no mention of contraception in its original NDA to the FDA.<sup>24</sup> In part this reflected the fact that the contraceptive trials were only just under way, but it also followed a well-established tradition for introducing new hormones onto the market. It was commonplace for pharmaceutical companies to seek approval for new drugs in a narrow range of indications and then to file supplemental applications seeking approval for expanded uses. The FDA deemed the evidence on Enovid sufficient to demonstrate the safety of the drug for use in the treatments detailed in the application. Although McCormick, Pincus's patron, called the FDA review "slow as molasses," the review was completed within the sixty-day statutory guideline, and final approval was granted on 10 June 1957.<sup>25</sup> Similarly, Searle released the same drug onto the market in Britain in 1957 (trademarked Enavid), without having to undergo any kind of formal governmental review.<sup>26</sup>

Once marketed in the United States and Britain, Enovid/Enavid was freely available to women whose doctors would prescribe it, either as a treatment for infertility or for menstrual disorders.<sup>27</sup> Medical doctors in both countries could then, as they can now, prescribe drugs for purposes other than those approved because neither country has ever sought to regulate the practice of medicine. The fact that so many women may (or may not) have had access to Enovid/Enavid years before it was formally approved by FDA as a contraceptive makes any discussion about the approval of the pill which centers upon numbers very difficult. The most commonly cited figure is that

24. Apparently McCormick approved of this strategy. She commented in 1957 that "of course this use of the oral contraceptive for menstrual disorders is leading inevitably to its use for pregnancy—and to me this stepping stone of gradual approach to the pregnancy problem via menstrual one is a very happy and fortunate course of procedure." Quoted in B. Asbell, *The Pill: A Biography of the Drug that Changed the World* (New York: Random House, 1995), p. 159.

25. *Ibid.*

26. The difference for the spelling of the drug in Britain and the United States was purely for commercial reasons. It had no chemical significance. They were exactly the same compound. See IPPF Press Conference, p. 11, 30 March 1960, SA/FPA/A5,161/4, Box 251, Archives and Manuscripts, Wellcome Library for the History and Understanding of Medicine, London (hereafter SA/FPA).

27. In July 1957, Searle sent a Dear Doctor letter to obstetricians, gynecologists, and general practitioners regarding the clinical applications of Enovid. The letter noted "There is adequate evidence to indicate that the drug will inhibit ovulation when the physician so chooses and that it is safe for this purpose in short term medication." G. D. Searle and Co. to Doctors, 22 July 1957, NDA 10-976, vol. 1, FDA Records.



by 1959 more than 500,000 women were taking the drug for menstrual disorders in the United States.<sup>28</sup>

APPROVAL OF ENOVID/CONOVID AS A CONTRACEPTIVE

When Searle notified the FDA in 1959 that it wished to submit a supplemental application for Enovid to expand the drug's labeling indications to include use as an oral contraceptive, it rapidly became clear that the American federal government wanted little to do with the process and saw it as no more than a routine bureaucratic process of new drug review and approval at the FDA.<sup>29</sup> As Critchlow and Watkins have discussed in great detail, the mere mention of contraception as a credible component of overseas aid had drawn the opposition of American Catholic bishops. Moreover, with the 1960 presidential election looming, neither President Eisenhower nor the Catholic presidential candidate, John Kennedy, wanted to make an issue out of contraception and the pending approval of the contraceptive pill.<sup>30</sup>

In Britain, the central government also vigorously refused to initiate debate over the pill. The British Ministry of Health had stated as early as 1955 that it did not want any involvement with contraceptive testing and approval.<sup>31</sup> Again, in 1956, when news emerged of the possible availability of a contraceptive pill in the United States, the Medical Research Council, the main British government body responsible for clinical trials since 1919, refused to sponsor any monitoring of the new drug on the grounds that it was too politically and morally sensitive an issue for them to handle.<sup>32</sup>

Even as politicians on both sides of the Atlantic scrambled to distance themselves from the social ramifications of an oral contraceptive, medical authorities stepped to the forefront, subjecting the drug

28. I. C. Winter, *J. Am. Med. Assoc.*, 1970, 212, 1067–68. See also Asbell, (n. 22) *The Pill*, pp. 163–64.

29. J. Crosson to P. DeFelice, 22 July 1960, NDA 10–976, vol. 16; E. Tyler to J. Crosson, 27 Jan 1960, NDA 10–976, vol. 16, FDA Records. Searle complained that it took nearly ten months for the approval of 10 milligrams, and nearly two years to approve Enovid, 5 milligrams.

30. Critchlow, (n. 3) *Intended Consequences*, 41–5, 66–74; Watkins, *On the Pill*, pp. 67–69. See also P. T. Piotrow, *World Population Crisis: The United States Response* (New York: Praeger, 1973).

31. See “Family Planning in Practice,” *The Times* (London), 17 July 1959.

32. Telephone conversation with Dr. Parkes, 28 Dec 1956, SA/FPA/127, Box 245; letter from O. Bird to M. Pyke, 15 March 1957, SA/FPA/A5/126, Box 245.

to considerably more scientific and medical scrutiny than it had undergone when approved as simply another gynecological hormone drug. FDA officials vowed that their evaluation of Enovid as a contraceptive would be made solely on medical grounds and a determination of whether the pill was safe for its intended use.<sup>33</sup>

From the start it was obvious to FDA officials that the approval of the pill would be anything but routine. This was not helped by the fact that new drug reviewers were in short supply. In 1958, at Congressional hearings on misleading advertising of tranquilizing drugs, Dr. Albert Holland, the FDA's Medical Director, had testified that the FDA had only three full-time physicians and four young part-time physicians just finishing their residency training at George Washington University to regulate all new drugs.<sup>34</sup> Pressure to approve new drugs was intense, leaving reviewers little time for research and professional education.<sup>35</sup> In 1962, the New York Academy of Medicine's Committee on Public Health reported that between 1952 and 1962, more than 4000 NDAs had been submitted to FDA, and supplemental NDAs since 1957 had averaged 3000 per year.<sup>36</sup>

Within the FDA, Dr. Jose deFelice was assigned Enovid's supplemental application for contraception. One of the new graduates recruited to the FDA, deFelice was an obstetric-gynecologist specialist still finishing his residency at the time he was assigned the NDA for the pill. As a result, the FDA also relied heavily on outside observers in its decision to approve Enovid as an oral contraceptive. From the

33. FDA's Deputy Commissioner reiterated this policy in writing to Senator Leonora Sullivan, "Although we recognize the presence of moral issues, they do not come within the jurisdiction of the FDA. Our consideration has to be confined to safety for intended use." J. L. Harvey to L. K. Sullivan, n.d., NDA 10976, vol. 21, FDA Records. As late as 3 March 1964, FDA's official disclaimer was that "Neither the FDA nor DHEW advocate or discourage the use of contraceptive products. We are in all aspects neutral on this subject. The Administration's approval of an NDA for safety and effect does not mean we agree or disagree with the contraceptive form of birth control." Boilerplate response to consumer inquiries, FDA History Office.

34. *Subcommittee of the House Committee on Government Operations, Hearings on False and Misleading Advertising (Prescription Tranquilizing Drugs)* 85 Cong. 2d (Washington D.C., 1958), pp. 150, 226.

35. *Ibid.*, p. 226.

36. Amidst this blizzard of paperwork, the committee noted that not more than 40 submissions a year were for new chemical entities, and that "the actually new drugs that represent improvement in therapy are fewer than six a year." *Subcommittee of the Senate Committee on Reorganization and International Organizations of the Committee on Government Operations, Hearings on Interagency Coordination in Drug Research and Regulation*, 87 Cong. 2d (Washington D.C., 1962), part 2, p. 529.

time of the original approval of Enovid in 1957, FDA officials attended meetings and corresponded with physicians using Enovid and other nor-19 progestin compounds in their practices.

Searle submitted twenty volumes of detailed clinical data on Enovid to FDA, the largest NDA submitted to the FDA up to that time. In general, the records submitted from trials in Haiti, Puerto Rico, Los Angeles, and Massachusetts all indicated that significant side effects had dissuaded some patients from continuing in the trials.<sup>37</sup> However, women who continued on the pill for many months, were still able to have normal and successful pregnancies after discontinuing the drug.

In February 1960, in an unusual but not wholly unprecedented move, the FDA sent out a questionnaire to 75 obstetricians-gynecologists at leading medical schools around the United States asking them to evaluate Enovid's potential safety as a contraceptive. Responses indicated that many physicians were pleased with their short-term experiences with the drug.<sup>38</sup> They claimed that Enovid had proven effective in treating endometriosis and preventing recurrent miscarriage. Interestingly enough, in light of the imminent crisis created by the use of thalidomide by pregnant women, the question of whether Enovid or any hormonal steroids should be given to pregnant women proved to be an important and divisive issue among the obstetricians and gynecologists surveyed. However, their use of Enovid as a treatment drug proved largely irrelevant to their concerns about its use as a contraceptive

Among those consulted was Dr. Edward Tyler, an eminent physician and head of the Planned Parenthood Clinic in Los Angeles. By 1958 Tyler had treated nearly 200 patients with Enovid and the Parke Davis product, Norlutin, as well as three similar 19 nor-progestin formulations, for menstrual problems and infertility for periods of up to two years. As early as October 1958, Tyler caught the attention of the FDA representative Dr. Gordon Granger when he reported serious reservations about the safety of the drug to a Planned Parent-

37. H. Harris, "Clinical trials of Enovid in Kentucky, 1958-1969," paper presented to American Association for the History of Medicine, April 1998.

38. Physicians Surveys, NDA 10-976, vols. 14 and 15, FDA Records. Similar canvassing went on in the CIFIC who also had continual contact with medical professionals dealing with Enavid. See for instance Third Meeting of CIFIC Clinical Trials Committee, 12 January 1961, SA/FPA/A5/157/1, Box 249.



hood Federation Medical Committee meeting in New York.<sup>39</sup> Tyler pointed to an abnormal bleeding rate of 30–40 percent. He also noted that many women gained 1 to 2 pounds of weight per month, suffering edema (swelling from fluid retention) not only of the hands and feet, as might be expected in pregnancy, but also in the face, which would not be expected. In addition Tyler found toxic hepatitis among some pregnant women who had been prescribed higher doses of the product. Biopsies from two women had also shown suspicious changes symptomatic of early menopause. Finally, Tyler was worried about the female newborns of pregnant mothers treated with these progestin–estrogen combinations who “not uncommonly,” he claimed, had adhesions of the labia and hypertrophy of the clitoris.<sup>40</sup> Most patients reestablished a normal menstrual rhythm after two months off the hormones, but Tyler feared that the pronounced changes in gonadotropin levels had resulted in some kind of permanent uterine change.<sup>41</sup>

Tyler’s expertise was valued as a counterpoint to the research data submitted by Pincus and his collaborators, who were conducting much of their testing in Puerto Rico and Haiti. Pincus’s testing methodology was designed to demonstrate the efficacy of Enovid, and it was believed that he and his colleagues were inclined to view side effects as nuisance variables in their research. Tyler’s studies, in contrast, because they were conducted with American patients under more typical American conditions and because Tyler had no vested interest in any particular pill formulation, were regarded as more neutral. Moreover, his personal experience with several different manufacturers’ formulations added considerable depth to add depth to the pharmaceutical understanding of the entire class of oral contraceptives as well as to the specific attributes of each formulation. Tyler’s data

39. G. Granger, Chief Drug and Devices Branch, to W. M. Kessenich, Deputy Medical Director, 3 Oct 1958, NDA 10–976, vol. 4, FDA Records.

40. For example, 35 cases of baby girls were reported as having been born with male sexual characteristics because their mothers had taken Norlutin (Parke Davis) during their pregnancy to prevent miscarriage. “Norethindrone (Norlutin),” *J. Am. Med. Assoc.*, 1959, 169, 1193.

41. G. Granger to W. M. Kessenich, 3 October 1958, AF 13505, vols. 5 and 6, Box 208, FDA Records. The following month Tyler addressed a meeting at Searle headquarters also outlining some of the problems he had experienced. See C. R. Garcia, J. Rock, G. Pincus, and W. O. Nelson, “Report on the Puerto Rican Contraceptive Study of Enovid,” paper presented at a Symposium on Enovid, 25 November 1958, held at Searle Research Laboratories, Skokie, Illinois, in FDA Records, NDA 10976, vol. 14.

were therefore influential and considered an important supplement to the official data being submitted by Pincus and his team in support of Enovid's approval.

Evidence collected from Tyler and other trusted sources, including the responses to the FDA's questionnaire, constituted important evidence in support of the drug's overall safety. As a final step in the approval process, an FDA official interviewed Tyler, who had reassessed his position on the safety of Enovid. Tyler assured him that his initial concerns about the drug, as expressed at the Planned Parenthood meeting in 1958, had been laid to rest, and that he was indeed still using Enovid in his practice.<sup>42</sup>

The FDA accepted Searle's supplemental application seeking approval to label Enovid as a contraceptive in December 1959 and issued final approval on 23 June 1960 (Fig. 4). As an added safety precaution, prescriptions for oral contraceptives were not to exceed two years until more evidence was accumulated on longer usage.

In Britain, Searle renamed the drug they marketed for use as a contraceptive Conovid. Conovid (5 milligrams), it should be noted, was half the strength of Enovid/Enavid. Theoretically, Searle was free to release Conovid onto the British market without any prior scrutiny, as had been the case for Enavid. In reality, this did not happen. All contraceptives, including Conovid, came under the scrutiny of a voluntary body, the British Family Planning Association (BFPA). During these years the BFPA was the main agency that taught medical professionals about contraception and was therefore the main distributor of contraceptives in Britain because most general practitioners, gynecologists, and obstetricians did not dispense contraceptive products in Britain at this time.<sup>43</sup> Unlike the FDA, which assessed information provided to it by pharmaceutical companies when approving new drugs, the BFPA conducted and sponsored clinical trials of contraceptives in addition to supervising the approval process.<sup>44</sup>

42. Weilerstein to G. Granger, 1 February 1960, NDA 10-976, vol. 15, FDA Records.

43. The medical profession's aversion to the provision of contraception in Britain stood in marked contrast to those in America, where a survey in 1947 showed that more than half of physicians in private practice were prescribing contraception to married women.

44. See W. H. Kessenich, "The FDA's views of new drug progress," *Pharmaceutical Manufacturers Association, Year Book 1960-1961* (Washington D.C., 1960), pp. 264-69. FDA made it clear to inquirers that: "We have not tested Enovid or any other product intended for use as a contraceptive. Our action in accepting the Enovid new drug application was based on sponsoring firm's proof of safety which is the essential element involved in considering a new-drug application. The claims as to Enovid's contraceptive effectiveness are entirely the

The BFPA had a long tradition of testing new contraceptives. Beginning in the 1930s, the BFPA had been at the forefront of new contraceptive knowledge, instituting stringent scientific testing of all contraceptive products.<sup>45</sup> In 1934 the BFPA established an ongoing "Approved List of Contraceptives" for their family planning clinic physicians—a list of all products meeting BFPA regulations. Reviewed by the BFPA, these products had been demonstrated to be safe and acceptable in clinical practice. Such testing continued into the post-Second World War period. In 1956, for instance, all spermicides had to pass certain chemical tests in monkeys before being released for human trial.<sup>46</sup> While lengthy and costly, such testing set a precedent for Conovid, which, like other contraceptives, was required to undergo thorough testing and monitoring before it could be placed on the BFPA Approved List. In 1957 the BFPA established a Council for the Investigation of Fertility Control (CIFIC) to specifically test and monitor oral contraceptives. This included not only testing new products, but also regularly reviewing oral contraceptives once approved for the BFPA Approved List.<sup>47</sup>

Under the auspices of the BFPA, CIFIC became an important player in both the testing and approval of oral contraceptives in Britain.<sup>48</sup> Although the CIFIC never set out to be a formal regulatory agency, many outside the BFPA rapidly came to regard CIFIC testing and approval as the major authority on the safe and appropriate use of oral

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firm's responsibility." Letter from M. L. Yakowitz to B. A. Beardsley, 19 July 1960, NDA 10-976, vol.16, FDA Records.

45. For the contrasting actions of FDA during this period, see A. Tone, "Contraceptive consumers: Gender and the political economy of birth control in the 1930s," *J. Social Hist.*, 1969, 29, 485–506. FDA, in contrast to the BFPA in Britain, had merely instituted a condom-testing program, seizing defective products and removing them from the marketplace. The American Planned Parenthood Federation (PPFA) had also long been involved in clinical trials of contraceptives, but they were not involved in initial study of the oral contraceptive pill. For more information on the PPFA and its testing of contraceptives and reluctance to test the pill, see M. Meldrum, "'Simple methods' and 'determined contraceptors': The statistical evaluation of fertility control, 1957–1968," *Bull. Hist. Med.*, 1996, 70, 266–95, p. 282; A. Clarke, *Disciplining Reproduction: Modernity, American Life Sciences, and the Problem of Sex* (Berkeley, Ca.: University of California Press, 1998).

46. Paralleling American concerns during this period, one of the reasons for the institution of testing was the proliferation of condoms and diaphragms in the 1930s stemming from the development of latex. By 1960 the FPA was testing rubber contraceptives. See SA/FPA/A5/167, Box 253.

47. CIFIC Second Meeting of Medical Advisory Council, 4 Oct 1961, p. 3, SA/FPA/A5/161/4, Box 251; CIFIC, *Fact Sheet*, November 1970, SA/FPA/A5/160/3, Box 250.

48. The FPA Approved List, n.d., SA/FPA/A5/167, Box 253; E. Mears to A. Parkes, 30 October 1959, SA/FPA/127, Box 24.



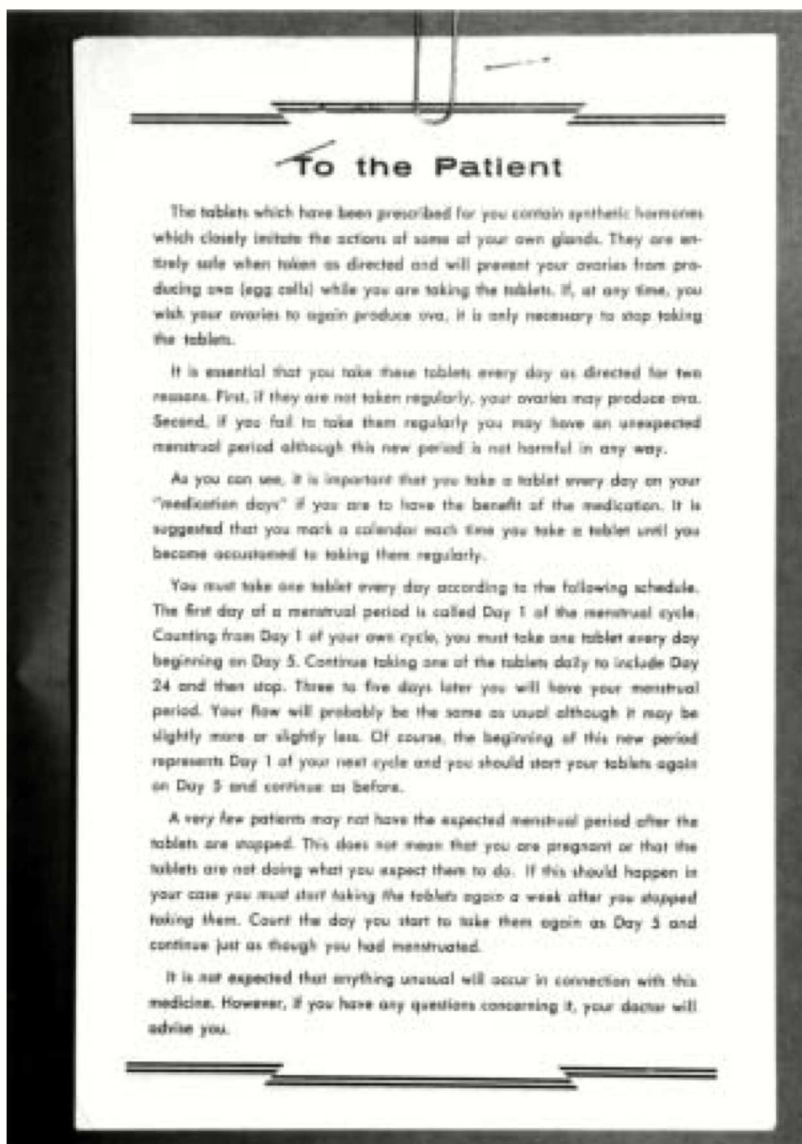


Fig. 4. An informational leaflet for patients about Enovid as a contraceptive. Patient compliance was a critical issue with this drug—it was only fully and assuredly effective if taken 100% of the time.

medication, and the regulatory process for new drugs during the second half of the twentieth century.

Developed in the 1950s, the pill was once optimistically hailed as a scientific cure for the world's rising population and its consequent social and political ills (Fig. 1). Historians, however, have begun to show that the oral contraceptive did not prove to be the social panacea envisioned by its inventors, and that its history is more complex. Much of its history cannot be disentangled from the wider political, economic, and social issues of the day. Watkins, for instance, has shown that the availability of the pill in the United States had a major impact on the relationship between doctors and female patients in the 1960s.<sup>3</sup> Similarly, Critchlow has illustrated how the contraceptive controversy in American politics started with the appearance of the pill and continued with the debates surrounding RU-486, the abortion pill.<sup>4</sup> More recently, Marks has challenged previous histories, which have championed the pill as a North American product that fuelled the sexual revolution, suggesting that its roots and subsequent adoption were much more diverse in origin and can only be understood within a wider international framework.<sup>5</sup>

Adding to the growing knowledge about the pill and its widespread influence on twentieth-century history, we offer a detailed cross-cultural (or at least transatlantic) history of the actual processes by which the first pill formulation, Enovid (U.S.) and Enavid (U.K.) came onto the market. Such a detailed account of the marketing of the pill emphasizes that the birth control pill was introduced in various stages, rather than simply approved at a single point in time. The drug was first marketed in 1957 for treating gynecological disorders. Only in 1960 was it allowed to carry a contraceptive claim, and only after 1961 did reports begin to appear that the drug could cause serious, albeit rare, thrombotic complications (blood clots). Between the time that Enovid was approved as a menstrual regulator and then as a contraceptive, attitudes regarding the perception of safety changed greatly, as did the evaluations carried out to assess risk and efficacy.

The pill redefined the very conception of contraception. In contrast

3. E. Watkins, *On the Pill: A Social History of Oral Contraceptives, 1950–1970* (Baltimore, Md.: Johns Hopkins University Press, 1998).

4. D. Critchlow, *Intended Consequences: Birth Control, Abortion, and The Federal Government in Modern America* (New York: Oxford University Press, 1999).

5. L. Marks, *Sexual Chemistry: A History of The Pill* (New Haven, Conn.: Yale University Press, 2001).

contraceptives.<sup>49</sup> While Searle began to market Conovid in Britain in late 1960, the company was unable to distribute the drug through BFPA clinics until it had undergone scrutiny by the BFPA, which was completed only in June 1961. This severely limited Searle's initial distribution of the drug.

CIFC's power was evident in 1962 when one pharmaceutical company agreed to a settlement out of court in a dispute over the misuse of the BFPA Approved List in advertising one of its oral contraceptives. For the company, the possibility of having their product withdrawn from the BFPA Approved List was considered more damaging than issuing a public apology over their misuse of the BFPA list.<sup>50</sup> The BFPA, therefore, was in a strong bargaining position with pharmaceutical companies developing oral contraceptives.

From the mid-1950s, when the results of early trials of the American scientists began to emerge, the BFPA began to examine the feasibility of conducting trials on the new product. BFPA officials, however, delayed starting their own trials until ample research had been conducted and evidence of safety and effectiveness had been collected by the American developers of the pill. Eleanor Mears, the medical secretary for CIFC, admitted that in 1961 they were particularly concerned about whether the pill would have any carcinogenic effects, whether its pituitary inhibition would be harmful, and whether its use would lead to sterility. Moreover, the BFPA refused to endorse the pill without screening it first themselves.<sup>51</sup>

All the testing and monitoring of the pill was done by CIFC. Supervision of the safety of the drug was allotted to a special Medical Advisory Council within CIFC. This Medical Advisory Council was composed of leading medical practitioners concerned about the long-term effects of steroids on health, including Sir Russell Brain, who had been a leading advocate of more stringent pharmaceutical regulation in Britain.<sup>52</sup> This body ensured, even in the absence of formal regulation,

49. G. Swyer's evidence to Meeting between Representatives from CIFC and Manufacturers of Pharmaceutical Products, 12 November 1970, FPA/A5/160/3, Box 250.

50. Notes of a Meeting readvertisement for Anovlar in Australia, SA/FPA/A7/109.

51. Minutes of Second Meeting of the Medical Advisory Council, 4 October 1961; Meeting between representatives from CIFC and Manufacturers of Pharmaceutical Products, 12 November 1970, SA/FPA/A5/160/3, Box 250; E. Mears, "Clinical Trials of Oral Contraceptives," *Br. Med. J.*, 4 Nov 1961, pp. 1179–83, p. 1179.

52. Press Cutting, n.d., in SA/FPA/A5/161/4, Box 251; General Secretary to Mrs. A. K. Court, 23 April 1960, SA/FPA/A7/110.3, Box 288; E. Mears to M. Davies-Westerman, 2 June 1964, SA/FPA/A5/161/3, Box 251.



that all products and clinical trials with the pill were centralized and carefully scrutinized in Britain.

CIFC had its own standards and criteria for testing the safety and effectiveness of contraceptives. Any compounds that had not been tried on a large scale in humans elsewhere were expected to undergo rigorous testing by CIFC before being used in clinical trials.<sup>53</sup> In 1957 CIFC had begun to test all available oral contraceptive formulations in rats and mice.<sup>54</sup> The pills were monitored for toxicity as well as hormonal and teratogenic effects and impact on fertility.<sup>55</sup> Once the pills passed tests in animals, the substances were screened in a small number of women. These tests were designed not only to test the contraceptive potential of the products, but also to evaluate them in terms of human toleration, inhibition of ovulation, and impact on the secretory action of the endometrium. The purpose of these tests was also to find the optimum dose that would postpone menstruation and prevent breakthrough bleeding. Prior to treatment and for six months thereafter, as precautionary screenings for cancer, each woman had to undergo various uterine and vaginal smears as well as endometrial biopsies, and in later years gonadotrophin assays, chromosome counts, and liver function tests.<sup>56</sup> In 1959, CIFC began human trials on a much larger basis.<sup>57</sup> From the start these trials were not intended to be a "straight forward repeat" of trials run previously elsewhere.<sup>58</sup> The main objective

53. CIFC Minutes, 13 March 1963, SA/FPA/A5/155.

54. The contraceptives included Schering and the British Drugs Houses as well as Searle. CIFC Minutes, 16 October 1958, p. 35, SA/FPA/A5/154.

55. "Screening test for oral contraceptives," 3 August 1960, SA/FPA/A5/162.3, Box 252. After 1964 the CSD took over the responsibility for scrutinizing the data on harmlessness supplied by manufacturers on oral contraceptives, but the CIFC continued to scrutinize the pill for efficacy. E. Mears, "Future of the CIFC," 6 May 1964, SA/FPA/A5/158B, Box 249.

56. Initially the substances were tested in five to ten women, who were mostly women attending a hospital for some medical reason. Only when the substances were proven safe in these women were they then put forward for trial on a contraceptive basis. At this point the substances were then further tested in twenty-five women for an indefinite period. E. Mears to Sir R. Brain, 12 Sept. 1961, SA/FPA/A5/158B, Box 249; "Report presented to Medical Advisory Council," 25 July 1962, SA/FPA/A5/161/4, Box 251; "Report of Work of the CIFC for OBT," in CIFC Minutes, 18 July 1963, p. 122A and Doctors' Meeting, 16 October 1962, p. 3 in SA/FPA/A5/155. G. I. M. Swyer, "Small-scale clinical trials of progestogens for control of conception," *Int. J. Fertil.*, 1964, 9, 11-16; Mears, (n. 48). For information on the small-scale tests conducted in earlier trials in the USA in the early 1950s, see Marks, (n. 12).

57. "The pill," *Eugenics Review*, August 1960, in SA/FPA/A5/161/4, Box 251. By 1959 more than 1000 women in Puerto Rico and elsewhere had already tried out the Searle pill, Enovid (10 milligrams of norethynodrel and 0.15 milligrams estrogen). Of these 150 women had received Enovid for 12 to 21 consecutive cycles, and 66 had taken it for 24 to 38 consecutive cycles. "Oral Contraceptives," c. 1960, SA/FPA/A5/167, Box 254.

58. CIFC Minutes, 1 October 1958, SA/FPA/A5/154.

was to find the lowest dose that would maintain contraceptive effectiveness, in order to limit side effects. However, initially all tablet doses were decided by the manufacturers and not CIFIC.<sup>59</sup>

#### SCRUTINIZING THE SAFETY AND EFFICACY OF THE PILL

In recent years, some writers have either implied or stated explicitly that the FDA was so swept up by the international demand for curbing population growth and was so impressed with data demonstrating the efficacy of Enovid as a contraceptive that it overlooked or compromised important concerns about the safety of the drug.<sup>60</sup> Linda Grant, in *Sexing the Millenium*, goes so far as to call the clinical trials on the pill, "the poorest-conducted, most cursory trials of any pharmaceutical ever licensed by the Food and Drug Administration."<sup>61</sup> This criticism implies that safety and efficacy were separate concerns.

Both Harry Marks and John Swann have shown that safety and efficacy judgments were frequently intertwined during this period, even though only a demonstration of safety was mandated for new drugs under United States law.<sup>62</sup> The approval of Enovid took place within this context. The supplemental application for Enovid, which formally requested approval to label the drug for explicit use as a contraceptive, was approved within a very narrow window of historical opportunity. More important, approval for the pill was granted before revelations about the dangers of thalidomide and was based on a very specific risk/benefit assessment that had been supplemented by reports from others boasting substantial clinical experience with the drug.

Over the years, officials at FDA had made it clear that the agency's determination of safety was often made with an eye to a drug's usefulness and that safety was often a relative term.<sup>63</sup> An assessment of a drug's risks and benefits was also a critical consideration. Important drugs were often either approved or allowed to remain on the market

59. E. Mears letter to *British Medical Journal*, n.d., c. 1963, in SA/FPA/A5/159, Box 249; N. G. Newbury to Mrs. Clifford Smith, 7 March 1960, SA/FPA/161/1, Box 251.

60. See, for instance, *The New Our Bodies Ourselves* (New York: Simon and Schuster, 1984), p. 237.

61. L. Grant, *Sexing the Millenium* (New York: Grove Press, 1994), p. 57.

62. J. Swann, "Sure cure: Public policy on drug efficacy before 1962," in G. Higby and E. Stroud, eds., *The Inside Story of Medicines: A Symposium* (Madison, Wis.: American Institute of the History of Pharmacy), pp. 223–61; H. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (Cambridge: Cambridge University Press, 1997).

63. Ibid.

(with suitable warnings) even though they could have significant side effects. At the time of the pill's approval, there were several examples of useful yet potentially dangerous drugs that were still available. Penicillin, for example, had been approved in 1943 and remained on the market in spite of the fact that it could cause life-threatening allergic reactions. Tetracycline, approved in 1953, was shown to interfere with bone growth and discolor teeth, yet it remained on the market as an important antibiotic, as did streptomycin, approved in 1945, which could cause nerve deafness. At the time of the pill's approval, pre-1938 sulfa drugs, some of which depressed the hemopoietic system, were still available. Likewise, dilantin and digitalis, also pre-1938 drugs, remained on the market for heart patients even though they frequently caused heart irregularities. Finally, the wonder drug cortisone, approved in 1949, remained on the market in spite of the fact that long-term use could lead to significant problems such as cataracts and glaucoma.

In the case of the pill, regulators in both countries ultimately adopted and adapted standards of safety originally established by birth control advocates and used in contraceptive testing. In particular, they accepted as fact that pregnancy and childbirth were hazardous and posed a measurable public health risk. A drug that truly prevented pregnancy, therefore, was already deemed to be protective of public health. The pill met the law's safety requirement precisely because it was so extraordinarily effective. Had Enovid/Conovid been ineffective, or even less effective than mechanical contraceptives already available (condom and diaphragm), then its safety would have been more difficult to establish.<sup>64</sup>

What many have found most offensive about the evidence of safety presented by drug companies and accepted by the regulators, is the fact that women were represented as "menstrual cycles" or "woman-years." In justifying the FDA's approval of the pill, for instance, the FDA's commissioner, George Larrick, stated, "Altogether in the entire clinical cases, 897 women representing 801.6 woman-years and 10,427 cycles have been studied."<sup>65</sup> A sociologist, Nelly Oudshoorn, has insight-

64. CIFIC, *Fact Sheet*, Nov 1970, SA/FPA/15/160/3, Box 250. FDA originally questioned the usefulness of the pill over available contraceptives, but Searle countered that the pill was "certainly more esthetic and presents no possibility of mechanical or spermicidal failure." W. Crosson to P. DeFelice, 9 October 1959, NDA 10-976, vol. 15, FDA Records.

65. *Hearings on Interagency Coordination in Drug Research and Regulation*, part 1, 235. See also G. Pincus, "Progestational Agents and the Control of Fertility," *Vitamins and Hormones*, 1959, 169, 81.



fully noted that this method of presentation “resulted in a major increase of scale: the grand totals of the trials now included much more impressive numbers than a focus on the individual subject might have achieved. The trials were thus presented as having met their purpose: the testing of progestins on large numbers of women over longer periods, as a prerequisite for its approval as a safe and reliable contraceptive.”<sup>66</sup>

Representation of women in terms of woman-years, as Oudshoorn and others have claimed, undoubtedly did mask some of the experience of individual women. It may have created a false impression for the public of the number of women who had taken the pill continuously, and it certainly did not reveal the number of women who dropped out in the trial process. Further, it is questionable whether or not the average physician, who would have had little or no exposure to statistical methodology in medical school, would have understood this statistical data sufficiently well to advise patients. Nonetheless, it would be a mistake to see this use of language as a deliberate distortion on the part of the investigators. For them, the key issue was whether the drug was an effective contraceptive (compared with the diaphragm and condom) and hence safer than alternatives (pregnancy).<sup>67</sup>

Moreover, the investigators did not invent the nomenclature that they used in evaluations of the pill’s effectiveness. They were using a shared and well-established methodological framework that had been formulated in the 1930s. Modified and tightened in the 1950s, this method aimed to verify a contraceptive’s effectiveness not simply by its physiological action (suppression of ovulation), but also by its effectiveness in use.<sup>68</sup> Accepting criteria established by birth control advocates, FDA and CIFIC officials required all oral contraceptives to meet both of these criteria.<sup>69</sup>

66. N. Oudshoorn, *Beyond the Natural Body: An Archaeology of Sex Hormones* (London, 1994), p. 132.

67. Many women experienced side effects that led them to discontinue the drug, both in the trials and once Enovid went onto the market. FDA understood the side effects physiologically and therefore they were not considered to be a safety issue in the review process. Rather, it was considered Searle’s marketing problem—an incentive for the company to improve their product. In the U.K., research and regulation went hand in hand and the product’s side effects were minimised by moving to a lower dosage sooner.

68. R. Pearl, “Contraceptions and fertility in 2,000 women,” *Human Biol.* 1932, 4, 363; C. Tietze, “The current status of fertility control,” n.d., c. 1960, in Box 50, Pincus Papers, Library of Congress (hereafter GP-LC); Meldrum, (n. 42).

69. CIFIC Minutes, 16 April 1959, SA/FPA/A5/154.

Animal testing and early clinical trials had already shown Enovid/Conovid to be physiologically effective in suppressing ovulation. This had been demonstrated in the evidence collected on Enovid when it was undergoing scrutiny for approval as a therapeutic drug in the United States.<sup>70</sup> Additional data collected between 1957 and 1959 indicated the pill's continued effectiveness in suppressing ovulation as demonstrated by physical examinations of women, including endometrial biopsies, cervical smears, breast examinations, temperature charts, and menstrual patterns. This was measured against the patients' reported incidences of sexual intercourse (exposure to the possibility of pregnancy).<sup>71</sup> To the regulating agencies, it was clear that Enovid/Conovid was having the desired physiological effect.<sup>72</sup> As Searle's assistant director, William Crosson, summed up in a report to the FDA:

Enovid is consistently effective in inhibiting ovulation and it has not been demonstrated to be harmful when given cyclically or continuously for long periods of time. It exerts this activity physiologically by suppressing gonadotrophin production which . . . occurs in the normal non-medicated female during each cycle of the childbearing years and . . . occurs also throughout the period of normal gestation for the specific purpose of preventing ovulation.<sup>73</sup>

Measuring the effectiveness of the pill as an average woman used it was, of course, more difficult. Often dependent upon variables such as formal education, socioeconomic background, and motivation to control fertility, this measurement was harder to obtain.<sup>74</sup> Nonetheless,

70. W. J. Crosson from Searle to P. DeFelice, 9 October 1959, NDA 10976, vol. 15, FDA Records.

71. See, for instance, C. R. Garcia, J. Rock, G. Pincus, and W. O. Nelson, "Report on the Puerto Rican Contraceptive Study of Enovid," paper presented at a Symposium on Enovid, 25 November 1958, Searle Research Laboratories, Skokie, Illinois, NDA 10976, vol. 14, FDA Records. For a summary of the animal tests and clinical trials done with Enovid in measuring its physiological effect, see V. A. Drill, "The experimental control of fertility by steroidal substances" in *Report of the Proceedings of the Sixth International Conference on Planned Parenthood*, 14–21 February 1959, New Dehli, India, pp. 167–76, contained in NDA 10976, vol. 22, FDA Records. Drill was a representative from Searle.

72. E. T. Tyler and H. J. Olson, "Fertility promoting and inhibiting effects of new steroid hormonal substances," *J. Am. Med. Assoc.*, 1959, 169, 1843–54, in NDA 10976, vol. 14, FDA Records.

73. W. J. Crosson from Searle to P. DeFelice, 9 October 1959, p. 5, NDA 10976, vol. 15, FDA Records.

74. C. Tietze, "The current status of fertility control," pp. 436–37; H. H. Cook, A. P. Satterthwaite, and C. J. Gamble, "Oral contraception by Norethynodrel: A three year field study," p. 7, in NDA 10976, vol. 21, FDA Records.

TABLE I

Pregnancies According to Number of Tablets  
Missed in Four Clinical Trials

<i>No. Tablets Missed</i>	<i>No. Pregnancies</i>	<i>Rate per 100 Woman-Years</i>
0	1	0.2
1-5	5	7.7
6-19	11	43.3

Compiled from Searle NDA 10976, FDA records.

the evidence presented to the FDA, and later collected by CIFIC, indicated that Enovid/Conovid was very successful in meeting use-effectiveness criteria as well. In fact, it was much more use-effective than any other contraceptive or contraceptive method currently available.<sup>75</sup> Final approval of Enovid/Conovid by both FDA and CIFIC was partly justified on the basis of the drug's extraordinary use effectiveness. FDA reported that investigations led by Pincus with Enovid 10 milligrams had resulted in 2.7 pregnancies per 100 woman-years, and the failures had been attributable to "irregular tablet taking."<sup>76</sup> As Table I shows, pregnancies were more likely to occur the more often a woman forgot to take the drug. As with other contraceptives, Enovid was most effective when used 100 percent of the time.<sup>77</sup>

Observers of the early clinical trials of the pill expressed concern that the side effects of the drug would outweigh its advantages as a contraceptive. Although regulators could have considered this a use issue, they did not do so. Enovid was a proprietary product. If side effects dissuaded women from using it, responsibility for reformulation rested entirely with Searle.

Short-term nuisance effects were largely believed by the investiga-

75. W. J. Crosson from Searle to P. DeFelice, 9 October 1959, p. 6, NDA 10976, vol. 15, FDA Records.

76. Edward Tyler reported a rate of "8.6% pregnancies (22 pregnancies in 3082 woman-months)," but a number of the women on his Los Angeles trial were taking progestational agents other than Enovid. Memo from Kessenich to G. P. Larrick, 11 May 1960, p. 2. NDA 10976, vol 15, FDA Records.

77. E. Mears, "The Clinical Application of Oral Contraceptives," presented at Symposium on Agents Affecting Fertility, Middlesex Hospital, 24 March 1964, in SA/FPA/A5/158B, Box 249.



tors to be a result of the fact that the hormones imitated the physiological effects of early pregnancy that included headaches, swollen breasts, depression, abdominal cramps, lethargy, breakthrough bleeding, and weight gain. Complaints of nausea (morning sickness) were widespread. Searle reassured its researchers that antacids would relieve the symptoms and that the problem generally dissipated with longer use. American physicians, however, reported that at least 20 percent of their patients suffered from nausea and that it did not necessarily diminish over time. Patients reported that antacids were worthless in treating it, and nausea did prove to be a major disincentive for women to continue taking the drug.<sup>78</sup>

Although unpleasant for the women under observation, these side effects did not represent a safety issue for FDA and CIFIC officials, since the phenomenon was understood physiologically and most patients who were severely affected by such symptoms simply discontinued taking the drug. They recovered fully once off the medication.<sup>79</sup> At least 20 percent of the women taking the drug in Puerto Rico, and 66 percent of those on trials in Los Angeles discontinued Enovid on account of such side effects.<sup>80</sup>

In the United States, untoward side effects from the drug were unwittingly exacerbated by the fact that the FDA approved 10 milligrams Enovid before approving the 5-milligram and 2.5-milligram dosages. Investigators worldwide soon learned that a much lower dose of hormones would effectively suppress ovulation just as well as the higher dose. Moreover, the lower doses produced fewer side effects (other than bleeding) and were cheaper to produce. Studies carried out in Puerto Rico and Japan demonstrated that the original 10 milligrams of the chemical progesterone compound could be successfully reduced to 2.5 milligrams.<sup>81</sup>

Searle had originally asked the FDA to consider simultaneously an application for three dosages of Enovid: 10, 5, and 2.5 milligrams.

78. Enovid: Brand of Norethynodrel with Ethynylestradiol 3-methyl ether for Disturbances of Menstruation and Pregnancy, Searle Reference Manual, No. 67, n.d., p. 12, FDA Records. Higher incidences of nausea were reported in CIFIC trials for Conovid. See "Oral contraceptives—side effects," 5 November 1963, SA/FPA/A5/159, Box 249. See also E. Mears, "Ovulation inhibitors: Large-scale clinical trials," *Int. J. Fertil.*, 1964, 9, 1–9.

79. Memo from W. H. Kessenich to G. P. Larrick, 11 May 1960, p. 2, NDA 10976, vol. 15.

80. Mears, (n. 71).

81. "The pill," *Eugenics Review*, May 1960, SA/FPA/A5/161/1, Box 251; "Oral contraceptives," c. 1960, SA/FPA/A5/167, Box 254.

Searle was particularly interested in promoting the lower dosage forms of Enovid because one of the chief criticisms of the pill up to this point had not been a medical one, but rather an economic one. Partly developed in response to concerns about world hunger, it was feared that Enovid would prove far too expensive for women in poorer countries. The cost of the hormone was directly proportionate to the cost of the drug and the dose. Lowering the dose significantly lowered the cost of Enovid. Searle, therefore, had great incentive to prove the safety and efficacy of its lower dosage pills. As far as Searle officials were concerned, the lower dose of Enovid should not have required a separate NDA because they considered it merely an alternative dose of the same drug. As one Searle representative wrote when seeking approval for the lower dosage: "[I find it] very difficult to understand how less of a drug can be more dangerous than a larger dose . . . a basic fact of any drug use is adjustment of the dosage to a particular individual's requirement. That's all we are trying to do with the lower dosage forms of Enovid. . . . I find it impossible to understand how one increases danger by reducing the dose."<sup>82</sup> The FDA, however, viewed the dosage question as an issue of efficacy and possibly safety in 1959. The lower doses produced an increased incidence of breakthrough bleeding. It was not immediately clear whether this was an indication that ovulation had not been effectively suppressed. If so, it would have undermined Enovid's effectiveness as a contraceptive, rendering it unapprovable.

The FDA was therefore very cautious in considering any alteration in the original dose formulation of the pill.<sup>83</sup> The agency required that Searle gain approval for the 10-milligram dosage first, and then file supplemental NDAs for the lower dosage forms. This decision initially operated in Searle's favor because the evidence demonstrating the safety and effectiveness of the 10-milligram dosage of Enovid was solid and unblemished. Problems, however, had already been observed with the lower dosages. The most important one was an increased incidence of breakthrough bleeding, a disturbing side effect for women. Researchers feared that the breakthrough bleeding was an indication that ovulation was not being effectively suppressed with lower dosages.

82. Crosson to W. Kessenich, 11 November 1961, NDA 10-976, vol.16, FDA Records.

83. A. E. Ledder, 24 March 1960, NDA 10976, vol. 15, FDA Records.

Had Searle insisted upon having all three dosages approved simultaneously, the approval would have been greatly delayed.<sup>84</sup> Approval for Searle to market 5-milligram Enovid tablets did not come until two years after the original approval of Enovid 10 milligrams.<sup>85</sup>

The importance of accurate dosing was illustrated clearly by one of the earliest large-scale CIFIC clinical trials. Soon after the British trial started, investigators discovered that many of the volunteers experienced unusual menstrual cycles, and some of them became pregnant even when taking the pill as directed. It was discovered that the manufacturer had unintentionally mislabeled the drug, resulting in physicians unknowingly distributing a pill with only a third of the originally intended estrogen. This accident underscored the importance of the drug's estrogen component in ensuring the inhibition of ovulation.<sup>86</sup>

Britain took a very different perspective from the United States on the lower dosage pills, with instructive consequences. Unlike the United States, Britain released the lower dose formulation first. The 10-milligram Enavid, approved for gynecological purposes in 1957 and still available on prescription in 1961, was never prescribed for contraceptive purposes.<sup>87</sup> The time lag between the United States and Britain in approval allowed CIFIC more flexibility in determining the most appropriate dosage. It also reflected the priorities of CIFIC trials that were designed to develop and approve lower dose pills.<sup>88</sup> Because it conducted its own clinical trials, the CIFIC could directly observe the greater tolerance and lessened incidence of side effects among women taking a lower dosage of Conovid. In this respect, the CIFIC enjoyed a certain advantage during this period precisely because British rules governing the establishment of the dosage of drugs were fairly relaxed. In the United States, NDA protocols were

84. "The pill," (n. 74); "Oral contraceptives," (n. 74).

85. P. DeFelice to W. H. Kessenich, 15 February 1961, NDA 10976, vol. 21, FDA Records.

86. CIFIC Clinical Trial Committee, Minutes, 13 October 1960, SA/FPA/A5/160, Box 250; E. Mears to editor of *The Guardian*, 6 November 1961, SA/FPA/A5/161/2, Box 251; P. Eckstein et. al., "The Birmingham Oral Contraceptive Trial," *Br. Med. J.*, 1961, 1172-79.

87. "Report of a medical conference of FPA medical officers and nurses," 19 November 1960, SA/FPA/A5/167, Box 253.

88. "Statement on the use of oral contraceptives," final version published in *Lancet*, July 1960, in SA/FPA/A5/161/1. CIFIC officials made a special point of stating that the product the United States approved was four times the strength they were testing on women in Britain, implying they were therefore using a safer drug.





Fig. 1. An early advertisement for Enovid; “unfettered . . . from the beginning, woman has been a vassal to the temporal demands—and frequently the aberrations—of the cyclic mechanism of her reproductive system. Now, to a degree heretofore unknown, she is permitted normalization, enhancement or suspension of cyclic function and procreative potential. This new medical control is symbolized in an illustration borrowed from ancient Greek mythology—Andromeda freed from her chains.”

more regimented, and FDA required that the company commit to a primary dosage early in the process.<sup>89</sup> Searle, of course, could have determined the optimum dosage before submitting its NDA.

It has been alleged that the evidence collected before approval of the pill was inadequate and that far too few women had been tested for far too short a time to detect the drug's chief danger, thrombosis. At the heart of the critique of the pill's approval, therefore, is the issue of numbers. Accurate figures for women who took the pill prior to its approval as a contraceptive prove somewhat elusive. While journalists and others seized upon the number 132 in the years following the pill's approval, this figure alone is quite misleading.<sup>90</sup> It is true that only 132 women in clinical trials for Enovid as a contraceptive had taken the pill continuously for periods varying from one to more than three years at the time of the FDA's approval, but many more women (including women in other countries) had actually taken the pill. Searle presented to the FDA detailed clinical data on a total of 897 women in clinical trials who had taken 10 milligrams Enovid as a contraceptive.<sup>91</sup> Table 2 gives a breakdown of the total cases submitted by Searle in their application for the approval of Enovid as an oral contraceptive. Additional data submitted by Searle suggests that by November 1959, 1200 women had received Enovid.<sup>92</sup> A total of 995 women had also taken 5 milligrams Enovid.<sup>93</sup> As mentioned above, between 1957 and 1959 an estimated 500,000 American women had also taken Enovid for therapeutic purposes.<sup>94</sup>

Although fewer women took the pill in Britain prior to its approval than in the United States, this partly reflects the smaller size of the British population. Nonetheless, CIFIC only approved oral contracep-

89. E. Mears, "Future of the CIFIC," 6 May 1964, SA/FPA/A5/158B, Box 249.

90. Gregory Pincus maintained that tests had been completed on 260 women prior to approval. Advisory Committee, Executive Session, 22-23 November 1965, p. 19. See also Grant, (n. 55) *Sexing the Millennium*.

91. W. J. Crosson from Searle to P. DeFelice, 9 October 1959, NDA 10976, vol. 15, FDA archives. See also Letter from DeFelice, 9 Dec 1959, NDA 10976, vol. 15, FDA Records; statement by FDA Commissioner G. Larrick to the *Hearings on Interagency Coordination in Drug Research and Regulation*, part 1, pp. 233-39.

92. J. Rock, "Inhibition of ovulation in the human," reprint from *Control of Ovulation* (Oxford University Press, 1961), p. 233, in J. Rock's Papers, Countway Library.

93. Leaflet information submitted by Searle for Enovid, NDA 10976, vol. 16, FDA Records.

94. Asbell, (n. 22) *The Pill*, pp. 163-64. In 1965 new FDA regulations stipulated that in order for a pill's efficacy to be tested it would have to be tried on a minimum of 1000 women. Memo of Meeting, 15 April 1965, NDA 10976, AF20-787, FDA Records.

TABLE 2

Data Collected from Trials Conducted with  
Women Taking Enovid, 10 milligrams

<i>Investigators</i>	<i>No. Patients</i>	<i>Total Woman-Years</i>	<i>Total Cycles</i>	<i>No. Cycles for Individuals</i>
Rock, Garcia, Pincus, and Paniagua	364	421.7	5483	66 patients, 24–38 cycles
Laraque and Nicola	121	77.4	1007	64 patients, 9–12 cycles
Pendelton	181	151.5	1970	80 patients, 12–21 cycles
Morris	47	15	196	47 patients, 1–10 cycles
Banks, Rutherford, and Coburn	20	9	120	20 patients, 6 cycles
Tyler	164	127	1651	70 patients, 12–22 cycles
Totals	897	801.6	10,427	

Source: Leaflet information submitted by Searle for Enovid, Publication no. 67, NDA 10976, vol. 16, FDA archives. Trial locations: Rock, Garcia, Pincus, and Paniagua, Puerto Rico, Haiti, Massachusetts, and New York City; Laraque and Nicola, Haiti; Pendelton, Puerto Rico; Morris, Fitzsimons Army Hospital; Banks, Rutherford, and Coburn, Seattle; Tyler, Los Angeles. None of these patients became pregnant while taking Enovid as directed.

tives on the completion of at least a six-month trial with a minimum of 100 women. By the time it was placed on the BFPA Approved List, only 91 women had taken Conovid on a trial basis for CIFIC, but at least 300 women were continuing in the trial at the time of its approval. Results from earlier trials conducted by American investigators were taken as supporting evidence.<sup>95</sup>

The numbers above show clearly that many more women had taken the pill than was acknowledged at the time.<sup>96</sup> In hindsight, and

95. CIFIC Minutes, Report 18 July 1963, SA/FPA/A5/155; “Analysis of approved products,” 24 February 1966 with “Memo re long-term trials,” SA/FPA/A5/157/1, Box 249. Mears, (n. 71), p. 1179.

96. The records do not make clear why there was such confusion concerning how many women actually took Enovid prior to its approval as a contraceptive. It may well be that Morton Mintz used the 132 figure exclusively to make his case against the approval of Enovid. FDA created some confusion in adhering to its statutory obligation to protect confidential, commercial information. Such confidential information was not even released



by comparison with today's standards, all of these numbers may appear quite small. By 1965, FDA required that new oral contraceptives be tested on no fewer than 1000 women before seeking new drug approval. In 1960, however, chronic disease epidemiology was still in its infancy. Although 132 patients was probably a large enough sample size in which to answer the anticipated questions (except for potential long-term cancer risk), it was—as had been the case with the side effects of an earlier drug, chloramphenicol—the unexpected risks for which the sample size proved inadequate. Indeed, many of the future advances in chronic disease epidemiology came in trying to demonstrate statistically, rather than verify clinically, the thrombotic phenomenon associated with the oral contraceptive.<sup>97</sup>

It is also important to consider these numbers within the context of other pharmaceutical investigations at that time. Protocols for appropriate sample sizes in clinical trials continued to be contentious even after the passage of the 1962 Drug Amendments in the United States, as did other aspects of the NDA process. After the thalidomide disaster, when there was great pressure for change, there were lengthy criticisms leveled at regulators for protecting manufacturers by maintaining strict secrecy policies. Such criticism led to hearings that revealed the process by which several new drugs, originally approved around this time period, were removed from the market because they posed what everyone agreed were unacceptable dangers to public health. Dornwall, a tranquilizer, approved in 1959, was removed from the market in 1961 and its NDA suspended in 1962 when it became linked with reports of agranulocytosis. Likewise, an antidepressant, Marsilid, was removed from the market in 1961 after eleven deaths linked with liver injury were reported. Similarly, FDA initiated lawsuits beginning in 1963 against makers of Mer-29, a cholesterol-

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to members of Congress. The 132 figure was cited in a memo written by the head of FDA's Drug Division, and was based on published information, so these figures may have been the easiest to release legally. Together, these cases seemed to provide solid evidence of both Enovid's safety and efficacy and were the stated basis of FDA Commissioner George Larrick's ultimate approval of the drug. Nonetheless, the agency was well aware of the numbers of women who had already taken the drug for shorter periods of time, apparently safely. Their concern in extending the indications to include contraception centred around concerns about Enovid's safety in continuous use. The agency determined that it would not recommend that the drug be used for any period longer than that for which data existed. This meant that the initial recommendation was that Enovid not be used continuously more than two years.

97. M. Susser, "Epidemiology in the United States after WWII: Evolution of technique," *Epidemiol. Rev.*, 1985, 7, 147-77; A. Lilienfeld, "Epidemiology of infectious and non-infectious disease: Some comparisons," *Am. J. Epidemiol.*, 1973, 97, 135-47.

lowering drug, approved on the basis of falsified animal studies, and Flexin, a urologic drug linked with hepatitis. It is clear in retrospect and by comparison that Enovid and its approval had none of these obvious flaws.<sup>98</sup>

To assess the adequacy of the data submitted to the FDA in support of the NDA for Enovid, especially as it compared with other approved drugs at the time, we have examined the evidence of safety submitted on behalf of Librium Hydrochloride, a drug passed by the FDA in the same time period. Librium was also a pre-1962 drug that was approved in February 1960 for the purpose of “removing ‘emotional overlays’ complicating the treatment of organic disease.”<sup>99</sup> Both Librium and the birth control pill (though not the same formulation as Enovid/Conovid) are still on the market and widely prescribed. Both Librium and Enovid presented particular problems in being promoted as drug treatments for conditions not widely regarded as diseases—namely, stress and pregnancy. Librium, like Enovid, also came to be hailed as a revolutionary drug, primarily helpful in treating psychiatric disorders.<sup>100</sup>

Librium was tested on a wide range of conditions ranging from spastic colon to cardiac neurosis and including eczema, frigidity, and heroin addiction, just to name a few.<sup>101</sup> Indeed, this treatment spectrum was far broader than the narrow range of gynecological purposes for which Enovid was clinically tested. Enovid was developed specifically to suppress ovulation and therefore could be tested only by reproductive specialists and only upon women of reproductive age. In contrast, prior to its approval, Librium’s value was less precisely defined. It could be prescribed by any medical practitioner for any patient of any age or gender. Librium’s distribution was therefore much wider than the pill. The overall number of patients who were tested with Librium totaled 1163, but Table 3 shows that, when broken down by specific conditions, the totals were much smaller. In some conditions, such as epilepsy, Librium was tried on as few as three patients. Psychiatric patients formed the largest trial group,

98. U.S. Senate, *Hearings Before the Subcommittee on Reorganization and International Organizations of the Committee on Government Operations, Interagency Coordination in Drug Research and Regulations*, 87 Cong., 2d (Washington D.C., 1962), Part 2, pp. 516–28.

99. NDA 12249, Librium Hydrochloride Tablets, FDA Records.

100. S. L. Speaker, “From ‘happiness pill’ to ‘national nightmare’: Changing cultural assessment of minor tranquilizers in America,” *J. Hist. Med.*, 1997, 52, 338–376.

101. NDA 12249 (n. 99).

TABLE 3

## Numbers of Patients Tested with Librium

<i>Specialty</i>	<i>Numbers of Patients</i>
GP/internal medicine	247
Psychiatry	570
Obstetrics/gynecology	35
Dermatology	275
Pediatrics	21
Surgery	15
Epilepsy	3
Total patients	1163

Source: NDA 12-249, Librium Hydrochloride Tablets, U.S. FDA.

totaling 570. This number, by comparison, is slightly less than our most conservative estimate (897) of women who took Enovid on a trial basis. The evidence collected for Librium also did not make clear how long each individual patient had taken the drug.

Numbers alone distort the kinds of evidence that investigators and pharmaceutical regulators were looking for in relation to the safety and efficacy of the pill. Both the FDA and CIFIC investigators sought crucial evidence not in the numbers of individual women tested, but in whether the pill was effective in suppressing ovulation without affecting future fertility. The general attitude of FDA officials on the association between numbers and evidence of safety had been summed up by one FDA representative as early as 1946: "Sheer volume of clinical reports or large numbers of cases are not sufficient in themselves to be decisive. Attention must be directed to the character of the investigators and the quality of the investigations."<sup>102</sup>

Another major criticism of the pill's original approval as a contraceptive was that it was tested for an inadequate length of time. But officials both in Britain and the United States took unprecedented precautions to limit the length of time Enovid/Conovid could be

102. W. Van Winkle, Jr., to P. Dunbar and R. Herwick, 30 Jan 1946, Drugs, Acc. 59A-2736, Box 220, FDA Records. Also cited in Marks, (n. 56) *Progress of Experiment*, p. 83.



prescribed for an individual woman.<sup>103</sup> This fact has been virtually ignored in all discussions of the pill's approval, probably because as a practical matter, it proved virtually unenforceable as women changed physicians and switched oral contraceptive brands to get around the two-year limitation.<sup>104</sup> When approved for gynecological treatments in the United States, Enovid had been restricted to between three to four months, with a maximum of ten months in the case of endometriosis.<sup>105</sup> Officials were well aware that approving the safety of the drug for use over a short period of time for menstrual disorders was very different from allowing it to be taken on an indefinite basis as a contraceptive. Initial FDA guidelines for Enovid as a contraceptive, therefore, recommended individual prescriptions be limited to two years.<sup>106</sup>

This two-year restriction continued well into the 1960s until enough evidence had been collected to show that the drug could be used safely by most women for longer periods of time. Because it was such a controversial drug, and in part as a safeguard pending the results of longer-term studies, FDA officials felt that such restrictions would "allay any severe criticism by large numbers of people" who might have opposed marketing of the drug as a contraceptive.<sup>107</sup> Physicians, as well, were always free to exceed the recommendations.

When considering the time limit to impose, what was uppermost in the minds of practitioners and researchers was a largely theoretical scientific link between the pill and cancer. The FDA's own Division of Pharmacology had declared Enovid safe based on animal studies, but had noted the possibility of a small carcinogenic risk due to the estrogenic component of the pill. Estrogens were known to be

103. P. DeFelice to Searle, 25 September 1959, NDA 10976, vol. 15, FDA archives; Third Meeting of CIFIC Clinical Trials Committee, 12 January 1961, SA/FPA/A5/157/1, Box 249.

104. These time limits seem to have virtually been ignored in the stampede to physicians for oral contraceptives, but evidence on this is admittedly scarce. B. Bailey "Prescribing the pill: Politics, culture, and the sexual revolution in America's heartland," *J. Social Hist.*, 1997, 30, 827-56.

105. W. J. Crosson from Searle to P. DeFelice, 9 October 1959, NDA 10976, vol. 15, FDA archives. Letter from DeFelice, 9 December 1959, NDA 10976, vol. 15, FDA Records. R. Weilerstein Memo to Dr Granger, 2 February 1960, NDA 10976, vol. 15, FDA Records.

106. Memo from Kessenich to G. P. Larrick, 11 May 1960, NDA 10976, vol. 15, FDA Records.

107. In 1965 the FDA Advisory Committee of Obstetrics and Gynecology pointed out that "Oral contraceptives were probably unique in that they were one of a very few and possibly [the] only class of drugs where these time restrictions had been inserted in their labelling." FDA Advisory Committee of Obstetrics and Gynecology, First Meeting Minutes, 22-23 November 1965, pp. 9-10, 16-17, FDA Records.

carcinogenic under certain conditions. The pharmacologists told the drug reviewers that this should be carefully considered, but pointed out that because the drug was discontinued once a month, and the estrogen component was small, the risk was considerably reduced.<sup>108</sup> Even if the risk had been deemed a significant one, however, the initial two-year limit would have precluded any revelation of an associated risk of cancer. While some physicians mentioned there might be a cancer risk after 10–20 years, many claimed to be totally unconcerned about this possibility.<sup>109</sup> They, too, agreed that any related cancers would not be evident for decades.

Similar concerns were voiced about the possible links between cancer and the pill in Britain.<sup>110</sup> CIFIC doctors were also aware of the potential for long-term carcinogenic problems with the drug, but did not consider this a major concern.<sup>111</sup> Special efforts were made by CIFIC officials to enlist the views of cancer experts to review the possible carcinogenic hazards of Conovid. One such expert, Dr. Georgina Bonser, replied in detail stating that “in the present state of knowledge there would be justification for using the drugs for *medical* reasons, even on a long term basis, but not for social reasons. . . . The induction period of all cancers in man is long (15–25 years) and therefore the effects of these compounds in cancer induction will not be seen for many years to come.”<sup>112</sup> In approving the pill for use in BFPA clinics, CIFIC thus did not dismiss the possibility of cancer; they were merely pragmatic. They moved to establish routine

108. E. J. Limberger Memo, 18 September 1959, NDA 10976, vol. 15, FDA Records. CIFIC officials also made similar statements, see Third Meeting of CIFIC Clinical Trials Committee, 12 January 1961, SA/FPA/A5/157/1, Box 249.

109. E. Umberger to P. DeFelice, 18 September 1959, NDA 10–976, vol. 15, FDA Records; G. I. M. Swyer to Editor, *Sunday Times*, 29 June 1964, in SA/FPA/A5/161/3, Box 251. Possibly, officials were reassured because these hormones were also being tested at NIH as a possible treatment for cancer.

110. The British Parliament was occasionally questioned about investigations to test for any long-term carcinogenic risks associated with the oral contraceptive pill. Written questions by Miss Joan Vickers, House of Commons, 7 April 1960; letter to A. J. Bradshaw, from Chairman of National Marriage Guidance Council, 5 April 1960; letter to Margaret Howard, from General Secretary of National Marriage Guidance Council, 31 March 1960; CIFIC General Secretary to Mrs. A. K. Court, 28 April 1960, SA/FPA/A5/161/1, Box 251.

111. E. Mears to M. Macaulay, 24 Aug 1961, SA/FPA/A5/161/2, Box 251, see also Extract from special article “Risk of Carcinogenesis,” *The Lancet* (30 July 1960), in SA/FPA/A5/161/2, Box 251; E. Mears to A. D. Donaldson, 4 April 1960, SA/FPA/A5/161/1, Box 251; G. I. M. Swyer to Editor, *Sunday Times*, 29 June 1964, in SA/FPA/A5/161/3, Box 251.

112. G. M. Bonser to E. Mears, April 1960, SA/FPA/A5/161/1, Box 251; CIFIC Minutes, 21 April 1960, p. 110, SA/FPA/A5/154.

cervical and breast screening of women taking the pill within BFPA clinics.<sup>113</sup>

#### FIRST WARNINGS

Both the American and British regulatory bodies were cautious in their initial evaluation of the first oral contraceptive. In the end, however, both countries allowed Searle to market Enovid/Conovid as a prescription drug, opening the floodgates for a proliferation of similar but competing versions of the pill over the next few years as every major pharmaceutical manufacturer marketed its own oral contraceptive. Both the FDA and CIFIC appear to have assessed these pills in accordance with the most stringent drug evaluation standards of the day, but this evaluation was almost certainly less comprehensive than it would have been had the NDA been submitted after 1962.

By the end of the fourth quarter of 1964, more than 4 million women had used Searle's pill.<sup>114</sup> Such unexpected and unprecedented popularity not only surprised the pharmaceutical industry, but amazed physicians, family planners, social reformers and politicians as well.<sup>115</sup> The early enthusiasm for oral contraceptives, however, was soon dampened as the high hormonal doses of the first pill produced nausea, headaches, and dizziness so severe that some women abandoned the pill as quickly as they had embraced it.<sup>116</sup>

In November 1961, more serious concerns were raised about the contraceptive, when a British physician reported the case of a young woman who had developed a blood clot and died while taking the pill (Fig. 5).<sup>117</sup> Within months of the British case, two fatal cases of

113. E. Mears, "Routine cervical smears for the diagnosis of cervical carcinoma," 17 July 1962, SA/FPA/A5/161/4, Box 251.

114. W. Searle, Vice President, Marketing, G. D. Searle, to A. Pierce, M. D., Division of Medical Review, Drug Surveillance Branch, Bureau of Medicine, FDA, 2 April 1965, R.G. 88, AF 13-505, vol. 10, Washington National Records Center, Washington D.C.

115. P. Vaughan, *The Pill on Trial* (London: Weidenfeld and Nicolson, 1970), pp. 52-53.

116. In fact, Searle's early figures estimating prescriptions for Enovid assumed that for every woman who took Enovid for the first time, another woman discontinued it. Early estimates were that 17% of women reported such side effects, but some suspected that there was a "large psychogenic element in the occurrence of these reactions." *Sixth International Conference on Planned Parenthood*. New Delhi, India, 14-21 February 1959 (London: IPPF, 1959), pp. 216-30.

117. W. M. Jordan (Suffolk) to the editor, *Lancet* (18 November 1961), 1146-7; FDA files indicate that on 13 December 1961, FDA in Washington received a phone call from their Los Angeles District Office advising that there were two deaths, one at UCLA Medical Center, and one at Mt. Sinai, in which Enovid might be involved. Both FDA and Searle followed up on all reported cases in the area. At the end of January, drug reviewer DeFelice



thrombosis were reported among American women who had taken the pill. By August 1962, twenty-six women had been reported to the FDA as having suffered from blood clots in their veins, six of whom had died.<sup>118</sup>

These preliminary warnings and concerns about the safety of the pill were swiftly eclipsed in 1961 and 1962 when the worldwide scandal over thalidomide broke. Originally developed in East Germany, thalidomide had been considered so safe that it could be obtained without a prescription in Germany. It had also been recommended for pregnant women both to combat severe morning sickness and as a sedative. The drug was quickly withdrawn from the European market when it was shown to have caused an epidemic of severe birth defects.<sup>119</sup> In the aftermath of the tragedy, many new regulations were imposed on pharmaceutical manufacturers in Europe. Stricter rules governing the introduction of new drugs were also passed in the United States, where a license for the drug had narrowly missed being granted. Although thalidomide was never marketed in the United States, the FDA had received an application for its license

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was awaiting more information. "At this time, I can do nothing except to note the occurrence of these deaths and wait with interest any further development including the results of the blood studies. However, I am inclined, based on present information, to agree with the company that these deaths occurred in women who only happened to be taking the drug, Enovid. We, therefore, will defer any action on the field and company reports until further data is available." NDA 10-976, Memorandum from DeFelice to Ralph G. Smith, M.D., 29 January 1962. The first published reports in the U.S. were: Memo from G. D. Searle to Shareowners, 9 August 1962, Smithsonian Papers; *New York Times*, 9 August 1962. At a conference on thrombophlebitis on 10 September 1962, Searle reported 132 cases of thromboembolic phenomena among Enovid users, and nine deaths. On 29 November 1962, FDA official Heino Trees noted that since that conference "the number of reported cases has more than doubled and the incidence of fatalities tripled." Trees went on to conclude that "the increasing incidence of deaths among young, healthy women in their early twenties has confirmed my previous opinion that this drug is a causative factor. I know of no convincing evidence that Enovid medication does not contribute directly to the cause of thrombophlebitis." NDA 10-976, Memo to Commissioner of FDA from Heino Trees, Division of New Drugs, 29 November 1962. FDA began a more detailed investigation, commissioned new studies and notified American physicians of the possibility of thrombophlebitis in patients taking Enovid in a "Dear Doctor" letter in early 1963.

118. Memo from G. D. Searle to Shareowners, 9 August 1962, Smithsonian Papers; *New York Times*, 9 August 1962; Memo to PPFA Affiliates from M. S. Calderone, 6 August 1962, Calderone's Papers, Box 12, fo.216, Schlesinger Library; *British Medical Journal*, 11 August 1962, p. 426; J. Davey, "How safe are the birth control pills," *Redbook*, February 1963, in Box 60, GP-LC.

119. Thalidomide caused severe birth defects, including phocomelia (flipperlike appendages in place of arms and legs) when taken in early pregnancy. A pregnant woman taking even a single thalidomide tablet early in pregnancy ran a substantial risk of giving birth to a seriously deformed child.

**AUTOPSY REPORT**

*With Parents & Relatives*

**DEPT. OF HEALTH, EDUCATION, AND WELFARE  
AUTOPSY ADMINISTRATION  
WASHINGTON, D.C. 20540**

**DRUG REACTION REPORT**

Form Approved  
Budget Bureau No. 47-1000-1

PATIENT'S INITIALS <b>H.A.H.</b>		SEX <b>F</b>	WEIGHT <b>160</b> (lb.)	IN SOURCE OF REPORT (Hospital, Physician, etc.) <b>Hospital Records</b>
DATE OF BIRTH (Mo., Day, Year) <b>1-27-28</b>		OCCUPATION <b>Physician</b>		ADDRESS (Street, City, State and Zip Code) <b>Minneapolis, Minn</b>
DATE OF ADMITTANCE <b>1-30-65</b>		DATE OF DISCHARGE <b>2-2-65</b>		
<input type="checkbox"/> CASE <input type="checkbox"/> RECORD <input type="checkbox"/> URGENT <input type="checkbox"/> OTHER		SIGNATURE (Dr. or other official) <i>[Signature]</i>		DATE <b>May 28, 1967</b>

**ADVERSE REACTIONS AND CLINICAL DESCRIPTION (Use reverse for continuation and footnotes)**

**Acute pulmonary embolism**

DATE OF ONSET <b>1-27-65</b>	3 RESULT OF RELEVANT LABORATORY STUDIES (Clinical Laboratory, Endocrine, Biopsy, Autopsy, etc.)  <b>See attached Hospital Records Copy 11r Dr. [Name] N.E.</b>
DATE OF DISCHARGE <b>2-2-65</b>	
4 SUMMARY OF REACTION <input type="checkbox"/> ROUTE <input type="checkbox"/> SLOWLY DEVELOPING	

NAME OF DRUG (Trade)	TOTAL DAILY DOSE	ROUTE (Oral, IM, etc.)	DURATION OF THERAPY	DATE OF ADVERSE REACTION	REASON OR REASON FOR USE OF DRUG
<b>Enovid</b>	<b>1</b>	<b>oral</b>	<b>14 days</b>	<b>1964-5</b>	<b>Contraceptive</b>

**1. List all potentially toxic agents to which patient has been exposed, and describe circumstances of exposure. Give any information available on dose or exposure. (Include radiation, household products, industrial and agricultural chemicals, etc.)**

NAME AND TYPE OF AGENT	TYPE AND DESCRIPTION OF EXPOSURE	AMOUNT OR DOSE
<b>None</b>		

**2. Has patient been exposed to suspected drug or agent before?** ☒ YES ☐ NO

**3. Was suspected drug used according to directions?** ☒ YES ☐ NO (Explain)

**4. OTHER DRUGS WHICH EXISTED PRIOR TO ONSET OF ADVERSE REACTION OR ARE NOW PRESENT**

**None**

<b>5. REACTION FACTORS (Check all applicable boxes)</b> <input type="checkbox"/> SELF-MEDICATION BY PATIENT <input type="checkbox"/> DRUG MISLABELED <input type="checkbox"/> ACCIDENTAL EXPOSURE <input type="checkbox"/> DECOMPOSITION OF DRUG <input type="checkbox"/> OCCUPATIONAL EXPOSURE <input type="checkbox"/> CONTAMINATION OF DRUG <input type="checkbox"/> SUBJECTS <input type="checkbox"/> DRUG OUTDATED <input type="checkbox"/> BY PHYSICIAN <input type="checkbox"/> INTERACTION OF TWO OR MORE DRUGS		<b>6. OUTCOME OF CASE</b> <input type="checkbox"/> RECOVERED <input type="checkbox"/> STILL UNDER TREATMENT <input type="checkbox"/> ALIVE WHEN REPORTED <input type="checkbox"/> DIED (Date and cause of death) <b>2-2-65 - Acute pulmonary embolism, etiology undetermined.</b>
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<b>7. SOURCE OF SUSPECTED DRUG</b> <input type="checkbox"/> PHYSICIAN <input type="checkbox"/> PHARMACY <input type="checkbox"/> DOOR-TO-DOOR SALES- <input type="checkbox"/> PHYSICIAN <input type="checkbox"/> OTHER RETAIL SOURCE <input type="checkbox"/> MAIL ORDER <input type="checkbox"/> UNKNOWN	<b>8. HAS PATIENT BEEN REPORTED TO ANY OTHER GROUP OR AGENCY?</b> <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> POISON CONTROL CENTER
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**9. JOURNAL REFERENCE (If any and/or designated publication)**

Fig. 5. Autopsy report of a woman who died of thromboembolic complications later attributed to Enovid. Note onset is described as “acute/explosive.”

to previous methods of contraception, which often presented innumerable messy problems, from leaky condoms to poorly fitting diaphragms and rhythm miscalculations, the pill transformed contraception into something seen as simple, straightforward, and very reliable. In contrast to short-acting barrier contraceptives, however, the pill posed significant safety concerns for regulators. The very fact that it could be taken for such extended periods of time and by healthy women raised some anxiety.<sup>6</sup> Such fears seem to have diminished quickly among the regulators between 1959 and 1960, the very time that the drug was being considered for approval as a contraceptive. Records do not reveal how regulators shifted their focus from potential problems with the pill to an overall appreciation of its medical benefits in comparison with botched abortions (which were never openly discussed) or with the risks of childbirth. The benefits of the pill compared to the risks of childbirth were calculated and defended openly during the approval process and used to defend the approval decision. As critics have charged in another context, it may well be that the drug's extraordinary effectiveness made these truths self-evident to scientific reviewers.

We explore the critical role that thalidomide played during this time in redefining, both legally and socially, the meaning of safety and efficacy in relation to drugs used by and for women. The close links in time between the approval of Enovid as a contraceptive in 1960 and revelations after 1961 about the worldwide epidemic of birth defects linked with thalidomide have often been noted, but not carefully analyzed. For most women, thalidomide came to epitomize the potential and unknown dangers posed by any drug used in pregnancy, while the horror that this drug inspired led directly to stronger laws governing the marketing of new drugs in Britain, the United States, and most of Europe between 1962 and 1964.<sup>7</sup> As a drug intended to prevent pregnancy, the pill played a special role in the debate about the safety and efficacy of drugs.

With access to the original New Drug Application (NDA) for Enovid and hitherto unexamined primary sources in Britain, we have

6. W. Crosson to P. Defelice, 9 October 1959, p. 5, NDA 10976, vol. 15, FDA Records, RG 88; U.S. National Archives (hereafter cited as FDA Records).

7. When the FDA was considering the reapproval of thalidomide for use in treating leprosy in the late 1990s, it was reported that a survey had found that more than 95% of all women older than 35 knew what thalidomide was, but few women younger than 35 even recognized the name.



in 1960, just three months after the FDA approval of Enovid as a contraceptive.<sup>120</sup>

After thalidomide's teratogenic dangers were revealed, any new drug with such widespread potential use in women of childbearing years such as Enovid would have encountered a far more cautious regulatory environment. It was the 1962 Drug Amendments in the United States which, for example, first required that patients be told of the experimental nature of any new drug they were given, and for all practical purposes eliminated women from phase I clinical trials.<sup>121</sup>

When the first reports of fatal thrombotic complications were announced within months of Enovid/Conovid's approval, the FDA required Searle to send a letter to physicians informing them of the reports. British officials lamented that they had no similar provisions. Instead, British officials concentrated their efforts on the intense epidemiological research eventually required to demonstrate a true association between the pill and this rare, but tragic side effect.<sup>122</sup>

Initially, it was not at all clear whether the complications occurred with oral contraceptives in general or were more frequently associated with a particular brand. Early adverse reports confused thrombophlebitis and phlebothrombosis.<sup>123</sup> This issue became a moving target because doses and formulations were changing frequently as more companies began marketing oral contraceptives. It was also unclear what the normal risks of thrombosis were for a healthy young woman of reproductive age.<sup>124</sup> Not until 1967, however, after millions of women had taken the pill, did British researchers quantified the thrombotic risks associated with oral contraceptives.<sup>125</sup> Their epidemiological studies conclusively demonstrated an association with pill

120. W. Grigg, "Drug tryouts permit no human guinea pigs," *Evening Star*, 7 August 1962, A-3. For detailed information on the 1962 Kefauver-Harris Drug Amendments, see R. Harris, *The Real Voice* (New York: MacMillan, 1964); R. McFadyen, "Thalidomide in America: A brush with tragedy," *Clio Medica*, 1976, 11, 79-93; H. S. Sjöström and R. Nilsson, *Thalidomide and the Power of the Drug Companies* (Baltimore, Md.: Penguin, 1972), pp. 23-28.

121. R. Merkatz and S. Junod, "Historical background of changes in FDA policy on the study and evaluation of drugs in women," *Academic Med.*, 1994, 69, 703-7.

122. L. Marks, "'Not just a statistic': The history of USA and UK policy over thrombotic disease and the oral contraceptive pill, 1960s-1970s," *Social Sci. Med.*, 1999, 49, 1139-55.

123. FDA Ob-Gyn Advisory Committee Meeting minutes, 20 January 1966, p. 4. Transcripts located in the FDA History Office, Rockville, Md.. Hereafter cited as Ob-Gyn Advisory Committee minutes.

124. Ob-Gyn Advisory Committee Meeting minutes, 22-23 November 1966, p. 21.

125. Ob-Gyn Advisory Committee Minutes, 7-8 April 1966, p. 4.

usage among previously healthy young women who had developed sudden and sometimes fatal episodes of blood clotting (venal thrombosis).<sup>126</sup> Once the dangers from the pill had been documented and revealed, heated debates over the drug's safety began on both sides of the Atlantic.

In Britain, publicity over the pill's potential risks reached a crescendo in late 1969, when a number of British medical journals and popular newspapers published articles accusing the medical profession of being too complacent on the links between the pill and thrombosis.<sup>127</sup> The debate intensified in December 1969 when Professor Victor Wynn, an endocrinologist and an expert on metabolic effects of anabolic steroids, appeared on a David Frost television program and detailed before millions of British viewers a panoply of risks associated with the pill. Appearing in a total of three Frost programs that month, one of which was broadcast to an audience in the United States, Wynn's testimony caused public and parliamentary uproar.<sup>128</sup> These broadcasts, together with the publication of the British epidemiological studies linking the pill with thrombotic complications, resulted in the British government warning doctors to no longer prescribe the higher dose (10-milligram) pills.

In the United States, an impassioned public debate on the safety of the pill had also been inaugurated with the publications of journal-

126. "Risk of thromboembolic disease in women taking oral contraceptives," *Br. Med. J.*, 1967, 2, 355-59, p. 356. No author is given for this article. The British studies estimated that that 1 in every 2000 women suffered blood clots serious enough to require hospitalization and that for 1 in 67,000 women under 34, this condition was fatal. For women over 35, the estimated risk of death grew to 1 in 25,000 women. W. H. W. Inman and M. P. Vessey, "Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age," *Br. Med. J.*, 1968, 2, 193-99; M. P. Vessey and R. Doll, "Investigation of relations between use of oral contraceptives and thromboembolic disease. A further report," *Br. Med. J.*, 1969, 2, 651-57; M. P. Vessey, and R. Doll, "Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease, A Further Report," *BMJ*, 2 (1969), 651-7; W. H. W. Inman, M. P. Vessey, B. Westerholm, and A. Englund, "Thromboembolic disease and the steroidal content of oral contraceptives," *Br. Med. J.*, 1970, 2, 203-9; M. P. Vessey, R. Doll, A. S. Fairbairn, and G. Gloger, "Postoperative thromboembolism and the use of oral contraceptives," *Br. Med. J.*, 1970, 3, 123-26. See also *Nelson Hearings*, vol. 1, 5921. For a more detailed history of the investigation into the thrombotic effects of the pill, see Marks, (n. 111).

127. "Impasse on birth control pill," *The Times* (London), 29 August 1969; "Birth pill killed wife," *The Times* (London), 16 October 1969; "Death risk from birth control pill 'inevitable'," *Daily Telegraph*, 17 November 1969.

128. The program was initiated as a result of the article "The Sun says a million women wait," *The Sun*, 29 November 1969. Interview with Victor Wynn by L. Marks, London, 2 July 1994, transcript, pp. 26-29. See also B. Yuncker, "Researcher predicts ban on the pill," *The New York Post*, 22 December 1969, p. 3.

ists Morton Mintz and Barbara Seaman.<sup>129</sup> Both journalists challenged what they characterized as the “diplomatic immunity” which had dominated news about the oral contraceptives up to that time by questioning not only the overall safety of the pill but the way in which the U.S. regulatory authorities had approved it.<sup>130</sup> Mintz, in particular, widely publicized as fact that the pill had been tested on only 132 women prior to its approval for contraception and that its safety had not been proven before it went on the market. By the end of 1969 Senator Gaylord Nelson called for congressional hearings (known as the Nelson hearings) on the safety of the pill. The primary focus of the Nelson hearings was on safety and informed consent: Had women been adequately informed about the risks and significant side effects of the pill? Should the pill be removed from the market, or should new studies be instituted?

As Watkins has discussed, the Nelson hearings infuriated many women. During the 1960s many feminists had begun to protest against the paternalistic attitudes of the state and male-dominated medicine.<sup>131</sup> After the hearings, women were critical of the process, which excluded testimony from female patients, and angry about the analogies to women as guinea pigs. Many responded by parading in front of the hearings carrying placards demanding “Feed the Pill to your guinea pigs at the FDA not live women.” After the hearings, women’s groups, particularly the Washington D.C.-based Women’s Liberation group, called for new separate hearings centered around women’s concerns, angrily arguing that, “In spite of the fact that it is women who are taking the pill and taking the risks, it was the legislators, the doctors, and the drug company’s representatives, all men of course, who were testifying and dissecting women as if they were no more important than the laboratory animals they work with every day.”<sup>132</sup> In this charged atmosphere, there is no doubt that what feminists took away from the writings of journalists and the Nelson hearing

129. M. Mintz, *The Pill: An Alarming Report* (Greenwich, Conn.: Fawcett, 1969); B. Seaman, *A Doctor’s Case Against the Pill* (New York: Wyden, 1969, rev. 1980).

130. According to Seaman, the quote about the pill’s enjoying “diplomatic immunity” came from David Clarke. Seaman states that she and Morton Mintz were practically the only journalists questioning it and that they were accused of “being nuts, inflammatory radicals, and in league with the Pope.” Conversation with Barbara Seaman, 7 August 1997. Notes in FDA History Office.

131. Watkins, (n. 3) *On the Pill*, pp. 106–23.

132. Statement by Washington Women’s Liberation, cited in *Nelson Hearings*, vol. 3, part 16, 6470–71, 6473; part 17, 7283–4.



proceedings was that women had indeed served as guinea pigs as drug companies prospered, and that, even ten years later, physicians were still not sure if the pill was safe.

During the Nelson hearings, the FDA never addressed the history of their original 1957 approval of the pill. The focus of the hearings, so far as the FDA was concerned, was strictly upon the definition of safety as it currently applied to oral contraceptives. So many changes had taken place in the regulation of new drugs (and in FDA personnel) following the thalidomide disaster that the history of the first approvals of Enovid back in 1957 and 1960 seemed confused and irrelevant.<sup>133</sup> The agency also had a strict policy in place, maintained until the early 1970s, of protecting its NDA records from outside scrutiny, even by Congress.<sup>134</sup> By the time of the Nelson hearings, in fact, the original reviewing officials had left the FDA, and the Department of Health, Education and Welfare had altered its earlier position on the “population problem” by appointing an Assistant Secretary to address the issue directly. Therefore, the agency’s traditional silence on the issue of the pill’s original approval remained unbroken. The conclusion first put forward by Mintz that the pill was tried on only 132 women before it was approved thus became a standard, but erroneous assertion.

By the 1970s, however, there had been a sea tide of change in the evaluation of the safety of oral contraceptives since 1960. In 1962, before the British researchers established the statistical link with thrombosis, many physicians felt that the whole question of the pill’s side effects had been magnified, not by the actual danger, but by the concerns over thalidomide.<sup>135</sup> No one disputed, however, that there was a need for more research to substantiate the concerns. By the time of the Nelson hearings, several large-scale studies of the pill and of thrombotic phenomena had been designed, and others were

133. For a detailed discussion of these changes, see R. G. Smith, “The pill and FDA: Changes in the control of new drugs,” policy paper submitted by FDA to the Johnson Administration, n.d., Johnson Library Papers, Johnson Presidential Library and FDA History Office.

134. Prior to 1972, 90% of FDA files were closed to public examination. After this, only 10% remained off-limits. Videotape transcript of presentation by P. B. Hutt to FDA Center for Devices and Radiological Health, “Legal series: The evolution of food practices and procedures,” n.d., FDA History Office.

135. Article in *Medical Tribune*, 20 August 1962, cited in U.S. Senate, *Hearings Before the Subcommittee on Reorganization and International Organizations of the Committee on Government Operations, Interagency Coordination in Drug Research and Regulations*, 87 Cong., 2d (Washington D.C., 1962), part 2, p. 614.

underway.<sup>136</sup> The American Cancer Society, to cite a single example, initiated a seven-year study comparing 5000 pill users with 5000 nonusers.<sup>137</sup> Experience with such large studies and interpretation of their results, as well as the new drug evaluation methods mandated by laws and regulations enacted in the wake of the thalidomide disaster, strengthened the entire new drug approval system worldwide.

The pill, of course, is still on the market, and although it is still controversial in some corners, the social and medical concerns it originally engendered have now been supplanted by concerns over the abortion drug RU-486, approved in the United States in 1999. The pill, like other drugs before and after it, added experience and knowledge that strengthened the regulatory process. Moreover, early and continuing public criticism of the pill and its approval was crucial in opening up the larger debate over the safety, labeling, and information provided to consumers of prescription drugs in both countries. Seaman's tireless, and at times heroic, efforts to mandate a "patient package insert" for the oral contraceptives cannot be overlooked as a major contribution to the history of the women's health movement.<sup>138</sup> Because of the knowledge gained from Enovid/Conovid, pharmaceutical researchers have gone on to create a new generation of oral contraceptives which are, in the words of journalist Robin Herman, "99.9% effective," but are generally safer and have far fewer side effects than any of the original pill formulations.<sup>139</sup> Only in 1995 was it established that a mutant gene (called factor V Leiden) puts some women at increased risk of venous thrombosis. With the recent commercial availability of genetic screening for this gene, women now have the option of being screened before they take the pill.<sup>140</sup>

136. ObGyn Advisory Committee Minutes, 7–8 April 1966, p. 4, 4–5 January 1968.

137. ObGyn Advisory Committee Minutes, p. 5; 22–23 November 1965, p. 17.

138. R. Finch, Secretary of Health, Education, and Welfare to B. Seaman, 27 April 1970. Copy of letter provided to authors by Barbara Seaman. Also B. Yuncker, "Woman in the news: Barbara Seaman, a reporter finds a cause," *New York Post*, 24 January 1970. For highlights of the debate: G. Meyer, Office of Legislative Services, FDA to Senator Percy, 10 May 1972, PPI Files, FDA History Office.

139. Robin Herman, "Researchers explain pill's link to clotting problem: Contraceptives' overall risk is low, but women with genetic defect may be more vulnerable," *Washington Post*, Health Section, 20 May 1997. Netherlands researcher Ale Algra has determined that stroke risk among pill users (whether first, second or third generation pills) is still twice the risk among nonusers; Laura Barclay, "New birth control pills, same old stroke risk," *Web MD*, 7 February 2002, p. 1.

140. P. M. Ridker, J. P. Miletich, C. H. Hennekens, and J. E. Buring, "Ethnic distribution of factor V Leiden in 4047 Men and women: Implications for venous thromboembolism screening," *J. Am. Med. Assoc.*, 1997, 277, 1305–7.

carefully examined and analyzed the drug approval process as it functioned in 1960 on both sides of the Atlantic.<sup>8</sup> Initially, we were intrigued by the fact that the United States had a formal regulatory process in 1960, whereas the United Kingdom lacked such a process, but that, in spite of this seemingly significant difference, Enovid and Enavid were marketed within months of each other. It was evident, however, that in this area the combined experience of individual physicians with the drug over a long period of time was decisive in its approval in both countries. Once on the market, it was the clinical experiences with the pill, rather than the often-cited thalidomide disaster, that proved more influential in prompting fundamental conceptual changes in the drug review process in both countries.

From the start it was clear to regulators that it would be difficult to establish the pill's safety for long-term use. In the absence of direct evidence from long-term use, and before allowing women wide access to the drug, regulators therefore adopted several lines of defense to minimize whatever theoretical dangers it could pose, including limiting prescriptions for the pill to two years. Such measures were soon challenged by the overwhelming and unexpected popularity of the pill. In a short time, moreover, in which the market was flooded with many other oral contraceptive brands. The strengthened U.S. food and drug law, enacted in the wake of thalidomide, provided some assistance. The law and its implementing regulations required companies, for the first time, to submit postmarketing reports every three months during the first year that a new drug was on the market, every six months for the second year, and once yearly thereafter. Adverse events had to be reported whenever they occurred. Within this framework it was not deemed necessary to withdraw the pill, even after reports began to question whether it could cause rare but frequently fatal thrombotic complications. Instead, one of the responses chosen was to initiate large-scale, long-term epidemiological studies of the drug on a hitherto unimagined scale.

By 1967, British scientists had conclusively linked the pill with thrombosis, but they did so relying largely on epidemiological data. This increasing reliance on statistical evidence supported and advanced a more analytical and less communally determined drug approval

8. G. D. Searle and the FDA have agreed that the NDA for Enovid will be given to the National Archives, but privacy regulations will restrict some information from that NDA from being made public, most notably patient names and investigators' names prior to 1976.



process. This change in the risk-benefit equation calculations of a new drug, of course, may have been inevitable and had been initiated with an earlier drug, chloramphenicol, but it was the stature and novelty of Enovid that propelled it forward so dramatically.<sup>9</sup> In the United States, concerns about the safety of the pill before 1967 led to the creation of the Food and Drug Administrations' first permanent advisory committee, further changing the nature of the drug approval process and initiating what Jasanoff would later call the "fifth branch" of government in the United States.<sup>10</sup>

Today the history of the pill is difficult to disentangle from the persistent criticisms that have been made of its safety since it was linked with thrombosis. As soon as the thrombotic problems were recognized, many criticized the original approval process for Enovid. Some feminists still insist that the pill poses an unrecognized threat to women's health.<sup>11</sup> It is clear, however, both from the records themselves as well as from the failure of lawsuits against Searle, that the process was not flawed. Like many drugs that are the first of their kind, Enovid/Enavid was an imperfect drug, soon improved upon even by its own inventors.

Much of the criticism of the pill, however, as Watkins has shown, arose from the fact that the pill altered the relationship between women and their physicians. In retrospect, it is clear that women's rejection of medical paternalism underlay much of the social criticism leveled at the pill. We believe that the unique decision-making processes that introduced oral contraceptives and allowed them to remain on the market even after potentially dangerous side effects were discovered are an important and instructive example of the intermingling of science, policy, and practicability in the approval process for a revolutionary twentieth-century drug (Fig. 2).

#### DEVELOPMENT OF THE FIRST PILL

By the early twentieth century, advances in endocrinology, chemistry, and gynecology had resulted in a plethora of sex hormones for medical treatments. Many synthetic progestins and estrogens had been synthe-

9. T. Maeder, *Adverse Reactions* (New York: William Morrow and Co., 1994).

10. S. Jasanoff, *The Fifth Branch: Science Advisers as Policymakers* (Cambridge: Cambridge University Press, 1990).

11. B. Seaman, *The Doctor's Case Against the Pill: 25th Anniversary* (Alameda, Ca.: Hunter House, 1995).



developing the pill. After being tested in animals, the compounds were tested in humans beginning in 1956 in the United States, Puerto Rico, and Haiti.<sup>14</sup> From these experiments Pincus and his team settled on Colton's Norethnodrel as the most viable formulation for an oral contraceptive. Trade-named Enovid, this compound contained a combination of nor-19 progestin with a small amount of a synthetic estrogen.<sup>15</sup> Although this combination was new, the basic progestogen component of the pill was well understood pharmacologically by the time that Searle submitted its original NDA to the U.S. Food and Drug Administration (FDA) in 1957.<sup>16</sup>

#### APPROVAL PROCESS

The process by which the pill came to be marketed in Britain and the United States differed, according to the distinct drug regulatory mechanisms of each country. The United States had some premarketing control over the introduction of new drugs onto the marketplace, which had been established in 1938, but Britain had no premarketing controls aside from a requirement that all pharmaceutical manufacturers be licensed. In the end, however, both countries had similar versions of the pill on the market within months of each other.

In the United States, new pharmaceutical drugs were subject to

14. P. Vaughan, *The Pill on Trial* (London: Weidenfeld and Nicolson, 1971), pp. 10–19; J. Reed, *The Birth Control Movement* (Princeton, N.J.: Princeton University Press, 1978, 1983); L. Marks "'A Cage of Ovulating Females': The History of the Early Oral Contraceptive Pill Clinical Trials, 1950–59," in S. de Chadrevian and H. Kamminga, eds., *Molecularizing Biology and Medicine: New Practices and Alliances, 1930s–1970s* (Amsterdam: Harwood Academic, 1997), pp. 221–47.

15. It was only after some time that investigators realized that it was the estrogen component, initially viewed as a contaminant, that was the crucial element in suppressing ovulation.

16. The class of 19-nor progestogens had been studied since 1952. However, Enovid was the first pill on the market. Parke-Davis' Norlutin was developed around the same time and was quickly marketed after Enovid's approval and early market success. Other companies soon followed suit. All created their own versions of the pill using the same basic formula, a synthetic nor-19 progestin combined with a small amount of a synthetic estrogen. Most major pharmaceutical companies already held patents on one or more of these synthetic hormones, so most simply combined their own patented hormones to create their own oral contraceptive pill. By 1965, NDAs were approved for Searle's Enovid, Ortho Pharmaceuticals' Ortho Novum, Upjohn's Provest, Syntex's Norinyl, Parke Davis's Norlestrin, Mead Johnson's Oracon, and Eli Lilly's C-Quens. When the first serious adverse reactions began to be reported, investigators could not determine whether the problem was caused by a particular brand or brands of the pill or by the overall formulation. In 1969 the British Committee on Safety of Drugs had isolated a number of pills that had higher amounts of estrogen, which seemed to be more strongly linked to thrombotic complications.



formal regulatory review from as early as 1938. Such guidelines had come into place after 109 people died from taking an untested new formulation of a sulfa drug in 1937.<sup>17</sup> Beginning in 1938 all pharmaceutical companies had to demonstrate to the FDA that their product was safe for use as intended before it was allowed on the market. Under the law, the FDA had sixty days to consider a company's NDA. Increasingly after World War II, complex reviews began taking significantly longer than sixty days, as was the case with the pill. NDAs included the results of all animal and human trials conducted with the drug as well as the advertising material the company proposed to use in marketing the drug.<sup>18</sup> Advertising was heavily scrutinized to ensure that the labeling and literature were both accurate (i.e., in accordance with the evidence presented), and free of false therapeutic claims. The law, however, regulates the behavior of pharmaceutical companies rather than that of physicians, who, once a drug is approved for one disease or condition, remain free to prescribe it for other uses—so called off-label use.

In Britain, government control over the manufacture and supply of pharmaceutical drugs had been tightened in 1947 and 1957. Such restrictions, however, primarily concerned dangerous drugs and self-medication drugs, as well as biological products (e.g., antibiotics, vaccines, and insulin, all of which had to be standardized by biological techniques). Products had to be scrutinized to insure that their manufacturing methods and potency testing met the stipulated requirements. Drugs subject to these restrictions were only a small minority in the pharmacopoeia. All other drugs could be released onto the British market without submitting to any formal procedure. In general, the British government took a laissez-faire approach toward pharmaceutical companies in the 1950s. The only restriction imposed on drugs in this period was that they could not be advertised as curing cancer, venereal disease, or Bright's disease. The overall structure for testing and monitoring drugs remained relatively weak in Britain

17. C. Jackson, *Food and Drug Legislation in the New Deal* (Princeton, N.J.: Princeton University Press, 1970); J. H. Young, "Sulfanilamide and diethylene glycol," in J. Parascandola and J. Whorton, eds., *Chemistry and Modern Society* (Washington D.C.: American Chemical Society, 1983), pp. 105–25.

18. Senate Committee on Government Operations, *Hearings on Interagency Coordination in Drug Research and Regulations, Part 3*, March 1963, p. 987; Maeder, (n. 7) *Adverse Reactions*, chapter 5.