Chapter 6

Reproductive Research and Contraceptive Development

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Reproductive Research and Contraceptive Development

Abstract

Reproductive research and contraceptive development are carried out by academic institutions, the pharmaceutical industry, private foundations, U.S. and foreign governments, and international agencies. U.S. Government support for contraceptive development began in the late 1960's when the National Institutes of Health's (NIH) Center for Population Research and the Agency for International Development's (AID) Office of Population were created. Although worldwide expenditures for reproductive research and contraceptive development rose from $31 million to $155 million between 1966 and 1979, when adjusted for inflation there has been a decline of 20 percent since 1973. Public sector expenditures (by governments and philanthropic and nonprofit organizations) constitute about 85 to 90 percent of these worldwide expenditures. In 1979, the U.S. Government's share of this total was 72 percent or $111.6 million. Government research agencies stimulate private sector initiatives in contraceptive development in two ways. First, they support basic research projects in academic and other nonprofit research institutions. Private firms can then build on these findings to develop new products. Second, Federal agencies can directly finance projects (e.g., clinical trials) that might otherwise require industry financing in order to stimulate industry to develop and market new products.

Before U.S. manufactured drugs and medical devices can be marketed, they must meet the safety and efficacy standards of the laws passed by Congress and administered by the U.S. Food and Drug Administration (FDA). Testing requirements for contraceptives are more stringent than for other drugs because they are used for long periods by healthy individuals rather than by individuals with disease. Drugs not approved for marketing in the United States cannot be exported for use abroad. Medical devices not approved for marketing in the United States can be exported under limited conditions. These export provisions will become more important as pharmaceutical manufacturers shift their marketing efforts from the United States, where population growth is close to replacement level, to the less developed countries (LDCs), where the number of people entering the reproductive ages is increasing. FDA's market approval process has been criticized as shortening effective patent life, leaving manufacturers too little time to recoup their investments. Drug patents run for 17 years, and the market approval process averages 7½ years-8½ years for hormonal contraceptives. However, for the oral contraceptives, patent holders have been able to increase prices and retain a dominant share of the market even after their patents have expired. Liability insurance costs have risen, and, in some cases, pharmaceutical manufacturers have had difficulty in obtaining satisfactory insurance coverage. These product liability problems may be deterring some pharmaceutical manufacturers from the contraceptive products line as well as affecting the kinds of future contraceptives to be developed. Liability problems have also affected the clinical testing that new contraceptives must undergo, as insurance is more difficult to obtain and its cost is substantially higher.

Introduction

As in other areas of pharmaceutical investigation, reproductive research and contraceptive development are comprised of the following activities:

- basic research (in both the reproductive process and in related fields; e.g., immunology);
- training of scientists;
- applied research (i.e., goal-oriented R&D); and
- evaluation of the safety and effectiveness of methods already in use.

These activities and, in some cases, the introduction and marketing of contraceptives, are carried out in varying degrees by the following entities:

. academic institutions;
- the pharmaceutical industry;
- private foundations;
- the U.S. Government;
- foreign governments; and
- international agencies.

In the following analysis, recent trends in the financing of reproductive research and contraceptive development are discussed. The major public sector organizations involved are described, and selected factors that affect reproductive research and contraceptive development are examined.

Support of reproductive research and contraceptive development

Trends in financial support

Throughout the 1940's and 1950's, contraceptive development was not directly supported by the U.S. Government. Oral contraceptives, for example, were developed with the support of private philanthropy (particularly the Rockefeller Foundation) and the pharmaceutical industry,

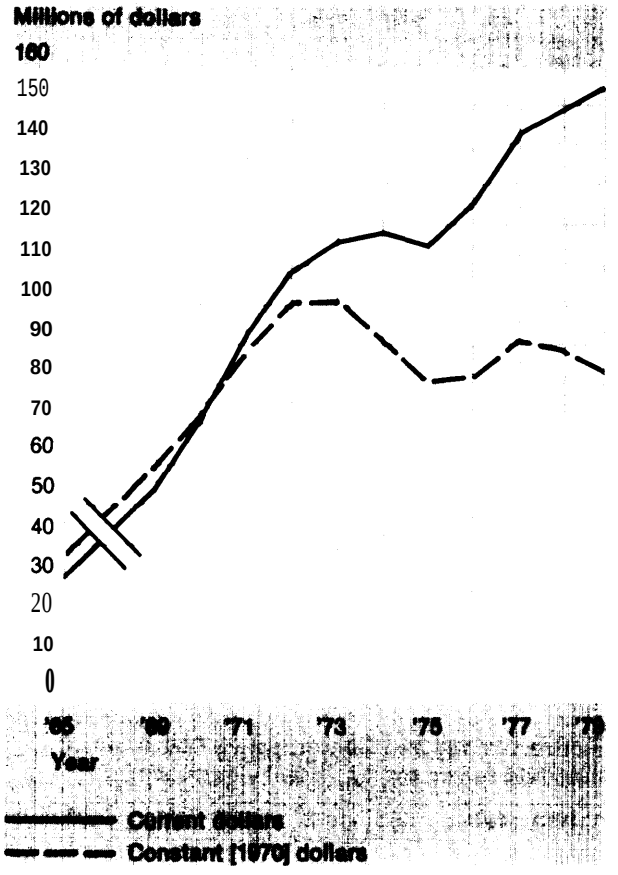
In the late 1960's, the U.S. Government created agencies that eventually began allocating relatively small amounts of research funds to contraceptive development. In 1967 the Office of Population was created within AID, and in 1968 the Center for Population Research was established in the National Institute of Child Health and Human Development within NIH. On the international level, the United Nations Fund for Population Activities (UNFPA) was created in 1969, and in 1972 the Special Programme for Research, Development and Research Training in Human Reproduction was established within the World Health Organization (WHO).

In 1979, worldwide funding for reproductive research and contraceptive development totaled approximately $155 million, an increase from $31 million in 1965. However, expressed in constant (1970) dollars, this $155 million was equal to $82.6 million, and the high point in funding was 1972-73 (fig. 20). There has thus been a decline in these funds of about 20 percent since 1973 (table 22).

During the 1970's, the U.S. contribution remained at approximately 70 percent of the worldwide total; the remaining 30 percent was provided largely by other industrialized nations and by the LDCs (table 22). The U.S. contribution in 1979 was $111.6 million (actual dollars), or 72 percent of worldwide expenditures.

U.S. contributions consist of funds from the U.S. Government, philanthropic and nonprofit organizations, and industry, and there has been a shift in relative contributions among these sources. In the 1960's, these three sources provided **roughly** equal percentages of the total

Figure 20.—Worldwide Expenditures for Reproductive Research, 1965-79



SOURCE: L. Atkinson, et. al., "Prospects for Improved Contraception," *family P/arming Perspectives,* 12(4), pp 173-192, 1900.

U.S. contribution, but by the late 1970's, the U.S. Government was by far the major contributor, providing 70 to 80 percent of the total U.S. contribution (table 23). The U.S. Government is thus the major current contributor to reproductive research and contraceptive development, providing more than 50 percent of total worldwide expenditures.

The components of worldwide total expenditures for reproductive research and contraceptive development are summarized in table 24 and figure 21. Worldwide public sector expenditures, by governments and philanthropic and nonprofit organizations, constitute about 85 to 90 percent of total expenditures (table 23). The components of these public sector expenditures are summarized in table 25. Approximately 70 percent of total funds go to basic research and training, 20 to 25 percent to contraceptive development, and less than 10 percent to safety assessments. In contrast, about 80 percent of public sector funds are spent on basic research and training, 10 to 15 percent on contraceptive development, and 10 percent on evaluation of current methods (compare tables 24 and 25). The public sector thus allocates proportionately more funding to basic research and less to contraceptive development than does the private sector.

The proportionate distribution of public sector expenditures in 1978 for contraceptive development (approximately 15 percent of total public sector expenditures) is summarized in table 26. Approximately 71 percent was spent on contraceptive methods for women, 6 percent on methods for men, and 23 percent on methods (such as sterilization) for female or male use. Of the 71 percent of expenditures on methods for women, 37 percent was spent on new approaches to use of steroids, including subdermal implants, improved oral products, injectable, and vaginal rings. Another 10 percent was spent on vaccines against pregnancy. The remaining 24 percent was spent on sterilization methods, antifertility and anti-implantation agents, intracervical and intrauterine devices, menses-inducing and abortifacient drugs, and barrier methods.

Major agencies involved in reproductive research and contraceptive development

The following organizations or scientific institutions currently either finance or conduct reproductive research and contraceptive development, largely for LDCs:

- The Center for Population Research (CPR) was established in 1968 within the National Institute of Child Health and Human Development at NIH. In turn, CPR established its Contraceptive Development Branch, which in 1979 spent about $7 million.
- The International Fertility Research Program (IFRP) was founded in 1971. It con-

Table 22.—Total Expenditures for Research in the Reproductive Sciences and Contraceptive Development, by Country of Origin, 1965 and 1969-79 (In thousands of current and constant [1970] U.S. dollars)

Country of origin[a]	1965	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979
Current dollars:												
United States	$25,928	$41,537	$55,009	$71,663	$ 79,724	$ 82,070	$ 79,104	$ 73,992	$ 82,787	$ 97,300	$104,800	$111,600
Other industrialized countries	4,886	11,992	15,267	21,126	28,811	33,039	38,029	39,176	39,720	45,600	44,200	43,200
Developing countries	208	1,017	1,186	1,694	1,689	2,321	1,590	2,385	3,329			
Total	31,022	54,546	71,462	94,483	110,224	117,430	118,723	115,553	125,836	142,800	149,000	154,800
Constant dollars:												
United States	32,010	44,188	55,009	68,906	73,819	71,991	62,287	53,232	56,318	62,300	62,400	59,500
Other industrialized countries	5,992	12,634	15,267	19,908	25,505	27,093	27,771	25,046	23,874	29,200	26,300	23,100
Developing countries	268	1,070	1,186	1,577	1,501	1,873	1,088	1,443	1,912			
Total	38,270	57,892	71,462	90,390	100,825	100,957	91,146	79,721	82,104	91,400	88,700	82,600
Percent distribution of expenditures (based on constant U.S. dollars):												
United States	83.6%	76.4%	77.0%	76.3%	72.4%	69.9%	68.3%	66.8%	68.6%	69.6%	70.3%	72.0%
Other industrialized countries	15.7	21.8	21.3	22.0	26.1	28.1	30.5	31.4	29.1	31.4	29.7	28.0
Developing countries	0.7	1.8	1.7	1.7	1.5	2.0	1.2	1.8	2.3			
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

NOTE: Totals may not add because of rounding.

[a]Countries reporting 1965-74: United States; other industrialized countries—Australia, Belgium, Canada, Denmark, Finland, France, Germany, Great Britain, Israel, Italy, the Netherlands, New Zealand, Norway and Sweden; developing countries—Africa, Egypt, Hong Kong, India, Iran, the Philippines, South Korea, Thailand and Turkey.
Countries reporting 1975-79 [data for governments other than the United States are based on 1976 estimates (e) and reports (r); United States; other industrialized countries—Australia (r), Belgium (e), Canada (r), Denmark (r), Finland (e), France (r), Germany (r), Great Britain (r), Israel (r), Italy (r), Japan (r), the Netherlands (r), New Zealand (e), Norway (r) and Sweden (r); developing countries—Africa (e), Egypt (e), Hong Kong (e), India (r), Iran (e), Latin America (r), the Philippines (e), South Korea (r), Thailand (r) and Turkey (e).

SOURCE: L. Atkinson, et al., "Prospects for Improved Contraception," *Family Planning Perspectives, 12(4),* pp. 173-192, 1980.

Table 23.—Estimated Worldwide Funding for Reproductive Biology and Contraceptive Development, 1965 and 1969-79, by Sector (in millions of constant 1970 dollars and by percent distribution)

Sector	1965	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979
United States:												
Constant dollars:												
Government	$11.4	$19.9	$25.3	$32.0	$43.3	$44.6	$38.0	$36.8	$41.4	$44.8	$45.8	$47.7
Philanthropic and nonprofit	8.2	11.1	16.8	22.6	16.9	14.2	12.7	6.2	3.8	8.5	8.3	4.4
Industry	12.4	13.2	13.0	14.3	13.7	13.3	11.7	9.9	9.5	9.0[a]	8.3[a]	7.5[a]
Total	$32.0	$44.2	$55.1	$68.9	$73.9	$72.1	$62.4	$52.9	$54.7	$62.3	$62.4	$59.6
Percent distribution[b]:												
Government	35%	45%	46%	46%	59%	62%	61%	70%	76%	72%	73%	80%
Philanthropic and nonprofit	26	25	25	33	23	20	20	12	7	14	13	7
Industry	39	30	24	21	19	18	19	19	17	14[a]	13[a]	13[a]
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
International												
Constant dollars:												
Governments	$6.2	$13.7	$16.3	$21.2	$24.7	$24.4	$23.3	$24.8	$25.8	$24.3[a]	$22.6[a]	$20.3[a]
Nonprofit	0.07	0.04	0.06	0.26	3.1	4.5	5.4	5.3	4.9	4.8	3.7	2.8
Total	$6.3	$13.7	$16.4	$21.5	$27.8	$28.9	$28.7	$30.1	$30.7	$29.1	$26.3	$23.1
Percent distribution[b]:												
Governments	98%	100%	99%	99%	89%	84%	81%	82%	84%	84%[a]	86%[a]	88%[a]
Nonprofit	2	1	1	1	11	16	19	18	16	16	14	12
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

[a]Survey data are not available for after 1976. It is assumed that expenditures remained at 1976 levels.
[b]Totals may not add up to 100 because of rounding.

SOURCE: L. Atkinson, et al., "Prospects for Improved Contraception," *Family Planning perspectives 12(4),* pp. 173-192, 1960.

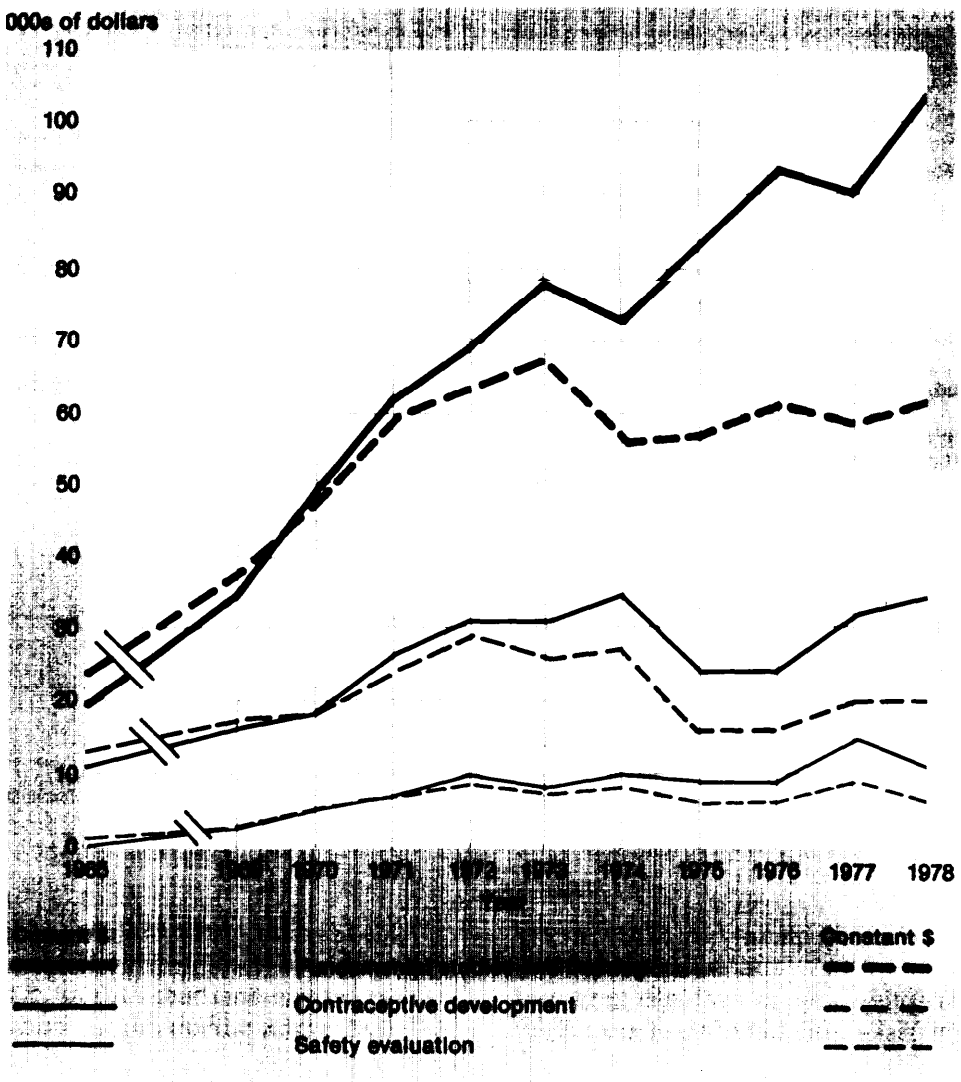
Table 24.—Percentage Distribution of Expenditures in the Reproductive Sciences and Contraceptive Development, by Purpose, 1965 and 1979-78

Purpose	1965	1989	1970	1971	1972	1973	1974	1975	1976	1977	1978
Fundamental studie/training	62.0	65.0	68.0	65.4	62.6	66.6	61.8	71.8[a]	73.8[a]	68.0	70.1
Contraceptive development	35.3	30.0	24.7	27.1	28.3	26.2	29.5	20.5	19.4	22.0	22.8
Safety	2.7	5.0	7.3	7.5	9.1	7.2	8.7	7.7	6.8	10.0	7.1
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	**100.0**

[a]Includes unclassified expenditures.

SOURCE: L. Atkinson, et al., "Prospects for Improved Contraception," *Family Planrrhrg Perspectives, 12(4),* pp. 173-192,1980

Figure 21.—Worldwide Expenditures for Fundamental Reproductive Studies and Training of Scientists, Contraceptive Development, and Evaluation of Contraceptive Safety, 1965-78 (in 000s of current and constant [1970] U.S. dollars)



SOURCE: L. Atkinson, et al., "Prospects for Improved Contraception," *Family Planning Perspectives,* 12(4), pp.173-192,1980.

Table 25.—Public-Sector Funding for Research in Reproduction and Contraception," 1969.79

Year	Annual public-sector expenditures in millions of current dollars[b] Total	Basic research training, and institutional support[c]	Contraceptive development	Research to evaluate current methods
1969	$ 42.2 (100%)	$ 35.5 (84.1%)	$ 4.0 (9.5%)	$ 2.7 (6.4%)
1970	58.6 (100%)	48.6 (82.9%)	4.8 (8.2%)	5.2 (8.9%)
1971	79.6 (100%)	61.8 (77.6%)	10.7 (13.4%)	7.1 (8.9%)
1972	95.2 (100%)	69.0 (72.5%)	16.2 (17.0%)	10.0 (10.5%)
1973	101.9 (100%)	78.2 (76.7%)	15.3 (15.0%)	8.5 (8.3%)
1974	103.6 (100%)	73.3 (70.9%)	19.9 (19.2%)	10.3 (9.9%)
1975	102.6 (100%)	83.0 (80.9%)	10.7 (10.4%)	8.9 (8.7%)
1976	111.8 (100%)	92.9 (83.1%)	10.3 (9.2%)	8.6 (7.7%)
1977	128.7 (100%)	97.1 (74.5%)	17.3 (13.4%)	14.3 (11.1%)
1978	135.0 (100%)	104.5 (77.4%)	19.9 (14.7%)	10.6 (7.9%)
1979	140.8 (100%)	NA	NA	NA

NA = Not available.
[a]Derived from *Reproduction and Human Welfare: A Challenge to Research,* R. O. Greep, M. A. Koblinsky, F. S. Jaffe, 1976, MIT Press; "Status of Funding and Costs of Reproductive Science Research and Contraceptive Development," L. Atkinson, 1979, in *Contraception: Science, Technology and Application,* National Academy of Sciences; and "Prospects for Improved Contraception," L. Atkinson, S. B. Schearer, O. Harkavy and R. Lincoln, 1980, *International Family Planning Perspectives,* vol. 6, pp. 43-59.
[b]The percentage of the year's total is indicated in parentheses after each figure.
[c]In any given year, over 90 percent is devoted to basic research and less than 10 percent to training and institutional support.

SOURCE: S. B. Schearer, "Contraceptive Development by Public Organizations: An Assessment of Progress and Problems," report prepared for the Office of Technology Assessment, 1980.

Table 26.—Percentage Distribution of Public Sector Expenditures for Development of New Contraceptive Methods, 1978

Type of method	Percent	Type of method	Percent
All female methods	71.2	Menses-inducing and abortifacient drugs	4.5
Steroidal	37.2	Barrier methods	2.2
Subdermal implants	(16.9)		
Improved oral contraceptives	(9.9)		
Injectables	(5.4)	**All male methods**	6.1
Vaginal rings	(4.4)	Systemic	5.5
Intranasal sprays	(0.5)	Reversible sterilization and improved vasectomy techniques	0.6
Vaccines against pregnancy[a]	10.1		
Sterilization	2.0		
Reversible	(0.4)	**Methods for couples and unclassified**	22.7
Nonsurgical	(1.6)	Releasing factors[a]	5.1
Antifertility and antiimplantation agents	8.3	Plant agents	3.9
Intracervical (ICD) and intrauterine (IUD) devices ..	6.9	Periodic abstinence	4.8
ICDs	(1.6)	Other and unclassified	8.9
Postpartum IUDs	(1.6)	Total	100.0
Other IUDs	(3.7)		

[a]The percentage of total expenditures for releasing factors, derived from 1978 data, is almost certainly higher because of increased interest in this line of research, while the proportion devoted to steroidal male methods and to antipregnancy vaccines has probably decreased because of problems encountered with research on these methods.

SOURCE: L. Atkinson, et al., "Prospects for Improved Contraception," *Family Planning Perspectives,* 12(4), pp. 173-192, 1980.

ducts clinical trials, mainly in LDCs, to develop and adapt new and existing methods of contraception and to evaluate long and short-term risks and benefits of use, IFRP also promotes the building of local research skills and the introduction and use of contraceptive methods. About $3.7 million of IFRP's $5.8 million annual budget is devoted

to contraceptive development. IFRP is supported by AID, NIH, and private donors (primarily the Hewlett Foundation).

- The Program for Applied Research on Fertility Regulation was established in 1972 and, through subcontracts, has established its own clinical testing network for new contraceptives. Its annual budget is about $1.9 million, approximately 90 percent of which is provided by AID.
- The International Committee for Contraception Research was founded in 1971 by the Population Council for contraceptive product development. Its $2.7 million annual budget is funded in roughly equal portions by the Rockefeller Foundation, the Ford Foundation, the International Development Research Centre (IDRC) (a Canadian Government agency), and AID.
- The Special Programme of Research, Development, and Research Training in Human Reproduction was established by WHO, a U.N. agency, in 1972. A little over $4 million of its 1979 budget of $16.9 million was allocated to applied contraceptive R&D. Other activities include developing scientific institutions and manpower in LDCs, setting scientific and technical standards, providing supplies and equipment for research, and providing information about the performance of existing family planning programs.
- The Program for the Introduction and Adaptation of Contraceptive Technology (PIACT) was founded in 1976 to serve as a bridge between the clinical researcher and the family planning program manager, and a significant part of its program effort is directed toward introducing new and improved contraceptive technologies into public sector family planning programs. It is currently helping several countries, including the People's Republic of China, establish the local capability to produce the contraceptives they require. PIACT was initially financed largely by the Ford Foundation. About 50 percent of its 1981 budget of over $4 million is provided by UNFPA, approximately 15 percent by IDRC, approximately 30 percent by American private foundations (primarily the Ford Foundation, the Andrew W. Mellon Foundation, and the Hewlett Foundation), and the remainder from other sources.

Factors affecting reproductive research and contraceptive development

Availability of R&D funds from public sector sources

Government agencies now provide most of the funds for reproductive research and contraceptive development. The U.S. Government provides over 50 percent of worldwide funds; other nations contribute about 25 percent (table 27). Philanthropic institutions, nonprofit organizations, and industry provide the remaining 25 percent in roughly equal proportions. Support from U.S.-based philanthropic and nonprofit organizations peaked in 1971-72, while nonprofit organizations in other countries have increased their contributions since that time (table 23). Industry's contributions have remained fairly stable, but its share of total funding has decreased from about 20 to 10 percent (table 27) while government contributions have increased.

Public sector funding has historically been largely devoted to basic research and training. Because funds from these sources increased from about two-thirds of the worldwide total in 1965 to about 90 percent in the late 1970's, funds for this purpose were adequate to keep pace with inflation. However, funds for contraceptive development did not increase enough to offset inflation. Funds for research on safety and other evaluations of current methods rose to about 10 percent of expenditures by 1972

Table 27.—Estimated Worldwide Funding for Reproductive Biology and Contraceptive Development, 1965 and 1969=79, by Sector (in millions of constant dollars and by percent distribution)

Sector	1965	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979
Constant dollars:												
U.S. Government	$11.4	$19.9	$25.3	$32.0	$ 43.3	$44.6	$38.0	$36.8	$41.4	$44.8	$45.8	$47.7
Other nations	6.2	13.7	16.3	21.2	24.7	24.4	23.3	24.8	25.8	24.3[a]	22.6[a]	20.3[a]
Philanthropic and nonprofit	8.3	11.1	16.9	22.9	20.0	19.7	18.1	11.5	8.7	13.3	12.0	7.2
Industry	12.4	13.2	13.0	14.3	13.7	13.3	11.7	9.9	9.5	9.0[a]	8.3[a]	7.5[a]
Total	$38.3	$57.9	$71.5	$90.4	$101.7	$101.0	$91.1	$93.0	$85.4	$91.4	$88.7	$82.7
Percent distribution[b]:												
U.S. Government	30%	34%	35%	35%	43%	44%	42%	40%	48%	49%	52%	58%
Other nations	16	24	23	23	24	24	26	27	30	27[a]	25[a]	25[a]
Philanthropic and nonprofit	22	19	24	25	20	20	20	12	10	15	14	9
Industry	32	23	18	16	13	13	13	11	11	10[a]	9[a]	9[a]
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

[a]Survey data are not available for after 1976. It is assumed that expenditures remained at 1976 levels.
[b]Totals may not add up to 100 because of rounding.

SOURCE: L. Atkinson, et al., "Prospects for Improved Contraception," Family Planning Perspectives, 12(4), pp. 173–192, 1980.

and have remained at approximately that level (see fig. 21).

Basic research is primarily investigator-initiated and administered through grants. The research enterprise has historically emphasized investigator-initiated research, and this emphasis is likely to continue. Contraceptive development and safety and other evaluations of current methods are goal-oriented and usually administered through contracts. In addition, concerns over the safety of drugs and medical devices—concerns that are especially acute in the contraceptive field—translate to pressures to increase safety testing. Contraceptive development thus faces competition for funds not only from basic research activities but also from the burgeoning field of safety assessment.

Government research agencies stimulate private sector initiatives in contraceptive development in two ways. First, they support basic research projects in academic and other nonprofit research institutions. Private firms can then incorporate these research findings into their product development activities. This avenue has recently been enhanced by a new patent law (Public Law 96-517), which contains more liberal provisions for the transfer of patent rights arising from inventions sponsored by the Government. This law creates a uniform set of procedures by which small businesses can gain licenses to develop federally sponsored inventions to which the Government retains title but that were previously left undeveloped. The new law seeks to: 1) use the patent system to promote the utilization of inventions arising from federally sponsored research; 2) encourage maximum participation of small business firms; 3) promote collaboration between commercial concerns and nonprofit organizations (including universities); 4) ensure that inventions made by nonprofit organizations are used to promote competition and free enterprise; (5) promote the commercialization and public availability of inventions made in the United States by U.S. industries and labor; 6) retain by the Government sufficient rights to protect the public against nonuse or nonreasonable use of inventions; and 7) minimize the cost of administering policies in this area.

Second, Federal agencies can directly finance selected research projects that normally would be financed by the industry itself. For example, the National Cancer Institute will conduct animal toxicity tests and clinical trials of anticancer drugs developed by the industry. This is also true for vaccines. The National Institute of Allergy and Infectious Diseases will finance basic and epidemiologic research, as well as clinical trials, to stimulate vaccine manufacturers to develop and market new vaccines (10).

The agency within NIH that finances contraceptive development is CPR in the National

Institute of Child Health and Human Development. In 1979, CPR's Contraceptive Development Branch (CDB) spent about $7 million, about 14 percent of CPR's research budget. Currently, CDB is helping the industry develop three contraceptives (3). For the past 6 years, CDB has jointly financed long-term animal toxicity tests and clinical trials of norethindrone enanthate with Schering A. G., a German pharmaceutical company. CDB will probably continue to help finance clinical testing of this drug through completion of the new drug application (NDA) process. For 3 years, CDB, Alza Pharmaceutical, and WHO have jointly financed the development of a biodegradable implant of a progestin-type contraceptive. CDB began financing a joint effort with Syntex pharmaceutical company in June 1980 to conduct early animal toxicity tests and clinical trials with a luteinizing-releasing factor agonist.

The market approval process

Before U.S.-manufactured drugs and medical devices can be marketed, they must meet the minimum standards of safety and effectiveness established by Congress through a series of legislative actions. The principal laws are:

- The 1906 Food and Drug Act;
- The 1938 Food, Drug, and Cosmetic Act;
- The 1962 Drug Amendments; and
- The 1976 Medical Devices Amendment.

The interpretation of these laws and the enforcement of the standards set are the responsibility of the FDA.

Although postmarketing surveillance is also conducted, U.S. laws are designed to screen drugs and medical devices before they are used by the public, so premarket testing is used to predict whether or not significant harm could occur with human use. FDA regulations thus emphasize the use of predictive methods which, given the state of current scientific knowledge, depend heavily on tests in laboratory animals.

The issues concerning the market approval process and its effect on contraceptive development are generic to FDA's role in the regulation of drugs and medical devices in general, but these issues are especially sensitive in the contraceptive area.

TESTING METHODS

FDA regulations specify the kind and length of tests that must be completed for market approval. Testing requirements for oral contraceptives are more stringent than for other types of drugs because they are used for long periods by healthy individuals rather than by individuals with disease. Table 28 summarizes the animal tests that must be completed before testing in humans can take place and an NDA is submitted. In each phase of testing, the regulations require longer testing periods and more animal species for oral contraceptives than for other drugs: 90-day studies in rats, dogs, and monkeys, v. 2- to 4-week studies in two animal species prior to Phase I; l-year studies in rats, dogs, and monkeys v. 90-day studies in two animal species prior to Phase II; 2-year studies in rats, dogs, and monkeys, and initiating 7-year

Table 28.—Preclinical and Clinical Requirements for Oral Contraceptives in the United States

Phase 1:	**Ninety-day studies in rats, dogs, and monkeys must be completed prior to Phase I studies, which involve 10-20 individuals for up to 10 days. (For other drugs, Phase I studies can be initiated after 2-4 week studies *in* two animal species.)**
Phase 11:	**One-year studies in rats, dogs, and monkeys must be completed prior to Phase II studies, which involve approximately 50 women for three menstrual cycles. (For other drugs, Phase II studies can be initiated after W-day studies in two animal species.)**
Phase III:	**Two-year studies in rats, dogs, and monkeys must be completed and 7-year dog and 10-year monkey studies must be initiated before Phase Ill testing may begin.**
Market ing approval:	**Progress reports on long-term studies in dogs and monkeys are required at the time of new drug application (NDA) submission. (For other drugs, chronic toxicity studies—including l-year dog, 18-month mouse, and 2-year rat studies—must be completed by the time of NDA submission.)**

SOURCES: M. Finkel: "Contraceptive Regulation in the U.S.," paper presented at the PIACT Workshop on Developing Countries and the Regulation of Contraceptive Drugs and Devices, Seattle, Wash., July 24, 1978; E. 1. Goldenthal, "Current Views on Safety Evaluation of Drugs," FDA *Papers,* May 1988, pp. 13-18; E. 1. Goldenthal, "Contraceptives, Estrogens, and Progestogens: A New FDA Policy on Animal Studies," *FDA Papers,* November 1969, p. 15.

dog and 10-year monkey studies v. l-year dog, 18-month mouse, and 2-year rat studies before an NDA can be submitted.

FDA regulations also require that the beagle be the breed of dog used to test oral contraceptives for safety. This requirement has raised the most controversy, because the appearance of breast tumors in beagles when given depot medroxyprogesterone acetate (Depo-Provera) was one of the reasons why the FDA denied Upjohn Co.'s supplemental NDA in 1978.

The reasons given for FDA's nonapproval included more than the appearance of breast tumors in beagle dogs. The complete list of reasons was:

- malignant breast tumors in beagle dogs;
- estrogen may be administered to women receiving Depo-Provera in order to control the irregular bleeding disturbances often caused by this drug. In FDA's opinion, the added risk of cancer from the simultaneous use limited the benefits that might be associated with a progestin-only contraceptive;
- the patient population originally targeted for Depo-Provera had diminished substantially as other methods of contraception and sterilization became increasingly available and accepted;
- doubts that the proposed postmarketing studies on breast and cervical carcinomas would yield meaningful data; and
- progestin and estrogen-progestin drugs increase the risk of congenital abnormalities in the fetus. Depo-Provera is a progestin, and a failure of contraception or an error made by injecting a woman already pregnant would result in exposure of the fetus to this hormone (9).

Depo-Provera is currently approved for use in the United States only for inoperable cancer of the uterus and renal cancer, a use approved since 1972. It is manufactured and used as an injectable contraceptive in other countries. Drugs produced abroad for use abroad are beyond FDA's regulatory reach.

Contraceptive drugs are given to young, healthy individuals and can potentially be administered over a period of 30 years. FDA requires testing in both the beagle and the monkey because the beagle is highly susceptible to spontaneous breast tumors, the monkey is relatively resistant, and the human female falls between the beagle and the monkey in the incidence of spontaneous breast tumors. FDA also points out that no contraceptive currently approved for marketing has shown a carcinogenic potential in the beagle dog assay similar to Depo-Provera (14).

In contrast, other internationally recognized agencies have taken the position that the beagle dog is not predictive of any risk of breast cancer in women using steroid hormones. These agencies include the Special Programme of Research, Development, and Research Training in Human Reproduction of WHO (october 1978); the Committee on the Safety of Medicines in the United Kingdom (February 1979); and the International Planned Parenthood Federation (IPPF) (November 1980). In addition, a recent review of Depo-Provera concluded that "a great deal of human data have been collected and these show no evidence of human risk at present" (7).

The Depo-Provera issue has focused much attention on the beagle dog, but this specific controversy should be viewed in its broader context. Safety testing for contraceptives is understandably more stringent than for other drugs in both the length of testing required and in the kinds of laboratory animals subjected to testing. Both requirements increase the time and expense incurred in contraceptive product development compared with product development for drugs in general.

EXPORT OF DRUGS AND MEDICAL DEVICES

A large, expanding market for contraceptives no longer exists in the United States but does in the LDCs, where large percentages of people are either in their reproductive years or about to enter them.

In general, the U.S. Food, Drug, and Cosmetic Act prohibits U.S. pharmaceutical manufacturers from exporting drugs not approved for marketing in the United States. Two categories

of drugs are at issue: 1) drugs unevaluated for use; and 2) drugs evaluated but found unacceptable for use. A few exceptions to this provision exist; e.g., investigational drugs can be exported for investigational purposes, provided that an importing country's government has approved such imports.

Medical devices that are not approved for marketing in the United States can be exported, provided: 1) they conform to the laws and specifications of the importing country; and 2) their export is not considered by the Secretary of Health and Human Services to be contrary to the public health and safety of the importing country.

Changes in the export provision of non-FDA approved drugs have been considered by Congress. In the 96th Congress, a bill adopting the medical devices export law for drugs passed the Senate but died in the House of Representatives.

The U.S. Government's policy of prohibiting the export of non-FDA approved drugs is based on safety and efficacy concerns. FDA recognizes that different standards may exist elsewhere but does not know which ones to apply when U.S. standards are not met, Some importing countries also do not have mechanisms to either evaluate or regulate the quality of drugs they import (18), so the United States is unable to defer to or apply these standards. There are also documented episodes of "drug dumping;" i.e., situations in which drug companies promote products in LDCs deemed unsafe or ineffective in more developed countries (MDCs), The analgesic drug Dipyrone, for example, was removed from the U.S. market because of its documented toxicity, yet it is marketed over-the-counter in several Central and South American countries (4). In addition, substantial differences in product labeling—e,g., indications for use and precautions—have been noted for selected products marketed in different countries (15), but attempts to develop international uniform labeling standards have been only partially successful.

Those who advocate exportation of drugs unapproved in the United States base their arguments on the right of a country to make its own risk/benefit analyses, differing risk/benefit ratios in other countries, and economic concerns.

The belief that an importing country has a right to assess the risk/benefit ratio for a drug's use among its people is consistent with the international legal principle of comity, which states that countries have a duty to respect the sovereign rights of other nations. Further, because of international variatio~s in life expectancy, standards of living, prevalence of diseases, and availability of health care, the relative risks and benefits of a given drug are different among different populations.

In order to market products unapproved in the United States, several American pharmaceutical companies have either established, purchased, or used manufacturing facilities in foreign countries, where their products are either approved for use or where laws permit the export of unapproved products. Some U.S. manufacturers argue that if they were able to export their nonapproved products from the United States, they would manufacture such products in this country rather than abroad. They further argue that such manufacturing would contribute to the U.S. economy (in terms of capital formation and employment) and thus help improve the United States' international balance of payments.

The Depo-Provera controversy has also contributed to this debate over current law on the exportation of drugs not approved for use in the United States. Because it is approved for U.S. use for the treatment of endometrial and renal cancer but not for use as a contraceptive, Depo-Provera manufactured in the United States cannot be exported as a contraceptive. But it is manufactured abroad, and in 1977 was in use in 42 countries (13).

AID has received requests from LDCs for financial assistance to purchase Depo-Provera for contraceptive purposes. But AID's usual position has been to refrain from providing other countries with drugs not approved by the FDA for use in the United States. A panel of external advisors to AID recommended in 1980 that the agency make Depo-Provera available to those nations that request it for contraceptive

use, despite FDA's nonapproval (17). In October 1981, FDA had chosen the members of a Public Board of Inquiry to evaluate the findings on Depo-Provera; AID is awaiting the Board's recommendations. However, AID does help finance UNFPA and IPPF, both of which purchase Depo-Provera. Because UNFPA commingles its funds, money from a particular donor cannot be earmarked for specific uses. IPPF, however, itemizes its expenditures by donor so that AID is assured that its funds are not used for purchasing Depo-Provera.

Here again, as with the case of the beagle dog findings for Depo-Provera's carcinogenic potential, the specific controversy surrounding the ban on export of U.S.-manufactured Depo-Provera for contraceptive use should be viewed in its broader context. That is, it should be taken as illustrating, and not controlling, the difficult issues surrounding current U.S. policy on the exportation of U.S.-manufactured drugs.

Patent life

Drug patents run for 17 years, but the industry has expressed concern that the FDA market approval process takes so long–an average of **71/2 years**—that effective patent life is shortened and too little time is left for them to recoup their investments (6). Patent life could be legislatively extended beyond the current 17-year limit, or effective patent life could be lengthened if the FDA approval process were shortened. How significantly does the shortening of effective patent life diminish incentives to research and develop new contraceptives?

The first company that puts a product on the market has the advantage of capturing a larger proportion of potential users than a company entering the market later. Its initial investment is also greater, since it must underwrite the research costs. Once its patent runs out, if other companies then enter the market and manage to cut into its sales, its return on investment is diminished.

In the field of oral contraceptives, Wyeth Laboratories and Ortho Pharmaceutical share approximately 70 to 80 percent of the market in the United States. Wyeth's patent on norgestrel is still in effect, but the patent on norethindrone (the progestin in the products marketed by Ortho, Syntex, Parke-Davis, and Mead-Johnson) expired in 1973. After the expiration of the patent on norethindrone, only Mead-Johnson and Lederle entered the market with oral contraceptives. Even though competitive pricing was utilized by these companies, they did not capture a substantial share of the market, and Lederle subsequently withdrew. No generic pharmaceutical house has entered the market.

The Pharmaceutical Manufacturers Association (PMA) reported in August 1980 that of all classes of pharmaceuticals, oral contraceptives experienced the greatest increases in price for the reporting periods 1969-79 (187 percent) and 1978-79 (23.7 percent). In contrast, for over 1,000 ethical drugs, PMA reports only a 37.4-percent average increase in price for the period 1969-79 and a 6.5-percent increase for 1978-79. Attractive profits would be expected from such price increases and would be expected to lead to price competition or the entry of new competitors. But these price increases occurred primarily after the patents on norethindrone and norethynodrel (Searle's progestin) had expired and during Mead-Johnson's and Lederle's entries into the oral contraceptive market.

PMA estimates that between 8 and 9 million women in the United States now use oral contraceptives, and a substantial number of women (between 500,000 and 1 million) currently initiate use of oral contraceptives each year. But because the U.S. birth rate is close to replacement level, the U.S. market is relatively static as new users of oral contraceptives replace those aging beyond the reproductive years and those who discontinue use for other reasons. Thus, pharmaceutical companies that seek to market generic versions of brand name contraceptives after patents expire must compete in a limited market, with high advertising costs the probable entry price.

Oral contraceptives have also had difficult product liability problems. These contribute to uncertainties in business profit/loss projections and project a negative image that may affect the public's confidence in a pharmaceutical com-

pany's other products as well as in its contraceptive products. The ability of the original oral contraceptive manufacturers to retain their market share and raise prices significantly despite expired patents may not be completely explained by a limited U.S. market and the negative image that may be keeping other pharmaceutical companies out of the field. However, this ability to keep the market captive in the face of patent expiration and rising prices does lead to the conclusion that, at least for the oral contraceptive market, initial entry into the market seems to be the determining factor, not the length of patent life as affected by the FDA market approval process.

Product liability

Product liability, its costs to business, and possible inhibition of new product development have been prominent issues in recent years. While not limited to the pharmaceutical and medical devices industries, its most visible impacts have been through the national swine flu immunization program of 1976 and in lawsuits involving the hormone diethylstilbestrol (DES), oral contraceptives, and intrauterine devices (IUDs).

Product liability problems, and the ability of manufacturers to pass on their insurance and litigation costs to purchasers, may affect the kinds of future contraceptives developed. Products that involve a single sale or limited repurchase, such as IUDs, provide little means to adjust for increasing liability exposure once the device is sold. Oral contraceptives, on the other hand, require periodic purchases. A. H. Robins ceased selling its Dalkon Shield IUD in 1974, and in 1980 some of the devices were still in place, so some users maintained the device in place for at least 6 years. An oral contraceptive would have required repeated purchases during that period of time, and the price of the monthly dose package could have been adjusted to reflect changing product liability risks. Or if the sale of the contraceptive had been terminated, existing supplies of the contraceptive would have been disposed of or consumed.

Although oral contraceptives represent only about 4 percent of the total ethical pharmaceutical market, more suits are filed on oral contraceptives per year than on any other class of ethical pharmaceutical products. Several manufacturers of oral contraceptives reported to OTA that they have more product liability claims for contraceptives than for all of their other pharmaceutical products combined.

Injuries from these causes do not usually result from negligence in their manufacture, distribution, or administration, but rather are statistically rare injuries that will inevitably occur in a few people. In legal parlance, these are "unavoidably dangerous" though socially useful products, and the U.S. courts have developed many legal doctrines as possible avenues through which the injured person might obtain compensation for the injuries suffered. That is, rather than leaving the economic burden of the injury on the injured persons, courts have tried to shift the economic loss to the "deep pockets" of the product manufacturers; for example, by imposing a "duty to warn" of serious side effects on the manufacturer and developing a test of whether the product user had given his/her "informed consent" to use the product after being warned of the possible side effects that could occur with use. But legally adequate "duty to warn" and "informed consent" do not avoid injury. Successfully meeting both tests simply means that the already injured plaintiff will fail in the lawsuit.

Product liability is part of business costs for manufacturers and has traditionally been covered by insurance. Expansion of product liability has led to uncertainties in pricing such insurance, which in turn has led insurance companies to treat such products as special risks or to move out of the market, leaving manufacturers to self-insure such losses by pooling funds among several manufacturers or by establishing "captive" insurance companies. These product liability and insurance problems have been examined in a previous OTA report, "A Review of Selected Federal Vaccine and Immunization Policies" (11). One result of that report

was a request by Congress to enumerate the elements that would constitute a Federal compensation program for injuries caused by vaccines. That report, "Compensation for Vaccine-Related Injuries," was released in November 1980.

Does product liability have an inhibitory effect on the propensity of the pharmaceutical industry to research and develop new contraceptives, to continue to produce proven contraceptives, and to enter established markets after the developer's patent has expired? These are difficult questions to answer for the contraceptive products field in isolation from what is happening in product liability in general (e.g., football helmet manufacturers) and in liability per se (e.g., professional malpractice, whether in medicine, law, engineering, the clergy, etc.), but the evidence does point to an inhibitory effect. Whether product liability does or will fundamentally affect the contraceptive field is speculative, but the following findings indicate that it is a significant problem.

product liability and the adverse publicity that attaches to a specific product can affect contraceptive development and use in two ways. First, product liability affects the predictability of business expenses and what profit margins can be expected. If these costs are predictable, the product's price can be adjusted. If not, the manufacturer cannot limit its exposure except by taking the product off the market. In addition, however, such costs may become so large that they affect the price to the extent that demand may be depressed. And adverse publicity about a specific contraceptive may: 1) turn consumers to other contraceptives (which would be justified if the information is correct; i.e., market forces and "informed consent" would be working appropriately); and 2) affect the manufacturer's decision on what kinds of contraceptives to develop and continue to sell (e.g., oral v. injectable contraceptives, IUDs v. oral contraceptives).

Predictability and the spreading of costs are fundamental insurance tenets. But two developments have affected their stability in recent years. Lawsuits are usually filed and contested in State courts, whose supreme courts develop and follow their own legal doctrines. However, a State's supreme court may adopt the doctrine of another State, and it is difficult to predict when and if this will happen.

Recently, the California Supreme Court (16) decided that an injured party who does not know which manufacturer made the product that led to the injury can sue any of those who act in '(conscious parallelism" and who may have produced the drug used by the patient. The plaintiff had developed cancer alleged to be caused by the hormone DES, taken by her mother 26 years earlier to prevent a miscarriage. No evidence existed as to which of the defendant companies manufactured the DES used by the mother. More than 200 companies manufactured DES at that time. Michigan has reached a similar result but on different legal reasons (l).

The variance in damages for a successful lawsuit may literally be millions of dollars. Spokespersons for manufacturers of oral contraceptives estimate that most jury verdicts for death or severe injury range from $100,000 to $4 million, and a suit involving its Dalkon Shield IUD resulted in a $6.2 million verdict against A. H. Robins.

In addition to judgment costs, there are administrative costs of handling claims, the great majority of which never reach the courtroom stage. For instance, A. H. Robins marketed its Dalkon Shield IUD from 1970 to 1974 and sold approximately 2 million. According to Robins, the first reports of problems (septic abortions) occurred in late 1973. As of September 30, 1980, there had been 4,660 claims filed against Robins, with 1,482 pending and 3,178 closed. Total settlements and judgments paid were $69 million, and Robins estimates its legal fees and expenses to be about $20 million, or a total of about $45 (and still growing) for each IUD sold. Robins was receiving 100 claims per month at the end of 1980, Robins' insurer increased premiums and deductibles for IUD coverage to the extent that Robins rejected the policy in 1978. Robins found that its loss record on the Dalkon Shield prejudiced its ability to obtain coverage on other pharmaceutical products. In order to

obtain product liability insurance on other pharmaceutical products, Robins had to pay a $1.4 million **surcharge (8).**

These escalations in the scope of liability costs have had two effects: raising the price of contraceptives that have remained on the market, and leading insurers to treat contraceptives as special risks. For example, one oral contraceptive manufacturer estimated that product liability expenses for a 20- to 30-percent share of the market have totaled about $15 million for the past 10 years and have been escalating at about $3 million to $4 million per year. Another oral contraceptive manufacturer estimates that 10 percent of its sale price is earmarked for product liability claims (10).

As for contraceptives as special risks, standard product liability policies for pharmaceuticals now specifically exclude only four types of products—swine flu vaccines, DES, oral contraceptives, and IUDs. Also, insurance usually comes in a trifurcated form—a deductible, the standard policy, and excess insurance—and these components have changed. For example, the deductible may have been several hundred thousand dollars, the basic policy for the next $5 million to $15 million, and the excess insurance up to a specific limit; e.g., $25 million to $30 million. This excess insurance would be provided at a separate premium, either through a pool of several insurance companies to spread the risk, or through a high-risk insurer such as Lloyd's of London. Today, the self-insurance requirement may be up to $5 million, the premium itself for the standard policy in the millions, and the excess insurance either not available or with a premium in the million-dollar range.

Organizations supporting R&D of contraceptive products are not immune to liability. For instance, the Ford Foundation and the Population Council both carry liability insurance. Even though such organizations may not manufacture or sell contraceptives in the United States, the fact that a contraceptive product that causes harm was developed under their support could subject them to liability.

The developer of a new contraceptive product also bears the risk of liability during clinical trials. The standards for liability are in general more varied with respect to clinical trials and often the doctrine of product liability does not apply. Uncertainties nevertheless exist. While many developers of pharmaceuticals and medical devices have asserted in an OTA telephone survey that they have had no liability problems in clinical trials, there have been reports of difficulties for contractors and developers in obtaining affordable and meaningful insurance.

Liability problems arise when the research is sponsored at institutions that do not belong to the pharmaceutical industry (3). The cost of liability insurance is included in contracts when necessary, but it is expensive and difficult to obtain. WHO has reported difficulty in securing contractors for clinical trials because insurance was not available to the contractor. In at least one instance, a potential NIH contractor could not procure adequate liability insurance for a phase I clinical trial. In another NIH-funded phase I clinical trial, the insurance for a 1-month, 12-woman study was in the neighborhood of $30,000, and the policy required considerable amounts of time and effort to procure.

There are clear indications that current product liability in the contraceptive field is more severe than for other classes of products, has raised costs, and is severe enough in cost escalation and unpredictability to have affected the insurance companies' way of doing business with pharmaceutical manufacturers. This situation is conducive to diminished interest in future contraceptive research by profitmaking companies. In addition, liability insurance in the clinical trial phase of development has become expensive and sometimes hard to obtain, thereby adding to developmental costs and, because of difficulty in purchasing such insurance, imposing another impediment to the developmental process.

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