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PROGRAMME ON THE PRODUCTION OF CONTRACEPTIVES IN DEVELOPING COUNTRIES

A techno-economic decision-preparatory study

Agreement No. CLT 95/105

Final Draft Report

Based on the work of Dr. László Szporny
expert in pharmaceutical industry research and development

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Chemical Industries Branch

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ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
CONRAD	Contraceptive Research and Development Programme
CPR/NICHD	Center for Population Research, National Institute for Child Health and Human Development
DMPA	Depot medroxyprogesterone acetate (Depo Provera)
ED	Effective dose
EE	Ethynil estradiol
FHI	Family Health International
FSH	Follicle Stimulating Hormone
GMP	Good Manufacturing Practices
GnRH	Gonadotropine-releasing hormone
hCG	Human Chorionic Gonadotropin
HIV	Human immunodeficiency virus
IUD	Intrauterine Device
ICMER	Instituto Chileno de Medicina Reproductiva
ICMR	Indian Council of Medical Research
INII	Indian National Institute of Immunology
IOCD	International Organization of Chemical Synthesis and Development
IRH	Institute of Reproduction Health

LAM	Lactational amenorrhea method
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
MCA	Methyl cyanoacrylate
MEL/NET	Melatonin and norethindrone
PATH	Programme for Appropriate Technology in Health
QA	Quality assurance
RTI	Research Triangle Institute
UNFPA	United Nations Population Funds
WHO/HRP	World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction
STD	Sexually transmitted diseases
UNIDO	United Nations Industrial Development Organization
WHO	World Health Organization

EXECUTIVE SUMMARY

5 pages

1. INTRODUCTION

The principal objective of the study is to translate the Resolutions and Programs of the International Conference on Population and Development held in Cairo 5-13 September into an UNIDO program.

Industrial development using new biomedical and pharmaceutical methods has been instrumental in giving more and more access to a greater range of safe and effective modern methods for regulating fertility.

The growing incidence of sexually transmitted diseases, including HIV/AIDS, demands substantially higher investments in new methods of prevention, diagnosis and treatment. Increased support is needed to bring a safe and affordable method of implementation.

Furthermore, a proposal for a new methodology for implementing the activities of the Pharmaceutical Industries Unit in the field of family planning needs to be worked out.

This study is based partly on literature search and partly on the several decades of experience of the author in research, development and international marketing of steroid contraceptives. Additional information was obtained from UNIDO project documents and technical reports.

2. GLOBAL DEMAND FOR CONTRACEPTIVES

2.1 Factors Affecting Demand

2.1.1 Contraceptive Methods

Table 2.1 Percentage distribution of contraceptive users by method in industrialized and developing countries in 1989

Method	Industrial countries	Developing countries	World
Female sterilization	10	33	26
Male sterilization	5	12	10
IUD	8	24	19
Hormonal pills	20	12	15
Condom	19	6	10
Hormonal injections	0	2	1
Vaginal barrier methods	3	1	2
Rhythm	13	5	7
Withdrawal	20	3	8
Other methods	2	3	2

The data in the table 2.1 suggest that women assume responsibility for about 72 percent of contraceptive use in comparison with men's 28 percent.

The modern methods of contraception -male and female sterilization, IUDs, the pill, injections, condoms and female barrier methods- accounted for approximately 83 per cent of contraceptive practices worldwide. Other methods include abstinence, douching and various folk practices.

There are significant differences between developing and industrialized countries as regards the choice of contraceptive methods. Of the modern methods, both female and male sterilization as well as IUDs prevail in developing countries while the pill and condom is more popular in industrialized countries.

Table 9. Estimated sources of supply of modern methods of contraception in developing countries, by method and by region, 1994 (percentage)

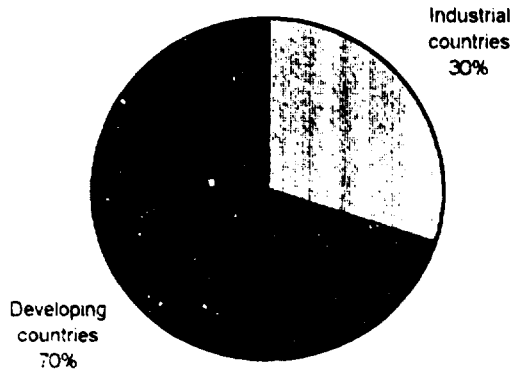
Source	Modern	Sterilization	Pill	Injection	IUD	Condom
Total						
Government	86.3	95	56.7	66.8	94.4	47.1
Private	13.7	5	43.3	33.2	5.6	52.9
Pharmacy	4.1	0	32.7	5.8	0.2	40.7
NGO	0.6	0.5	0.8	0.5	0.5	0.4
Other	9.1	4.5	9.8	26.9	5	11.8
Sub-Saharan Africa						
Government	65	53.2	67.4	81.3	62.9	35.5
Private	35	48	32.6	18.7	37.1	64.5
Pharmacy	4.3	0	7.1	0.3	0	18.6
NGO	3.2	0.6	3.4	2	5.5	3.4
Other	27.4	46.3	22.1	16.4	31.6	42.5
Arab States and Europe						
Government	42.5	82.3	32.6	47.9	49.8	22.2
Private	57.5	17.7	67.4	52.1	50.2	77.8
Pharmacy	31.6	0	62.3	6.8	2.7	72.9
NGO	0.7	0	0.9	2.7	0.9	0.1
Other	25.2	17.7	4.2	42.5	46.6	4.8
Latin America and Carribean						
Government	38.2	58.7	12.6	17.1	58.3	18.4
Private	61.8	41.3	87.4	82.9	41.7	81.6
Pharmacy	33.3	0	82.7	71.6	1.3	71.7
NGO	5.4	6.6	1.5	1.1	11.1	2.4
Other	23.1	34.8	3.2	10.2	29.3	7.4
Asia and the Pacific						
Government	93	98.4	79	68.9	98.3	50.7
Private	7	1.6	21	31.1	1.7	49.3
Pharmacy	0.3	0	8.6	0.2	0	37.3
NGO	0.1	0	0.2	0.1	0	0.2
Other	6.7	1.6	12.2	30.8	1.7	11.8

Notes: IUD = Intra-uterine device. NGO = Non-governmental organization.

Industrial countries	30
Developing countries	70

Industrial countries	84
Developing countries	16

Consumers of Contraceptives



Revenues from Contraceptive Markets

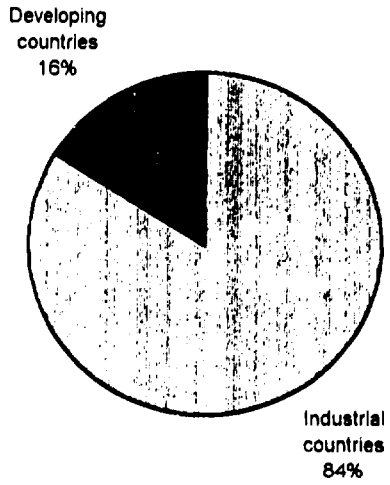


Table 2.2 Number of contraceptive users worldwide, by method, 1994-1995 (Numbers in millions)

	Sterilization				Inject-		Con-		
Year	All	Female	Male	Pill	ion	IUD	dom	Other	Total
1994	233,600	183,300	50,300	92,100	11,900	127,200	51,500	79,000	595,300
1995	239,200	188,200	50,900	94,700	12,600	123,000	52,300	82,100	603,900

Table 2.3 Contraceptive demand in developing countries, by method, 1994-1995 (Numbers in thousands)

	Sterilization				Inject-		
Year	All	Female	Male	Pill	ion	IUD	Condom
1994	14,200	11,400	2,800	819,900	56,900	32,300	3,791,300
1995	14,600	11,800	2,800	857,400	60,100	33,100	3,945,400

Table 2.3 reveals that about 820 million women used the pill in 1994, 57 million opted for contraceptive injection and 32 million chose the IUD. The global demand for condoms was close to 3.8 trillion.

2.1.2 Contraceptive Users

The contraception market is largest in developing countries, where the majority of contraceptive users live. The contraceptive market in industrialized countries is relatively small in terms of users.

Table 2.4 Global population by sex, women of 15 to 49 years of age and MWRA, 1994-1995 (numbers in thousands)

	Population				
Year	Total	Female	Male	Women 15-49	MWRA
1994	5,646,200	2,842,790	2,803,400	1,415,800	976,700
1995	5,738,800	2,889,700	2,849,100	1,440,700	996,500

Table 2.5 shows that at present there are about 446 million contraceptive users among married women, including those who live in union with a man, in developing countries: 57% of MWRA.

Table 2.5 Contraceptive use by married women in developing countries, by method, 1994-1995 (numbers in thousands)

	Sterilization				Inject-		Con-		
Year	All	Female	Male	Pill	ion	IUD	dom	Other	Total
1994	200,100	161,100	39,000	51,400	10,500	112,100	24,800	46,800	445,700
1995	206,000	166,000	40,000	53,600	11,100	114,800	25,800	49,400	460,700

Of the 446 million contraceptive users among married women in developing countries, 399 million - almost 90% - use modern methods. A little more than 10 % of the total use traditional methods. Of all users of modern methods about 80% use clinical methods and 20% use supply methods (pills and condoms). Of the modern methods 5% are methods for females. Almost half of the population in Asia are contraceptive users and 26% in Latin America, but only 3% in Sub-Saharan Africa and 2% in the Arab States and Europe.

Fertility in Europe and North America has declined gradually, and has reached very low levels, in some places below replacement fertility. In the US, it took 58 years for fertility to decline from 6.5 to 3.8 births per women. The same level of decline took 27 years in Indonesia, 15 years in Colombia, 8 years in Thailand and 7 years in China.

2.1.3 Contraceptive Prevalence

Table 2.6 Contraceptive prevalence among MWRA in developing countries by region (percentage of users)

Region	1960 - 1965	1985 - 1990
Africa	5	0.1
East Asia	13	70
South Asia	7	40
Latin America	14	60
All developing countries	9	51

Source: UNFPA 1991

Contraceptive prevalence has increased in developing countries only in the past few decades and has depended primarily on breakthrough contraceptive technologies.

Industrialized countries are characterized by higher contraceptive prevalence rates than developing countries. However, contraceptive prevalence is increasing in developing countries whereas the trend in industrialized countries is stagnating or even decreasing.

2.1.4 Cost of Commodities

The cost of commodities may vary greatly, depending upon when the commodities are purchased, the volume of each purchase, and packaging and shipping. The figures shown here are estimated average figures. To cover delivery to the port of entry, they include an allowance of 15% added to the "Free on Board" (FOB) price of the goods.

Condom	$ 0.0278 per piece
Pills	$ 0.20 per cycle
Injections:	
Depo-provera	$ 0.92 + 0.05 for needles, spring and swabs
Noristerat	$ 1.00 + 0.05 for needles, spring and swabs
IUDs - TG 380 A	$ 0.74 + 0.94 for equipment and supplies used for insertions
Sterilization	$10,375 for procedure
NORPLANT'	$26.45 for set of implants + 5.23 for equipment and supplies.

Table 2.7 Cost of contraceptive commodities for developing countries, if purchased on the international market, by method, 1994-1995 (1994 USD)

	Sterilization				Inject-		Con-	
Year	All	Female	Male	Pill	ion	IUD	dom	Total
1994	147,100	118,600	28,400	164,000	57,400	54,300	105,300	528,100
1995	151,400	122,200	29,100	171,500	60,700	55,600	109,600	548,800

Cost per Couple-year Protection

The cost of contraceptive commodities is a relatively good proportion of the costs of a family planning delivery system in most countries. However, it is an easily specified cost. Also, for most countries contraceptive commodities must be purchased from outside the country, which requires foreign exchange and at a particularly significant cost. The cost of a single condom, or a cycle of pills is quite low, but the price per unit or procedure should also take into account the average cost per couple-years of protection (CYP) and the results of estimations are given below:

IUDs	$0.48
Sterilization	$0.73
Pills	$3.00
Injections	$4.85
Norplant'	$8.43

The basis for these estimates is as follows:
Sterilization: Cost per procedure = $10,375. It is estimated that on the average sterilization is a good 1/.07 = 14.2857. The cost per CYP is $10,375 x 0.7 = $.073.

IUDs: Cost of CuT 380 A is $0.74 + $0.94 for related equipment and supplies. The average period IUDs are worn is estimated to be 3.5 years. $1.68/3.5 = $.048.

Pills cost $0.20 per cycle. It is estimated that 15 cycles (including non use and waste) provide one year of protection against pregnancy. Therefore, the cost for one year of protection against pregnancy is $0.20 x 15 = $3.00.

Condom: Cost $4.00 per gross ($0.0278 each). It is estimated that 150 condoms provide one year of protection. This includes an allowance for postage. The cost per year of use is $0.0278 x 150 = $4.17.

Injections: Depo-provera costs $0.72 and Novethinsert $1.00. The average cost per year, estimated 60% use of Depo-provera and 40% use of Novisterat is ($0.72 x 4 x 6) + ($1.00 x 6 x 4) = $2.208 + $2.4 = $4,608. Related supplies and equipment are estimated to cost $0.05 per injection, and on the average there are 48 injections a year per person, thus related supplies and equipment cost $0.05 per injection x $4.8 - $0.24. Therefore, the cost per year of protection against pregnancy is $4.608 + $0.24 = $4,848 or $4.85. Noriplant': The cost of the 6 rods is $23 plus 15% for shipping = $3.45 or a total of $26.45. Related equipment and supplies is estimated to cost $5.23. Thus, the total cost per insertion is $24.45 + $5.23 = $31.68. The average period of use per set of NORIPLANT' is estimated at 3.76 years. Therefore, the cost per CYP = $31.68/3.76 = $8.43.

IUDs and sterilization cost less than a dollar per couple-years of protection; pills cost about $3.00 per CYP; condoms and injections are somewhat more expensive at an estimated cost of $4.17 for condoms and $4.84 for injections per CYP. The NORIPLANT' implant has many advantages. However, its average cost per CYP is more than eight times the cost of IUDs or sterilization; and 28 times the cost of condoms and pills - although its effectiveness is much greater than that of pills and condoms.

Product prices are markedly higher in developed countries, creating a larger consumer base for sale of modern more temporary contraceptive methods.

INSERT TABLE CONTAING AMERICAN, AUSTRIAN, HUNGARIAN AND GENERIC PRICES

2.1.5 Social and behavioral factors

Women have always felt a need to regulate and control their fertility. Until the modern era, they had neither the power nor the means to do so unless they were willing to risk their health, their future fertility, and even their lives in the process.

Men, on the other hand , had the power and the means to control sexual relations and fertility from the beginning. The ancient method of withdrawal is as old as mankind. The condom has also been available for a long time.

In many societies, the predominant objection to contraceptive use has been reproductive control to women rather than the contraception itself.

Family planning services are among the most cost-effective means of improving maternal and child health. There is much scope for improving services in developing countries, where more than one women in five who wants to avoid pregnancy is not using contraception. The cost of supplying family planning services to women without access (numbering an estimated 120 million in the developing countries) is estimated at about USD two billion annually for the developing countries as a whole. Satisfying the expressed needs might each year avert as many as 100,000 maternal deaths and 850,000 deaths among children under 5 years of age.

Fertility by choice, not by chance, is a basic requirement of women's health, well-being and quality of life. A woman who does not have the means or the power to regulate and control her fertility cannot be considered in a "state of complete physical, mental and social well-being," the definition of health in the constitution of the WHO. She cannot have the joy of a pregnancy that is wanted, avoid the distress of a pregnancy that is unwanted, plan her life, pursue her education, undertake a productive career, or plan her births to take place at optimal times for childbearing, ensuring greater safety for herself and better chances for her child's healthy development.

In most industrialized countries, marital fertility reached low levels before modern contraceptives were invented. In contrast, men and women in developing countries had access to contraceptives through family planning programmes that promoted clinic and supply methods.

Women are frequently left outside the policy-making process. Governments and others that use modern methods to control women rather than empower them to control their fertility fail to recognize that they interfere with women's basic human rights: health and welfare. One social dilemma comes from the hypothesis that without safe abortion as a backup, the use of less effective contraceptive methods will not meet women's need for fertility regulation. For example, the issue of preventing abortion to the exclusion of R&D on postovulatory methods has had serious consequences for both health and fertility.

According to The World Development Report 1993 - Investing in Health, Romania's experience is the most striking example of the impact of abortion laws on maternal health. In 1966 the government banned abortion and contraception and took steps to enforce the law. The consequences were dramatic: by 1970 the abortion-related maternal mortality rate had risen to 74 per 100,000 live births from 19 in 1965. Before 1966 Romania's maternal mortality rate was similar to the those in other Eastern European countries. By 1989 it was at least 10 times the rate of almost any other European country. In 1990 Romania's new government legalized abortion, and the abortion-related maternal mortality rate declined from 146 per 100,000 live births in 1990 to 43 in 1991.

Where safe pregnancy termination services are available and acceptable, the need for highly effective contraception lessens, and women can more comfortably use barrier methods which will also protect against infection. Reproductive tract infections, mostly resulting from STDs, are a major cause of morbidity and seriously undermine the quality of life of women, especially in developing countries. The traditional venereal diseases have declined but the second generation of sexually transmitted microorganisms such as Chlamydia trachomatis, human herpes virus, human papilloma virus, and the Human Immunodeficiency Virus are more difficult to identify, treat and control.

In women, lesions often occur in the inner genitalia and quite often remain asymptomatic. STDs in women can cause pelvic inflammatory disease, increase the risk of ectopic pregnancy and result in permanent infertility. Several STD pathogens may possibly be transmitted to the fetus.

The most effective means available against STDs, the use of condom, is entirely controlled by the man.

Table 2.8 Microorganism producing sexually transmitted diseases

Microorganism	Acute disease	Pregnancy-associated conditions	Chronic conditions
Neisseria gonorrheae	Urethritis Cervicitis Salpingitis	Premature birth Septic abortion Ophthalmia Postpartum endometritis	Infertility Ectopic pregnancy
Chlamydia trachomatis	Urethritis Cervicitis Salpingitis	Septic abortion Ophthalmia Postpartum endometritis	Infertility Ectopic pregnancy
Treponema pallidum	Primary and secondary syphilis	Spontaneous abortion Stillbirth Congenital syphilis	Neurosyphilis Cardiovascular syphilis Gumma
Human papilloma virus	Genital warts	Laryngeal papillomatosis of neonate	Genital cancer
Herpes simplex virus-2	Genital ulcer	Premature birth Neonatal HSV	Possibly genital cancer

2.1.6 Relation with infertility research and reproduction disorders

Table 1b. World population by sex, women 15-49, and married women of reproductive age, 1996-2005

(Numbers in thousands)

Year	Population			Women 15-49	MWRA
	Total	Males	Females		
1996	5,832,980	2,937,243	2,895,747	1,465,457	1,010,835
1997	5,926,370	2,984,470	2,941,910	1,490,280	1,027,889
1998	6,019,760	3,031,697	2,988,073	1,515,103	1,044,943
1999	6,113,150	3,078,923	3,034,237	1,539,927	1,061,996
2000	6,206,540	3,126,150	3,080,400	1,564,750	1,079,050
2001	6,298,256	3,172,348	3,125,916	1,588,008	1,092,338
2002	6,389,972	3,218,549	3,171,432	1,611,266	1,105,626
2003	6,481,688	3,264,744	3,216,948	1,634,524	1,118,914
2004	6,573,404	3,310,942	3,262,464	1,657,782	1,132,202
2005	6,665,120	3,357,140	3,307,980	1,681,040	1,145,490

Notes: Data for total population, males, females, and women 15-49 for the years 2000 and 2005 are from the United Nations 1992 estimates and projections. Data for other years are interpolations. Most countries with a population of less than one million are not included in the Population Council Databank. Subtotals may not add precisely to totals in as much as data are stored only to six significant figures in the Population Council Databank. MWRA = Married women of reproductive age.

Table 1d. Entire World: Number of Contraceptive users, by method, 1996-2005

(Numbers in thousands)

Year	Sterilization			Pill	Injection	IUD	Condom	Other	Total Users
	All	Female	Male						
1996	244,710	193,121	51,589	97,263	13,234	132,767	53,080	85,261	626,314
1997	250,266	198,020	52,246	99,865	13,911	135,573	53,895	88,411	641,920
1998	255,822	202,919	52,903	102,466	14,588	138,378	54,710	91,561	657,526
1999	261,379	207,818	53,561	105,068	15,266	141,184	55,524	94,712	673,131
2000	266,935	212,717	54,218	107,669	15,943	143,989	56,339	97,862	688,737
2001	271,668	216,676	54,991	110,155	16,629	145,656	56,864	101,181	702,153
2002	276,401	220,636	55,765	112,640	17,316	147,323	57,389	104,500	715,569
2003	281,133	224,595	56,538	115,126	18,002	148,991	57,915	107,818	728,985
2004	285,866	228,555	57,312	117,611	18,689	150,658	58,440	111,137	742,401
2005	290,599	232,514	58,085	120,097	19,375	152,325	58,965	114,456	755,817

Table 3b. Contraceptive usage among married/in union women in developing countries, by method, 1996-2005

(Numbers in thousands)

Year	Sterilization			Pill	Injection	IUD	Condom	Other	Total Users
	All	Female	Male						
1996	211,790	170,799	40,991	55,856	11,649	117,581	26,749	52,029	475,653
1997	217,611	175,645	41,966	58,108	12,244	120,314	27,734	54,625	490,634
1998	223,431	180,491	42,940	60,360	12,838	123,046	28,719	57,220	505,615
1999	229,252	180,337	43,915	62,612	13,432	125,779	29,705	59,816	520,595
2000	235,072	190,183	44,889	64,864	14,026	128,512	30,690	62,412	535,576
2001	239,827	194,153	45,674	67,212	14,632	130,225	31,692	65,355	548,944
2002	244,582	198,122	46,460	69,560	15,239	131,939	32,695	68,298	562,312
2003	249,337	202,092	47,245	71,907	15,845	133,652	33,697	71,242	575,681
2004	254,092	206,061	48,031	74,255	16,452	135,366	34,700	74,185	589,049
2005	258,847	210,031	48,816	76,603	17,058	137,079	35,702	77,128	602,417

Notes: "Other" includes vaginal methods, NORPLANT and traditional methods.

IUD = Intra-Uterine device

Table 4b. Entire World: Number of Contraceptive users, by method, 1996-2005
(Numbers in thousands)

Year	Sterilization			Pill	Injection	IUD	Condom	Total Use.s
	All	Female	Male					
1996	244,710	193,121	51,589	97,263	13,234	132,767	53,080	626,314
1997	250,266	198,020	52,246	99,865	13,911	135,573	53,895	641,920
1998	255,822	202,919	52,903	102,466	14,588	138,378	54,710	657,526
1999	261,379	207,818	53,561	105,068	15,266	141,184	55,524	673,131
2000	266,935	212,717	54,218	107,669	15,943	143,989	56,339	592,875
2001	271,668	216,676	54,991	110,155	16,629	145,656	56,864	602,973
2002	276,401	220,636	55,765	112,640	17,316	147,323	57,389	613,071
2003	281,133	224,595	56,538	115,126	18,002	148,991	57,915	623,170
2004	285,866	228,555	57,312	117,611	18,689	150,658	58,440	633,268
2005	290,599	232,514	58,085	120,097	19,375	152,325	58,965	643,366

Table 6b. Contraceptive commodity requirements of developing countries 1996-2005 (Numbers in thousands)

	Sterilization			Pill	Injection		Condom
Year	All	Female	Male	Cycles	Doses	IUDs	Pieces
1996	15,004	12,127	2,877	894,815	63,381	33,919	4,099,600
1997	15,419	12,473	2,945	932,280	66,631	34,715	4,253,775
1998	15,833	12,819	3,014	969,745	69,882	35,512	4,407,950
1999	16,248	13,166	3,082	1,007,210	73,132	36,309	4,562,125
2000	16,663	13,512	3,151	1,044,675	76,382	37,106	4,716,300
2001	17,003	13,797	3,206	1,083,945	79,676	37,611	4,873,230
2002	17,343	14,081	3,261	1,123,215	82,970	38,115	5,030,160
2003	17,682	14,366	3,317	1,162,485	86,264	38,620	5,187,090
2004	18,022	14,651	3,372	1,201,755	89,557	39,125	5,344,020
2005	18,362	14,935	3,427	1,241,025	92,851	39,629	5,500,950
1994-2005	196,342	159,141	37,201	12,338,385	897,737	436,107	55,711,875

Notes

Pills	15 cycles a year of use
Condoms	125 a year of use, plus 20 per cent of wastage
Injection	Depo-provera, 4 injections per year; Noristerat, 6 times a year. The ratio of the two types of injectable is 60/40.
Sterilizatior	The average number of uses of a minilap kit, a vasectomy kit and laprocator systems was estimated. Similarly, the number of gloves, gauze pads, sutures and cold sterilization solutions were estimated.

Table 7b. Cost of contraceptive commodities for developing countries, if purchased on the internationalmarket, by method, 1996-2005 (Numbers in thousands)

Year	Sterilization			Pill	Injection	IUDs	Condom	Total
	All	Female	Male					
1996	155,664	125,816	29,849	178,963	64,015	56,983	113,878	569,503
1997	159,967	129,408	30,560	186,456	67,298	58,322	118,160	590,203
1998	164,270	133,000	31,270	193,949	70,580	59,661	122,443	610,904
1999	168,574	136,593	31,981	201,442	73,863	60,999	126,726	631,604
2000	172,877	140,185	32,691	208,935	77,146	62,338	131,008	652,304
2001	176,403	143,139	33,264	216,789	80,473	63,186	135,368	672,218
2002	179,929	146,093	33,836	224,643	83,800	64,034	139,727	692,132
2003	183,456	149,047	34,409	232,497	87,126	64,881	144,086	712,046
2004	186,982	152,001	34,981	240,351	90,453	65,729	148,445	731,960
2005	190,508	154,955	35,554	248,205	93,780	66,577	152,804	751,874
1994-2005	2,037,051	1,651,091	385,960	2,467,677	906,714	732,660	1,547,552	7,691,654

Notes: IUD = Intra-uterine device.

2.2 Development of the Market for Hormonal Contraceptives

Widespread contraceptive use is a recent phenomenon in human history. The invention of the condom is not documented scientifically but history researchers believe that it was invented in England in the 1600s. The development of modern contraceptive methods for women began only in the late 19th century. Published reports about the diaphragm first appeared in Germany in the 1880s.

Before 1960, men and women had limited choices of contraception. Existing methods have been significantly improve in the 1960s and 1970s. The most important new method was the development of oral hormonal contraceptives which are short-acting and administered daily and the long-acting injections administered 4 to 6 times yearly or implants offering protection for 5 years.

The first contraception technology revolution was made possible by convergence of three factors. First, there was the sense of need and clarity of a mission, dictated by demographic consensus. Second, science was ripen with new advances in reproductive biology and particularly endocrinology. Third, industry, seeing the rapidly expanding markets and opportunities provided by science, positioned itself for an active role.

2.2.1 Pharmacological history

The oral contraceptive market was not created in 1960 by the serendipitous or methodological discovery of a single researcher but resulted from the investigations of many scientists over a long period of time.

2.2.1.1 Progestins

The corpus luteum attracted the attention of scientists already in the 17th century (Malpighius, 1648 and De Graff, 1672).

A French histologist proposed first that the corpus luteum was an organ of internal secretion (Prenant, 1898). A hypothesis was advanced and some experimental evidence was accumulated already around the turn of the 20th century that the corpus luteum has a suppressive action on the ovulation.

The systematic research work on hormonal contraception started in Innsbruck, Austria with

animal experiments on the antiovulatory action of the corpus luteum (Haberlandt, 1921). Haberlandt hypothesized first that the administration of corpus luteum could result in the temporary sterilization of women. He reported also the first successful oral contraception in mice (Haberlandt, 1927). Today, Haberlandt is considered as the pioneer of birth control by progestins in women. He even formulated -with the pharmaceutical company Gedeon Richter in Hungary- an oral preparation named INFECUNDIN[1] for clinical trials (Von Brucke, 1932).

Corner and Allen (1929) reported that the extracts of the corpus lutea contained a special hormone. This important discovery was soon followed by the isolation and synthesis of progesterone.

Industrial R&D activities were initiated in 1950 by Margaret Sanger -who established the US family planning movement and founded the International Planned Parenthood Federation) and Katherine Dexter McCormick, who financed the project on the development of a safe and effective contraceptive. Pharmacological experiments with the administration of high doses of progesterone first to rabbits then to rats confirmed that progesterone inhibited ovulation (Pincus & Chang, 1953). Another series of experiments followed in 1953, in which newly synthesized 19-norprogestins were tested and found the most effective for the prevention of ovulation (Pincus et al., 1956). Clinical trials with progesterone and derivatives began in 1953 (Rock et al., 1957). Pincus reported the results of their clinical trial with progesterone at the Fifth International Conference on Planned Parenthood in Tokyo in October of 1955 and stated publicly the possibility of progestational compounds for oral contraception.

During the early clinical investigations, it turned out that norethynodrel was contaminated by estrogen which interestingly allowed better cycle control. It was discovered much later that the estrogen had a synergetic action with the progestin in ovulation inhibition.
In 1958, 125 women were given 20 tablets containing 10mg of norethynodrel plus 0.15 to 0.23mg of mestranol to be taken from the 5th to the 24th day of the menstrual cycle. The clinical trials demonstrated that reliable contraception occurred if the regimen was followed faithfully. The combination was immediately patented by G. D. Searle Company as ENOVID-10. In 1960, the Food and Drug Administration (FDA) of the United States approve ENOVID-10 as a contraceptive agent and a new pharmaceutical market was born.

The synergism between estrogen and progestins permitted dosage reductions leading ultimately to the current, widely used low-dose oral contraceptives

The use of long-acting injection contraceptives -medroxyprogesterone acetate or norethindrone enanthate- was first reported in the professional literature in 1966 (Zanartu et al., 1966)

2.2.1.2 Estrogens

As early as 1912, Adler (1912) and Fellner (1912), in Vienna, and Iscovesco (1912) prepared ovarian extracts that showed estrogenic activity.

Fellner (1927) published that his ovarian extracts had different effects at different doses and that they prevented pregnancy by destruction of ova and by inhibition of the formation of corpus luteum.

Allen and Doisy (1929) reported the isolation of crystalline estrone. In 1930, the concept of contraception with sex steroids was published and the antifertility action through pituary inhibition was correctly inferred (Reiprich, 1930). By 1933 estrone was converted to estradiol, demonstrated to be another physiological substance (Doisy).

In 1945, Albright clearly identified the potential of ovulation-inhibiting doses of estrogen as a contraceptive method.

Nothing particular happened on the estrogen front until 1975 when Goldzieher and others demonstrated that a daily dose of 20mcg. of mestranol was not sufficient but 50mcg. showed a consistently effective contraceptive dose.

Recent pharmacokinetic studies (Bródy, et al., 1989) have shown that plasma ethynyl estradiol levels from a single oral dose of 50mcg. mestranol are comparable to those produced by a 35mcg. dose ethynyl estradiol. New contraceptive formulations tend to use ethynyl estradiol.

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2.2.2 Industrial history

2.2.3 Market development and current situation

There are 200 million married men and women who have been sterilized, of this number 80.5% are women and 19.5% are men.

More than 50 million women in developing countries use the pill: from one forth to 30% of all users in Sub-Saharan Africa, the Arab States and Europe and Latin America, but only 8% use the pill.

Injection use is probably increasing rapidly in developing countries. However, survey data indicate that a little more than 10 million women, or 2.3% of all users, are using injections. The largest proportion - 13% of users - is in Sub-Saharan Africa.

THE PILL

The International Planned Parenthood Federation listed the principal manufacturers in the latest edition of the Directory of Hormonal Contraceptives, as follows: Gedeon Richter Ltd., Budapest, Hungary (GR), Organon International B.V., Oss, The Netherlands (ON), Ortho Pharmaceutical Corporation (Cilag Ag. International), New Jersey, USA (OT), Syntex Laboratories Inc., Palo Alto, USA (SY), Upjohn International Inc., Kalanazov, USA (UP), Warner-Lambert International, Morris Plains, USA (WI) and Wyeth-Ayerst International Inc., Philadelphia, USA (WY).

All pills contain a gestagen in different doses. Some pills contain also an estrogen, typically ethynilestradiol or mestranol. There are three different kinds of pill.

1. The combined pill contains a gestagen and an estrogen. Representatives of this group are included in the latest list of Essential Drugs of the WHO, in the following compositions:

□ethinylestradiol + □levonorgestrel	tablet, 30mcg + 150mcg, 30mcg + 250mcg
□ethinylestradiol + □norethisterone	tablet, 35mcg + 1mg

Apart from these contraceptives, this group has many gestagens such as chlormadinon acetate, ethinodiol diacetate, synestranol, norethisterat, norethisterone acetate, norethynodrel, norgestrionene, quingestanol, desogestrel, norgestimate and megestrol.

Oral contraceptives are administered in different doses. According to Pincus schedule, the very first pill is given on the fifth day after the start of menstruation and the administration of a daily single pill is continued for the following 20 days. After discontinuation of the treatment, bleeding is over in about eight days. Thus the schedule is 20 days of treatment followed by eight days of pause (20 + 8 days) which means a complete cycle of 28 days. Several other regimens -such as 21 + 7 days, 22 + 6 days, etc.- have been proposed since the introduction of the Pincus schedule. Therefore many contraceptive pills are first administered on the fifth day of menstruation followed by 20 days of treatment and eight days of pause. The sequential administration has the undeniable advantage that dosage follows the hormonal fluctuations of human cycle which means a favorable hormonal method from the viewpoint of the endometrium. Many manufacturers provide seven placebo pills of different color only to facilitate patient's compliance with the recommended time schedule. Women are advised to take the daily pill always at the same time, e.g., when going to bed. If a pill is missed at the usual time, then it should be taken as soon as possible next day.

The advantages of oral contraceptives can be summed up as follows:

- practically 100 per cent reliability;
- no genetic after-effect according to extensive observations;
- reliably low incidence of side effects;
- relatively easy application;
- no interference with coitus and its experience;
- hygiene;
- possibility of protection before the first coitus of virgins;
- low cost;
- puts decision-making about prevention into the hands of women.

2. The phasic pill contains two phases of gestagen which differ in dosage from each other. The third phase contains estrogens. The active ingredient of these preparations is chlormadinon acetate, synestranol, norethisterone, norethisterone acetate, levonorgestrel, desogestrel or gestodene.

3. The third group contains only a gestagene in a rather low dose and this is administered during the whole menstruation cycle. The active ingredient of these preparations is ethynodiol diacetate, synestranol, norethisterone, norethisterone acetate, levonorgestrel or norgestrionene.

EMERGENCY CONTRACEPTION

The term emergency contraception refers to the particular type of contraception that is used as an emergency procedure to prevent pregnancy following unprotected intercourse which may be expected to cause pregnancy. Defined in this way, emergency contraception has the following characteristics: (a) it is a one-time procedure and not a routine approved for contraception, (b) it is used after an intercourse, hence it is also known as postcoital contraception, © its aim is to prevent unplanned pregnancy and, therefore, it includes all those procedures that can be employed before pregnancy has become established around the time of expected menstruation. The often used popular description of "the morning-after pill" is therefore inappropriate since morning-after suggests a need for immediate action that is not required. References to postcoital preparations for oral or vaginal use as well as for vaginal douching can be found as far back as 1500 BC in Egyptian papyri.

The combined estrogen-progestogen administration, often referred to as the Yuzpe regimen after its discoverer, was introduced in the 1970s and is now the most often used form of emergency contraception. Although there is some debate about the magnitude of the protective effect, few people question the important role emergency contraception can play in preventing unwanted pregnancy. The standard Yuzpe regimen consists of giving two tablets of a combined contraceptive pill, each containing 50 mg of ethynilestradiol and 0.5 mg of norgestrel (or 0.25 mg of levonorgestrel) as soon as possible but not later than 72 hours after an unprotected intercourse. Another two pills need to be taken 12 hours after the first dose. As a result, estrogen related side-effects such as nausea and vomiting occur less often than before the Yuzpe regimen was introduced.

There are some progestogen pills like Postinor (Neogest, Ovrette) which contain 0.0375 mg of levonorgestrel. It is proven that levonorgestrel administered immediately after coitus in a single dose of 0.4 to 1.0 mg effectively prevents pregnancy. It was obvious right from the very beginning that a preparation with such a high hormone content can only be used for the protection of women who practice coitus rarely and occasionally, and this method is prohibited to those with regular sexual life requiring almost continuous dosage. Levonorgestrel can be recommended to women who have maximum four intercourses per month. Levonorgestrel should be taken immediately (but not later than one hour after) coitus; the dose is then one tablet. If intercourse is repeated after more than three hours, another tablet should be taken postcoitally. After the use of the tablets, mild nausea and bleeding can be experienced. The mechanism of action of postcoital contraception is not perfectly clear.

We have to go to antiprogestins where a new form of emergency contraception is established. Some encouraging results in this respect have been obtained with levonorgestrel administered in two doses of 0.75mg taken 12 hours apart. When tested in a randomized trial in Hong Kong in women requesting emergency contraception within 48 hours of unprotected intercourse, the levonorgestrel regimen was found to be as effective as the Yuzpe regimen but associated with significantly less nausea, vomiting and fatigue.

Incidence of side effects after emergency contraception

Side effect	Levonorgestrel N = 410		Yuzpe regimen N = 424	
Nausea	66	16.1%a	197	46.5%a
Vomiting	11	2.7%b	95	22.4%b
Fatigue	98	23.9%c	156	36.8%c
Breast tenderness	65	15.9%	88	20.8%
Intermenstrual spotting/bleeding	14	3.4%	18	4.2%

a, b and c indicate significant differences ($P < 0.001$) between the two groups.

SAFETY OF CONTRACEPTIVES DURING BREAST-FEEDING

Many women use contraceptives while breast-feeding. It is important therefore that the method they use does not interfere with milk production or have any harmful effect on the infant. Previous studies have shown that oral contraceptives containing both an estrogen and a progestogen adversely effect the quantity and even the composition of breast milk. But progesterone-only pills have little if any effect on the quantity and quality of breast milk. Two studies have been carried out to investigate whether the use of progestogen-only contraceptives, including implants and injections, during breast feeding have any effect on the growth and development of infants, particularly in developing countries where both mother and child are sometimes undernourished. The Programme has addressed this issue by conducting a study in seven centers (Chile, Egypt, Hungary, Kenya and Thailand) in which 2466 mother-infant pairs participated. Mother and infant pairs were admitted to the study at six weeks postpartum and were followed up until the infant became one year old. It was concluded that in this study the progesterone-only methods did not adversely affect infant growth or development during the first year of life.

ADOLESCENTS AND CONTRACEPTION

The Programme convened a meeting in 1992 to review the research needs and priorities with regard to contraceptive requirements of adolescents. The participants assessed the available information on the safety of hormonal and non-hormonal methods and of induced abortion during adolescence, service delivery to adolescents, and adolescent sexual behavior. They concluded that the highest priority should be given to research on adolescent sexual behavior and contraceptive service delivery to young people. The participants felt that although there were certain other research areas of scientific importance and of relevance to adolescents -for example. the effect of steroidal contraceptives on the breast tissue of young women and the consequences of unsafe abortion for the subsequent fertility of young women. it would not be feasible to study then in developing countries.

UNWANTED PREGNANCY AND FERTILITY REGULATIONS

Half of all pregnancies are unplanned and a quarter certainly unwanted. Unwanted pregnancy is a major public health problem with potentially serious consequences for health of the girl or woman. Not only is a denial of a woman of reproduction's fundamental right to control her fertility, it also exposes her to the hazards of pregnancy and childbirth, or possibly an abortion done under unsafe conditions. In developing countries one in 50 women dies from complications of pregnancy and childbirth, compared to only one in 2700 in industrialized countries. Also when a mother dies, the chances of death for her child under five years of age increase by 50 percent.

Many unwanted pregnancies end in abortion. Around 50 million abortions are performed each year around the world. In developing countries many pregnancies are terminated under clandestine or otherwise unsafe conditions. This exposes women to a high risk of mortality and morbidity. The estimated annual number of unsafe abortions in the world is 21 million. At least 180 women die every day from unsafe abortion.

Induced abortion exists in every society but not all women have access to safe services. Where abortion is legal and safe services are available, there is a minimum risk to women's health. In societies where women do not have access to safe services -usually but not exclusively in countries where the procedure is illegal- women are exposed to clandestine and often unsafe practices that entail high risks of morbidity and mortality. In many developing countries it is estimated that 20 to 30 percent of all maternal deaths result from complications from unsafely induced abortions

EPIDEMIOLOGICAL RESEARCH IN CONTRACEPTIVE HEALTH

Epidemiological research conducted by the Programme is focused on the identification major side effect (beneficial as well as adverse) associated with the currently available methods of fertility regulation. The Programme places special emphasis on the study of potential side effects of public health relevance and on efficiency of current methods in developing country settings.

Some epidemiological research, particularly studies involving follow up or those using combined methodology. are conducted over several years.

HORMONAL CONTRACEPTIVES AND CANCER

In 1979, the Programme started a major multinational cancer control study to investigate the possible relationship between the use of hormonal contraceptives and cancer. Eleven countries, five industrial and eight developing, participated in this collaborative study. Following completion of data analysis, more than 40 papers have been published in different journals.

The study was concerned primarily with cancer of the breast, cervix, endometrium, gallbladder, liver and ovary, respectively. This study has greatly contributed to the body of knowledge on these neoplastic diseases in developing countries, not only with regard to their relationship to methods of fertility regulation but also to other factors which associated with their occurrence. An important finding from this study has been that most results from the studies in industrial countries of hormonal contraception and risk of cancer are likely to be applicable to women in developing countries. The main findings of the study were reviewed at two WHO meetings, one in 1990 and the other in 1993.

The meeting in 1990 concentrated on oral contraceptives and neoplasia. The report of that meeting was published in the WHO Technical Report Series - Oral contraceptives and neoplasia (Report of a WHO Study Group, World Health Organization, 1992, WHO Technical Report Series, No. 817). The background papers for the meeting were published in the Journal of Contraception (1991, Vol. 43. 521-710). The 1993 meeting dealt mainly with depot medroxyprogesterone acetate (DMPA). The participants concluded that among DMPA users there was no evidence for an overall increase in risk of cancer at any of the four sites reviewed (breast, cervix, endometrium and ovary). Thus it was recommended not to restrict the use of DMPA on the groups of neoplasia

The meeting gave much attention to the question of possible question between DMPA use and the risk of breast cancer. They agreed that it was unlikely that these observations represented new tumors. The participants also concluded that there was evidence to suggest that DMPA had a protective effect with regard to endometrial cancer.

HORMONAL CONTRACEPTIVES AND CARDIOVASCULAR DISEASES

A few years after combined oral contraceptives were brought to the market, reports of cases of cardiovascular side effects appeared in medical journals. Epidemiological studies conducted to date indicate that the use of hormonal contraceptives may increase the risk of cardiovascular diseases such as certain types of stroke, venous thromboembolism and among women who smoke myocardial infarction. Most of these data come from studies conducted in industrial countries and relate to pills of earlier type which contained considerably greater quantities of hormones than present day counterparts. Furthermore, there is virtually no firm information on the risk of cardiovascular disease from the use of hormonal contraceptives in developing countries. These problems make it difficult to assess from previous studies how much risk to cardiovascular health the new pills carry, particularly in developing countries. In order to address these concerns, the Programme initiated a multinational case-control study in 17 centers in Africa, Latin America, Asia and Europe. The study is concerned with acute myocardial infarction, venous thromboembolism and stroke in smoking women of reproductive age. After completion of a pilot phase enrollment of the subjects in the main phase of the study started in 1989. Field work for this study was completed in 1993 for the components concerned with venous thromboembolism and stroke, while for myocardial infarction it will continue through 1994 in selected countries.

HORMONAL CONTRACEPTION AND ENDEMIC DISEASES

Gallstones

The prevalence of gallstone disease varies widely among countries and women are of higher risk of being affected than men. Reproductive factors such as female sex hormones and pregnancy are considered risk factors for the disease. Although some studies have reported an association between gallstones and hormonal contraceptives, it is not yet well understood whether these contraceptives initiate the formation of gallstones or precipitate clinical manifestations of asymptomatic latent disease. In countries such as China, where gallstone disease is common among women of reproductive age, any alteration in its incidence would be of public health importance. A study supported by the Programme is in progress in many hospitals of the Sichuan province of China, in which 830 cases of

surgically confirmed gallstone disease are being compared to an equal number of controls to find out if the use of oral contraceptive pills affects the risk of developing the disease. Data collection has been completed and the results are expected in 1994.

Hepatitis B infection

Many family planning programmes recommended that women with a history a jaundice should not be prescribed hormonal contraceptives unless their liver function has been proven to be normal. This advice is based on studies of combined oral contraceptives (mainly high dose, older preparations) that have reported effects on liver function in some women.

In developing countries, where hepatitis B infection is common, testing of liver function involves a considerable expense for potential users of contraceptive pills. There is also a possibility that some family planning programmes may be unnecessarily disqualifying certain women for using hormonal contraceptives. Therefore, the rationale for this recommendation is being examined in the context of the low-dose pills currently in use. The Programme is supporting a study in China and Thailand where asymptomatic chronic carriers if hepatitis B virus (HBV) who choose to use low-dose combined oral contraceptives are being investigated. Liver function and replication rates of HBV are among the study objects will be compared to those in a group of chronic carriers of HBV using a non-hormonal contraceptive method.

Gestational diabetes mellitus

It is widely accepted that oral contraceptives slightly alter carbohydrate metabolism in some women. However, it is not known whether the effect is different or more severe in women with a history of gestational glucose intolerance. The Programme has recently initiated a three-year study in Venezuela to evaluate changes in carbohydrate metabolism resulting from the use of a low-dose oral contraceptive preparation as compared to the use of non-hormonal contraceptive methods in women who had gestational diabetes mellitus in their most recent pregnancy. The findings from the study would be useful in formulation of prescription policies for oral contraceptives.

Hormonal contraceptives and bone density

Osteoporosis -loss of bone with age- is a universal phenomenon which is more pronounced in women than in men. Because of secular trends in life expectancy its

magnitude is expected to increase in both developing and industrial countries. Dietary factors, levels of physical activity, smoking, hereditary factors and race have been identified as risk factors for osteoporosis. Although it is known that estrogens and some progestogens prevent bone loss in postmenopausal women, there is no consensus on whether the use of hormonal contraceptives has a beneficial, adverse or no effect.

The IMS MARKETLETTER reported in late 1974 that "The Danish national health service banned the sale of five oral contraceptives because of their high estrogen content." The regulatory authority noted that most of the companies affected had other lower-estrogen oral contraceptives on the market.

THIRD-GENERATION COMBINED CONTRACEPTIVES

Oral contraceptives have continued to be in the limelight. On 19 October 1995, the UK Department of Health issued a warning about seven brands[1] of combined contraceptive pills:

Brand name	Active substances (Manufacturer)
Femodene	ethinylestradiol/gestodene (Schering Health Care)
Femodene ED	ethinylestradiol/gestodene (Schering Health Care)
Minulet	ethinylestradiol/gestodene (Wyeth)
Tri-Minulet	ethinylestradiol/gestodene (Wyeth)
Marvelon	ethinylestradiol/desogestrel (Organon)
Mercilon	ethinylestradiol/desogestrel (Organon)

[1] An estimated 1.5 million British women, representing about 50 percent of the current oral contraceptive market, are users of these products

The common characteristic of the above brands is that they contain gestodene or desogestrel as the progestogen ingredient.

The UK authority referred to new evidence -unpublished data from three epidemiological studies- which suggested that the risk of venous thrombosis (mainly deep vein thrombosis and pulmonary embolism) with the third-generation combined contraceptives is still small but higher than with older products.

The German Federal Institute for Pharmaceutical and Medical Products issued a similar warning to the about one million German women taking third-generation combined pills. The regulatory authority invited comments on the issue from the companies involved.

The WHO also issued a statement at the end of October 1995 which was in line with the warning of the UK authority.

Commenting on the situation, the spokesman of the FDA said that it was well aware of the three cited studies and was currently reviewing the data. A preliminary verdict is expected within the next few weeks.

CONTRACEPTIVE INJECTIONS

Hormonal injectable preparations have been available for over 20 years. The two most widely preparations in the world are the three-monthly depot medroxyprogesterone acetate (DMPA) used by about nine million women, and the two-monthly norethisterone enanthate (NET-EN) used by one million women. Both contain a single hormone, a progestogen, and are highly effective. However, like all progestogen-only methods, their use is associated with menstrual disturbances such as irregular and unpredictable vaginal bleeding or spotting, or a complete cessation of menses. Because this side effect is poorly understood and its treatment is largely empirical, the Programme is supporting research toward a better understanding of the mechanisms of menstruation and how it may be affected by hormonal contraceptives. It is hoped that these studies will lead to the formulation of more effective treatment modalities and possibly to the development of new methods free from this side effect.

Although these menstrual irregularities are inconvenient and often unacceptable, there is no evidence that they have adverse health effects. In fact, on average, users of progesterone-only methods experience less blood loss than with their normal menses. However, in order to be able to offer an alternative injectable preparation to women who find these vaginal bleeding irregularities unacceptable, the Programme has developed injectable contraceptive methods which produce a menstruation-like pattern. They contain two hormones, an estrogen and a progestogen, like the combined pill. The induced bleeding episodes which are not true menstruation but withdrawal bleedings resulting from clearance of the injected hormones from the body. This is very similar to the bleeding experienced by users of the combined pill during the pill-free week. The greater cycle control is offered by the fact that they need to be given on a monthly basis. The Programme, in collaboration with the pharmaceutical industry, has developed two such once-a-month injection: Cyclofen (25mg DMPA + 5mg estradiol cypionate) and Mesigynon (50mg NET-EN and 5mg estradiol valerate). Both have been shown to be very effective and to allow a faster return to fertility after discontinuation than either DMPA or NET-EN. In 1993 a group of experts by the Programme concluded that "Both Cyclofen and Mesigynon are safe and effective products for fertility regulation which can be added to the existing arsenal of contraceptive methods. They can be used by all potential contraceptive users provided that precautions are taken to assess potential risk factors. They provide high efficacy and low incidence of side effects, and the vaginal bleeding patterns are better than those seen with progestogen-only injections.

Both preparations have been registered in several countries. As with other contraceptive methods, efforts are under way to develop improved injectable preparations, with even less side effects, by lowering the overall steroid dose and by changing the formulation so as to prevent the occurrence of high blood levels of hormones which immediately follow the administration of the injection. This can be achieved with delivery systems such as microspheres which slowly release the hormone as they break down, or by modifying the size of the steroid crystals so they act as a depot slowly releasing the drug in the body. The Programme has chosen the latter, less expensive approach to develop a new three-monthly injection. The compound under study, levonorgestrel butanoate, is an ester of the progestogen levonorgestrel which is present in many oral contraceptives.

NORPLANT[R]

Norplant[R], developed by the Population Council, has been used by more than 60,000 women in more than 50 countries all over the world and is currently registered in 23 countries including the United States.

The Norplant[R]-1 contraceptive system consists of six silastic capsules (2.4mm by 34mm) each containing 36mg of levonorgestrel to be inserted under the skin (usually of the central portion of forearm) under local anaesthesia utilizing an applicator.

In order to determine the daily dose of levonorgestrel (LNG) delivered and the lifespan of implants, CROXATTO and his coworkers (Diaz et al. 1984 = Diaz S., Pavez M., Miranda P. et al.: Performance of Norplant[R] subdermal implants in clinical studies in Chile in Za....., Goldsmith A, Shelton J.D., Sciarra J.J. eds. Long-acting contraception delivery systems, Philadelphia, Harpen and Row, 1984, 482) measured the steroid remaining in capsules removed after different lengths of use. The average dose per day was calculated by dividing the total amount of drug delivered by the number of days in situ. The total amounts of LNG delivered by implants removed between 500 and 2000 of use. The amount delivered in the first 500 days was approximately 80mg, an estimated average daily dose of about 30mcg/day. Some people showed that there is a higher delivery rate of 100mcg. during the first months after insertion. This may be due to multiple factors. A local inflammatory process may induce a higher rate in the first days but later the organization of a thin layer of fibrous tissue may stabilize the release rate. Then, for the first year, the release rate averages from 50 to 80mcg/day, finally from the second through the sixth years of use, the release rate is approximately 30 to 35mcg/day. When monitoring plasma LNG levels during Norplant[R] use, CROXATTO et al. (1981) (Croxatto H.B., Diaz S., Miranda P., Elansson K., Johansson EPB et al.: Plasma levels of levonorgestrel in women during long-term us of Norplant[R], Contraception, 1981, 23, 197) found that the concentrations were between 3 to 4 mcg/ml during the first three years and then declined gradually with the lowest level observed during the eight year.

The plasma concentration of LNG shows considerable variation s depending on individual factors as clearance rate and body weight, the levels is a given individual remain however relatively constant.

During the first and second years, only 0.2 and 0.5 percent , respectively, of all continuing users became pregnant. During the year from three to five , the pregnancy rate rose to over one percent with differences among women of different weights. In particular, women who weighed 70kg or more had the highest pregnancy rate. Fifty percent of all pregnancies occurred between the third and fifth years of Norplant[R] use.

The bleeding pattern in the majority of women using Norplant[R] is characterized by frequent, irregular and/or prolonged bleeding during the first 12 months of use. Several studies confirmed that unlike other progestin-only methods, bleeding patterns with Norplant[R] improve with time, indeed the most altered patterns and most terminations for menstrual reasons occur during the first year.

ANTIPROGESTOGENES

Mifepristone (RU 486) is the only antiprogestogen which is manufactured by industry and has been studied extensively in humans. There were two other antiprogestogenes which were also manufactured by industry, namely libopristone and onapristone.

The hormone progesterone is indispensable for the normal reproductive function. After ovulation progesterone, secreted by the corpus luteum, facilitates the transport of the fertilized egg through the Fallopian tube. It acts on the uterus making its surface a secretory type which is required for implantation and the nourishment of the conceptus. During pregnancy progesterone keeps the uterus in a quiescent state. It follows from its hormonal function that progesterone is plays an important role in any mechanism of action which has an antiprogestive effect.

Antiprogestogenes are compounds which have a very close affinity to the receptors of progesterone from target cells. They achieve their antiprogestic effect by preventing progesterone from occupying its binding site on the receptor and from the exerting effect.

Antiprogestogenes for early pregnancy termination

Most of the research carried out to date with mifepristone is focused on the abortifacient activity of the compound. After mifepristone had been registered in France, the United Kingdom and China, it was approved in Sweden for clinical use in September 1993. In all

four countries, the regimen for a single 600 mg dose of mifepristone is followed 36 to 48 hours later by a suitable prostaglandin preparation.

In France 15,709 women were treated. The efficiency rate (complete abortion rate) was 95.3 per cent. The 4.7 per cent failures included 2.8 per cent incomplete expulsion and 1.2 per cent persisting pregnancies, and 0.7 per cent of women required a hemostatic surgical procedure.

Work supported by the UNDP/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (hereinafter the Programme) has generated important information on the following four questions: a) the minimum effective dose of mifepristone; b) the maximum duration of pregnancy for which the treatment remains effective and safe; c) the most appropriate type and dose of prostaglandin; d) for women, who are choosing this non-invasive technique of abortion, the acceptability to users and the service facilities.

In multicentre clinical trials conducted by the Programme with mifepristone a lower dose than the 600 mg is recommended currently. For example, 25 mg were administered at 12-hour intervals and 200 mg was found as effective as 600 mg. In this case the vaginal prostagiandin analogue geneprost was used. These findings have had an impact on clinical practice. For example in China, which produces its own mifepristone, tablets containing 25 mg of the compound are now being manufactured and a regimen of five or six times 25 mg has become the standard treatment.

In European countries, where mifepristone is registered, the marketed tablets contain 200mg of the compound. In multicentre clinical trials using 50 mg and 200 mg mifepristone in combination with either a whole suppository or half a suppository of geneprost it was found that complete abortion rate showed a downward trend from a value of 95 per cent in groups receiving the higher dose of mifepristone (200 mg) and of geneprost (a whole pessary of 1 mg). The lower antiprogesterone dose (50 mg) and geneprost (half a 1 mg pessary) had 86 per cent less effect than the higher dose. Therefore, a 200 mg dose appears to be close to the minimum effective amount of mifepristone when given as a single dose.

In contrast to France, the current approval for mifepristone use applies only to pregnancies

of up to 49 days of amenorrhoea. All women participating in these trials had pregnancies of less than 56 days. In both Sweden and the United Kingdom mifepristone was approved for use in pregnancies of up to 63 days.

Until 1991 a major obstacle to using mifepristone in developing countries was the fact that prostaglandin analogues were used predominantly until that time, namely intramuscular sulprostone and vaginal geneprost, were expensive and needed to be stored in a refrigerator.

The tablets of the orally active prostaglandin E_1 analogue, misoprostol -which was independently discovered at the WHO Collaborative Centre in Edinburgh and in France - resulted in a major advance. Although not a potent uterotonic agent when given orally, misoprostol proved to be as effective as sulprostone and geneprost when used in combination with mifepristone. Misoprostol is marketed in more than 60 countries for the treatment and prevention of peptic ulcers. Some studies also support the fact that misoprostol may be more effective when administered vaginally rather than by oral route.

Women's preferences regarding the facilities that should be available to the during this observation period were evaluated in a study at the WHO Collaborating Centre in Edinburgh.

Women receiving mifepristone followed by prostaglandin for the termination of early pregnancies are almost always kept for observation for three to four hours after the administration of prostaglandin. An appropriate analgesia can be provided as required for any lower abdominal pay the women may have. Women who received oral misoprostol required significantly less analgesia than those who were given vaginally 1 mg of geneprost.

In this study, a total of 180 mifepristone-pretreated women admitted for administration of the prostaglandin (vaginal geneprost or oral misoprostol) were randomly assigned to observation in a sitting room or in a ward. It was concluded from the results of these investigations that the majority of women undergoing medical abortion prefer to be treated in a group rather than in a hospital ward. This choice is highly cost-effective.

The data obtained were reviewed at a scientific group meeting convened by the

Programme in 1994. Data are available on efficacy, safety, acceptability and service methods for inducing abortion through treatment with antiprogesterones and prostaglandin.

Antiprogestogenes as contraceptives

Because most research to date has been focused on pregnancy termination, antiprogestogenes such as mifepristone have become known inevitably as the "abortion pill". In fact, in the field of fertility regulation, the ability to prevent pregnancy may well prove to be much more characteristic of antiprogesterones than their abortifacient activity. One very promising application is emergency contraception.

Research studies in female voluntaries -carried out by investigators supported by the Programme and other workers- have shown that antiprogesterones as mifepristone can either block ovulation or retard endometrial development depending on whether the compound is given before or shortly after ovulation. The observations have led to the hypothesis that mifepristone may be useful as a new method for emergency contraception for the prevention of pregnancy. To examine this possibility, the Programme supported two randomized trials to compare the efficacy and side effects of a single dose of 600 mg of mifepristone with those of the Yuzpe regimen (combined estrogen/progestin). The two studies, carried out in the United Kingdom and published in 1992, confirmed the potential usefulness of antiprogestogenes such as mifepristone for emergency contraception. In the two trials combined, 597 women were given mifepristone and none of them became pregnant. 35 pregnancies would have been expected if mifepristone had not been administered. The 26 per cent failure rate (9 observed pregnancies from 34 statistically expected pregnancies) of the Yuzpe treatment observed in these two studies is similar to that generally seen with this approach.

	Mifepristone	Yuzpe regimen
Number of women treated	597	589
Expected number of pregnancies	35	34
Observed number of pregnancies	0	9

Not only was mifepristone more effective but the women treated with this agent reported less nausea and vomiting as well as lower rate of other side effects than the women treated with the Yuzpe regimen. They were, however, more likely to have a delay in the onset of the next menstrual period presumably because ovulation was inhibited in those

who had not yet ovulated at the time of taking the antiprogestogene. The observed delay in the onset of the next menses precludes the use of mifepristone, at least in the 600 mg dose used in these studies, as a postcoital method of contraception for regular use. Since emergency contraception is generally a one-time procedure for occasional use, this menses delay in close half of the treated women should not cause a significant problem in routine practice provided the women are forewarned and it can be assumed that a delay in the onset of menses, when it occurs, is not due to the failure of the treatment to prevent pregnancy.

Viewed from the perspective of family planning services, mifepristone has several advantages in comparison to the Yuzpe regimen. Menstrual delay is common but this should not be a major problem with proper counseling and follow up. The main interrelated obstacles to more widespread use at the present time are the cost of the drug and the fact that the 600 mg dose shown to be effective is also the dose recommended by the compound's manufacturer when the antiprogestogene is used in combination with prostaglandin for the termination of early pregnancy. To see if these obstacles can be circumvented and to further document the efficacy and side effects, the Programme has initiated a large multicentre dose-finding study. A subsidiary objective of this trial is to determine if mifepristone remains effective when used after 72 hours, i.e., after the generally accepted limit for the Yuzpe regimen.

Even if this additional research shows that antiprogestogenes such as mifepristone can be used for emergency contraception in doses that are substantially lower than those employed in pregnancy termination, availability of the drug may still remain problematic in countries that have restrictive abortion laws.

The research supported by the Programme in the area of emergency contraception, particularly the very promising results obtained with mifepristone, was widely reported in the mass media. Without doubt, this research has played a significant role in the current move on both sides of the Atlantic to make emergency contraception more widely known and used. Given that the emergency methods that are currently most often employed, namely the Yuzpe regimen and IUD insertion, use techniques that have been available for 30 years it is surprising, indeed regrettable, that so few family planning programmes seem to provide services for emergency contraception which after all could be a life-saving measure for women who otherwise would have to resort to clandestine, unsafe abortion.

Probably the most important single measure to increase to use of emergency contraception is to make postcoital pills available without prescription. If available over the counter, emergency contraception could prevent, for example, an estimated 1.7 million unplanned pregnancies every year in the USA where currently 1.6 million unwanted pregnancies are terminated each year.

The Programme's research on the efficacy of mifepristone and levonorgestrel for emergency contraception is widening available options and family planning programmes should seize these opportunities to educate the public about emergency contraception and promote its use.

2.3 Condoms

The estimates indicate that there were 25 million users of condoms for family planning in 1994. However, given the increasing concern about the use of condoms for prevention of the acquired immune deficiency syndrome (AIDS) this estimate is likely to be low.

2.4 Pessary

2.5 Intrauterine Devices

IUDs have freed women from taking precaution at every sexual act and provided an alternative to permanent contraception and offer protection up to eight years.

The intra-uterine device (IUD) is the second most widely used contraceptive method. 25% of all contraceptive users. 14% (112 million use IUDs) equal the population of all users in Asia and the Arab States and Europe; 27.5%, 1:10 users in Sub-Saharan Africa and Latin America use IUDs.

2.6 Sterilization

The techniques of female sterilization were simplified in the 1960s and 1970s to the extent that interventions did not require general anaesthesia or hospitalization.

Fewer contraceptive users choose sterilization in industrialized countries than in

developing countries.

2.7 Others

The current technology for pregnancy termination, even using mifepristone (RU 486), is still clinic-based. Even in countries that permit abortion, its availability is limited by the availability of clinical services.

3. FUTURE SCENARIOS

3.1 Market Projections

The predominant factor influencing a private sector decision to develop a new contraceptive is a projected market for that product. The contraceptive market can be defined either by the number of products or the dollar value, when viewed in terms of number of contraceptive user.

During the period of 1994 - 2005 the number of women 15 - 49 years of age in developing countries is expected to increase by 22 million a year, from 1.107 million in 1994 to 1.309 million in 2005. Married women of reproduction age MWRA and women in union (hereafter referred to as married women) in developing countries are expected to increase by 14 million a year: 169 million (21.5%) over the same 12-year period. This is written in the Technical Report Number 18, Contraceptive Use and Commodity Costs in Developing Countries 1994 - 2005, UNFPA.

As mentioned already, the number of MWRA is expected to grow significantly from 797 million women in 1990 to 959 million women in 2000. Contraceptive prevalence in developing countries from its current 51 per cent to 59 per cent in 2000. Applying these rates the number of contraceptive users will grow from 381 million in 1990 to 567 million in 2000.

Because of a large increase in the number of MWRA during the period of 1994 - 2005, in order for contraceptive use to remain at the same level as in 1994 there would have to be almost 100 million additional contraceptive users by the year 2005.

The estimates of contraceptive prevalence average about three percent points higher than estimates by the United Nations of the total fertility rates (TFRs). Countries that have significantly higher levels of contraceptive prevalence than would be estimated by the United Nations TFR include Algeria, Botswana, Brazil, China, Costa Rica, the Islamic Republic of Iran, Jordan, Kenya, Viet Nam and Zimbabwe.

To keep population growth at no more than 950 million persons during this period, there must be an increase in contraceptive prevalence in developing countries from 57% to 63%.

This small increase of about one half of a percentage point annually in contraceptive prevalence, combined with a large increase in the number of MWRA produces an increase of 157 million to a total of 602 million users, the number needed to achieve fertility levels at least as low as the United Nations medium population projection.

To reach the low population projection, the effect would need to be somewhat greater than altering the medium population projection, an increase of about 176 million (to a total of 602 million) as compared with the medium goal of 157 million additional contraceptive users. The ambitious goal of attaining replacement fertility for each country in the world would require 269 million additional users, 60% more than the number in 1994.

Despite high number of potential contraceptive users will grow in developing countries various factors (government family planning policies result in social marketing and low prices in comparison with those in industrialized countries) makes unattractive to the large portion of private sector. Nonetheless, several large pharmaceutical companies have been actively involved in contraceptive market in developing countries. Despite the low market value, large pharmaceutical companies such as Shering A.G., Organon and Wyeth-Ayerst recognize the long-term profit potential in developing countries. These firms have oral contraceptive (OC) manufacturing plants in over 20 developing countries including Bangladesh, Egypt, India, Indonesia and Pakistan.

Estimates and Projections of Contraception Commodity Requirements and Costs

The estimates and projections in this chapter are based on the estimated number of users showing all women 15 - 49 years of age, not just married women of reproduction age.

Commodity Requirements

Commodity requirements are assumed to be the same for new and continuing users and, therefore, there was no need to make separate estimates for receivers and users. Table 4 shows the present estimates of contraception commodity requirements in terms of the number of sterilization procedures, IUD insertions, the number of injection applications, and millions of cycles of pills and millions of condoms. The calculations are based on the following assumptions:

Pills: 15 cycles a year in use
Condoms: 125 a year, plus 20% waste
Injection: Depo-provera, 4 injections per year, and
Novisterat, 6 times a year is the ratio of two types of injection 60/40
Sterilization: the average number of users of minolap kits, vasectomy kits and lapracolor systems is estimated.

Similarly, the number of gloves, gauze pads, sutures and cold sterilization solutions were estimated. The costs were then estimated for a vasectomy, minolap and sterilization by laparoscope, and the costs averaged on the basis of the estimated mixture of these methods.

No cost escalation has been included in the projections of the current costs. The costs of condoms, pills, injections and IUDs were the same in 1993 as they were in 1990. The value of NORPLANT^{R} implant has increased about 15% since 1990. Equipment and supplies required for sterilization have increased in price by about 5% from 1990 to 1993.

Table .. presents estimates of contraception commodities, if produced on the international market, using the cost figures cited under ..... The estimated cost of commodities increases from 528 million in 1994 to 752 million in the year 2005. The total for the 12 year period 1994-2005 is estimated to be $7,692 million for family planning plus $406 million condoms for STD/HIV prevention.

The raw numbers are very large - about 196 million sterilizations, 436 million IUD insertions, 898 million injections, more than 12 billion cycles of pills and 55.7 billion condoms for family planning. An additional 14.6 billion condoms are estimated to be needed for STD/HIV prevention. Thus, the total number of condoms required during this period would be 70.3 billion.

The annual number of receivers of IUDs and sterilization are much lower than the total number of users.

Sterilization was estimated to be 200 million in 1994, and 262 million in 2005. This increase will require a further 196 million voluntary sterilizations over a 12-year period because substantial numbers leave reproduction age each year.

Similarly, to increase in the number of IUD users from 113 million to 139 million, 438 million IUD insertions will be required. Again, the large number is the consequence in part of IUD renewal (on the average, after 3.5 years) and to a lesser extent, the aging of women of reproduction age.

The figures for injections are more dramatic; in order to increase the number of persons using injections from almost 12 million to about 19 million 898 million injections would be required on the average. 4.8 million persons received injections this year: 60% using Depo-provera which requires four injections yearly, and 40% using Nomisterat, which requires six injections yearly.

3.2 Funds for Contraceptive Research

The mission has been confused by the population debate. As to science holds less promise for future. Expanding output of any science requires a regularly replenished and expanding scientific pool of trained scientists. There is a concern about the aging of scientist active in contraception development. Industry for a number of reasons retrenched. From the major pharmaceutical companies the following ones were active in contraceptive research and development: Syntex Laboratories, G.D. Searle and Co., Parke-Davis and Co., Merck, Sharp and Dome Co., Upjohn Company, Mead Johnson, Wyeth-Ayerst Laboratories and Eli Lilly and Company.

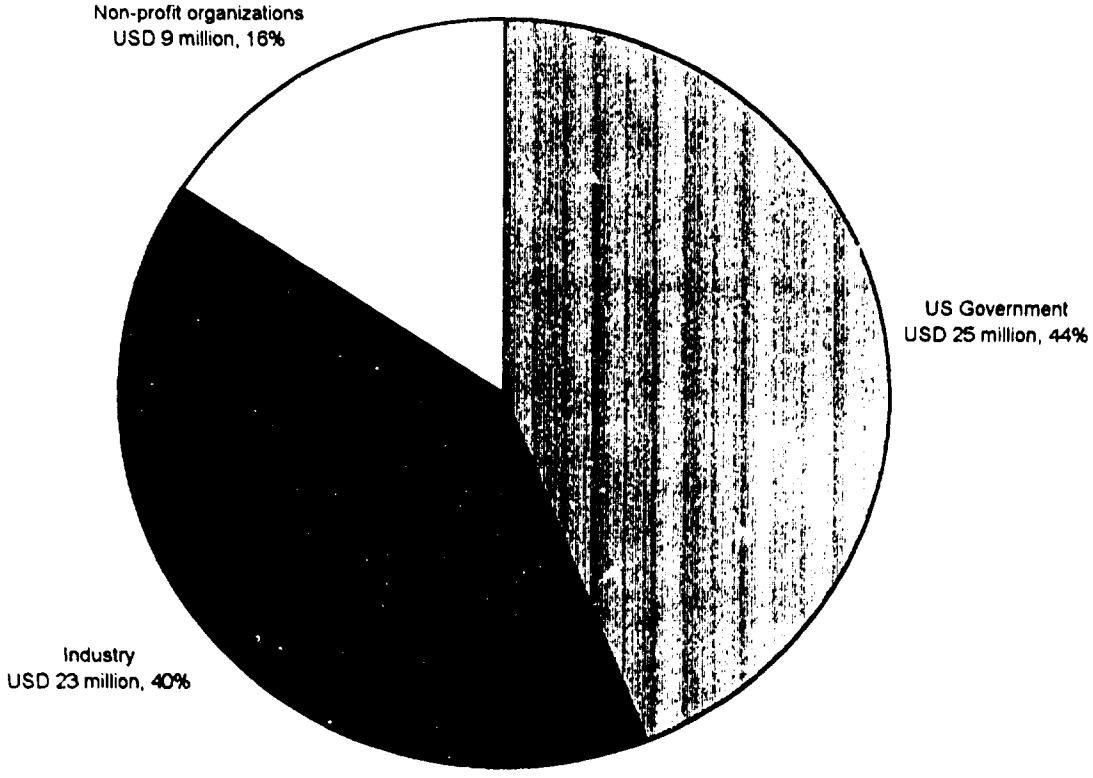
In the 1980s, there were only four companies. Ortho Pharmaceutical Corp. (a subsidiary of Johnson and Johnson), Organon International, Schering A.G. and Russel-Uclaf (a subsidiary of Hoechst Pharmaceuticals).

From smaller companies, Leiras Oy invented and marketed the NORPLANT^{R}.

Alza Coposition has been involved in contraception-related product development but not in research for new chemical entities.

US Government	25
Industry	23
Non-profit organizations	9

Figure .. Estimated Global Funding of Contraceptive R&D in 1993



The structure international research in reproductive health

The structure of international health research in general and of international research in reproductive health in particular, can be viewed at two levels -funding and conducting activities- which may appear to be distinct but there is a lot of overlap when the structure of research looked at in close detail. Beside the primary sources of funding, intermediate organizations may be involved in both funding of research and also conduct of research. They may also be involved in providing technical support, a middle function between funding and conduct research. Private industry is also a special case, in that it plays both roles funding as well as conduct of in-house research.

Funding of international research in reproductive health

Funding for health research basically comes from either public sources (Government funds) or private sources (not for profit agencies such as Philantropic Organization and NGOs and the profit-oriented pharmaceutical industry).

Public funds

1. Industrialized countries:

Developed country governments vary in a level of support for international research in reproductive health in developing countries. Some are conspicuous for their strong commitment. Some are more conspicuous by their absence. Where there is a strong commitment for international research in reproductive health, the focus of governments varies between population concern and broader reproductive health issues. Where population is concern, the emphasis also varies between the development of new and improved contraceptive technolcgies and social science and operations research to enhance acceptance of family planning.

The funds of governments of industrialized countries for international health research are directed to national research organizations in their own countries, to national research in developing countries as a part of bilateral aid programmes and through the intermediary of international agencies and programmes.

National

(a) Publicly funded national research organizations. Many developed countries provide limited support to their own institutions to study health problems of developing countries, an investment that was estimated by the Commission on Health Research for all health about $354 million in 1986 (about 2 per cent of total publicly funded health research in industrialized countries). These modest method, however, constitute a substantial share (about 21 per cent) of research funding available for research on health problems of developing countries.

USAID provides major support to international research in reproductive health, mostly through collaborating agencies, based in US. These are discussed under international research programmes. We have included in this survey a number of national research council or their equivalents. Information was readily available from two publicly funded national research organizations in developed countries because of their clear mandate in reproductive health. The Center for Population Research (CPR) of US National Institute of Child Health and Development (NICHP) and UK Medical Research Council (MRC) Reproductive Biology Unit. Some information has also been provided from France and Germany. The CPR is responsible for primary US Federal extramural effort is population research. It carries out its programmes through the support of research and research training in the biomedical, demographic and behaviourial sciences. With a total budget of contracts and grants of US $141,124,000 in 1992. It supports institutions largely in USA and also conducts research in its own testing facilities.

The MPC Reproductive Biology Unit, twinned with University Department of Obstetrics and Gynecology to constitute the University of Edinburgh Center for Reproductive Biology receives a beget of about US $3.7 million from the UK MRC and raises a further 2.1 million per annum from other sources. The main objectives of the Center are to develop new methods of contraception for use through the world and new treatment for the management of infertility and other reproductive disorders. Clinical and basic research are conducted in the center.

International

(b) Bilateral official development assistance: Health research and research capacity

building are funded a part of bilateral aid to contribute to health improvements in developing countries. The Commission of Health Research for Development estimated the total of funds allocated in 1986 for bilateral official development assistance support of developing country health research of all types to be about US$130 million.

© Contributes to multilateral agencies: These are contributions to the budgets of multilateral organizations (mostly UN agencies but also including regional grouping such as the European Communities) that allocate part of their funds for health research or direct contributions to international research programmes.

(d) Publicly supported, semi-autonomous development research funding agencies. In Canada the International Development Research Center (IDRC) and in Sweden, the Swedish Agency for Research in Developing Countries (SAREC) provide a special mechanism for assistance in international research to solve developing country's problems, including reproductive health research.

The IDRC funds research institutions in the South to assist Southern researcher in creating their own long-term solutions to pressing development problems. IDRC sponsored research in reproductive health is spread evenly over most developing regions with regional offices in Singapore, New Delhi, Montevideo, Dakar, Johannesburg and Cairo. For fiscal year 1992/93 the Center in grants of US $1.2 million for reproductive health research, representing 3 per cent of the Center's total research budget. Fields of activity include family planning, safe motherhood, STD/AIDS as well as research capacity building.

SAREC is an independent Government Agency with main objective to strengthen endogenous research capacity in developing countries. Approximately $2.5 million were allocated for reproductive health research in 1992. Special initiatives on STDs/HIV are supported with about $2 million/year. SAREC provides support to WHO/HRD and WHO/FHE it also supports reproductive health research in bilateral programmes in Mozambique, Zimbabwe, Tanzania and Nicaragua. Support is also provided in Swedish research institutions for research on developing country problems.

2. Developing countries

The contribution of developing country government should not be underestimated. The Commission on Health Research for Development made the observation that a relatively substantial amount of investment in health research in developing countries is made by developing governments (an estimated $650 million out of a total of $1.0 billion).

Developing country governments contribute to international research in reproduction health indirectly through their contribution to the multi-lateral UN agency UNFPA, and directly through modest contributions to the WHO Special Programme of Research, Development and Research Training in Human Production (HRP) and through their support to national research organizations which collaborate in international research.

Private Funds

a) Philanthropic organizations: These are based primarily in North America, but in growing numbers in Europe and Japan. The Commission on Health Research for Development estimates suggest that the total foundation contribution to research on developing country health problems was about $50 million in 1986. These funds are directed partly as contributions to international health research programmes, and partly as direct support for research in industrialized countries (to serve developing country needs) or in developing countries. The level of interest in reproductive health research varies among foundations. Within reproductive health research, the focus also varies from one foundation to the other and also in the same foundation overtime. We have included in this survey foundations which have specific programmes related to reproductive health. The Andrew W. Mellon Foundation, The Ford Foundation, the John P. and Catherine T. MacArthur Foundation, and the Rockefeller Foundation provided detailed information on their activities, which is included in the next section of this report.

The population programme of the Mellon Foundation (with grants totaling roughly $8-10 million a year) supports biomedical research in reproductive biology and contraceptive developments, social science research and training, as well as services and population policy research. Virtually all Mellon grants are made to US organizations, although the majority of grants relate to research on developing countries and/or are in collaboration with developing country investigations and institutions.

The reproductive health and population programme of the Ford Foundation (with a budget of approximately $16.7 million) seeks to improve sexual and reproductive health. Funds support grantees in Eastern and Southern Africa, the Middle East and North Africa, West Africa, Asia (China, Bangladesh, Indonesia, India, Thailand, Philippines), Latin America and the Caribbean (Mexico, Brazil), as well as undeveloped countries.

The MacArthur Foundation's population programme supports a limited amount of research on the social aspects of reproductive health. Grant making is centered in four countries: Mexico, Brazil, Nigeria and India. In 1992 the Foundation made 23 grants of $3,816,300 toward social science research projects related to reproductive health.

The Population Sciences Division of the Rockefeller Foundation, in collaboration with the Health Sciences Division (with grants totaling about $14.9 million), supports research for developments of new technologies for fertility regulation, social sciences research, research on family and community reproductive health initiatives, as well as research capacity building, particularly in Africa.

Non-governmental organizations (NGOs)

Many non-governmental organizations with access to private funds, often with headquarters in industrialized countries, undertake action programmes addressing health problems in developing countries. The NGOs are, however, primarily oriented toward action, not research, and so spend only a small share of their funds on research. Often innovative experimental field action is undertaken, but they are infrequently analyzed or disseminated broadly. The Commission on Health Research for Development made a rough estimate of $10 million for health research by NGO sources.

The largest NGO is the population and family planning field. The International Planned Parenthood Federation (IPPF) does not fund, support or conduct research in any large way. However, it does collaborate with organizations/agencies actively involved in research.

C. Pharmaceutical Companies

Pharmaceutical companies based in industrialized countries traditionally invest large sums

in research and development (R & D). The Commission on Health Research for Development estimated that the 10 largest companies invest 16% of revenue from sales in R & D and that industry as a whole invested about $13 million in 1986. The Commission highlighted that only a very small share of the large research investment by industry is addressed to the health problems of developing countries, and perhaps US $300 million may be so directed, principally aimed at new vaccines against malaria and schistosomiasis, anti-parasite drugs and better insecticides. Moreover, most of this small investment on developing countries' problems is made in industrialized countries.

The Commission estimated about US $20 million were invested in research and development by pharmaceutical companies that are based in developing countries.

In the field of contraceptive research and development, private industry has other disincentives, including concerns about litigation (particularly in the USA), stringent drug regulatory requirements and controversial political climates.

Perhaps even more significant is the perception of the market as "mature" in developed countries and not very profitable in developing countries and of science as drying up with no major breakthroughs. The number of major international pharmaceutical companies involved in this field has diminished from 13 to only 4 in 1980. Although global contraceptive sales are estimated to be 2.6 and 2.9 billion expenditures by industry on contraceptive research and development are about $22 million.

Intermediaries in international reproductive health research

The layer of intermediary support serves as a bridge between funding layers and the actors conducting research. It includes multilateral agencies and international research programmes.

Multilateral agencies

a) Multilateral agencies of the UN system: These agencies channel funds to international research programmes, to country programmes through bilateral agreements, and directly to research institutions. In some agencies, such as the World Bank, research is also done by staff.

Detailed information on activities in reproductive health research was provided by the United Population Fund (UNFPA) and the World Bank. It is our understanding that the World Health Organization (WHO) is preparing a special report in this area. The UNFPA supports research in reproductive health at the interregional level through the agencies that conduct research and at regional and country levels within the frame of programmes of assistance which UNFPA supports. The research activities supported include family planning, biomedical and operational research in the area of family planning and HIV/AIDS and research on attitudes and knowledge of family planning service providers and recipients, safe motherhood, STDs, including HIV, training in research methodologies, capacity building of national institutions in research . The exact amounts provided by the UNFPA for reproductive health research are difficult to extract since such research often forms part of a larger project. For 1992 UNFPA has provided at least $8 million for reproductive health research at the international, regional and country levels.

The World Bank supports reproductive health research in four ways: through participation in international collaboration programmes in its own research activities managed or conducted by Bank staff, through components of population, health and nutrition projects in its lending programme and grants from the Population NGO and Safe Motherhood Special Grant Programmes. The Bank's support covers all fields of reproductive health research, including family planning, maternal and child health, and AIDS. Since reproductive health research is usually carried out as part of wider projects or programmes, the Bank records are kept in such a way as to allow an accounting of the monetary amounts involved. A review of research in Bank-funded Population, Health and Nutrition projects estimated that abut 1% to 2% of the loan-supported research components, 1% of lending for family planning would amount to $1 million in 1992 and $1.8 million for 1993. The Bank's contribution to international research programmes in 1992 totaled $3,375 million.

The United Nations Development Programme co-sponsors and provides support to the WHO Special Programme in Human Reproduction

b.) Other multilateral agencies: The Commission of European Communities support health research in countries of the communities and also collaborate research in developing countries.

International research programme:

In several areas of health research there are now international research programmes (or centers) that are funded by governments of both developed and developing countries, by multilateral UN agencies, and by Foundations. These programmes are collaborated with industry. International Research Programmes exclusively focus on one or more areas of reproductive health research, including the Contraceptive Research and Development Programme (CONRAD), Family Health International (FHI), the Institute for Reproductive Health of Georgetown University, Mother Care, the Population Council, the co-sponsored WHO Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Wellstart International, the WHO Adolescent Health Programme, and Maternal Health and Safe Motherhood Programmes. The Programme for Appropriate Technology in Health has a reproductive health programme, including research as major components of its activities.

The CONRAD Programme is conducted by the Eastern Virginia Medical School under a Co-operative Agreement with the United States Agency for International Development (USAID) to develop more effective, safe and acceptable contraceptive methods that are suitable for use in developing countries. With a budget of $5.6 million (for the year 1992) the programme supports extramural research and development projects worldwide at universities, medical institutes and private companies, as well as international clinical and laboratory research at the Jones Institute for Reproductive Medicine within the Department of Obstetrics and Gynecology at the Eastern Virginia Medical School. The Programme also provides fellowships for training in contraceptive research and development and convenes symposia on important issues in contraceptive technology.

FHI, with funding from USAID, NIH foundations and pharmaceutical companies totalling about $18 million (in 1992), support research in more than 90 countries worldwide in the fields of family planning (including biomedical research for contraceptive technology development, epidemiological research on the benefits of contraception, social/behavioral research and operations research), safe motherhood and HIV/STD prevention. Strengthening the capacity of developing country organizations to plan and implement reproductive health programmes and research is an underlying principle of FHI's work, and its programmes also include a major initiative to access and utilize reproductive health research.

The Institute for Reproductive Health (IRH), Georgetown Medical Centre, is a USAID-funded collaborating agency, serving as a global centre of expertise on national means of fertility regulation, with a budget of $1.2 million, which includes administrative and personnel costs.

Mother Care is a USAID-funded programme established in 1988 and dedicated to reducing natural and prenatal mortality and related mortalities, and to promote the health of women of reproductive age and their newborns. Applied research is one component of its activities. The total first five-year budget for all activities was approximately $13 million.

PATH focuses on enhancing appropriateness, safety, availability and delivery of technologies for health and family planning. Activities include biomedical research for product development, social research for the development of educational and communication material, operations research for technology assessment and market research. The fields of activity cover family planning, safe motherhood, STD/HIV, as well as research capacity building. Grantees are in Eastern Europe, sub-Saharan Africa, Asia and China. Funds designated solely for reproductive health research are difficult to estimate because, for the most part, research is a component of larger projects but the budget for 1992 for reproductive health activities which had a research and evaluation component was $7,755,000.

The Population Council, with a 1993 budget exceeding $46 million, gets more than half of its funds from government and United Nations agencies. The Council has its headquarters in New York and regional offices in Bangkok, Cairo, Mexico City and Nairobi, and ten additional country offices. Research is conducted in 48 countries in Latin America, the Caribbean, West Asia, North Africa, South and sub-Saharan Africa. The Council's reproductive health programmes cover a broad range of activities: biomedical research to develop and improve methods of contraception, efforts to improve the quality of care of family planning programmes; the Egbert Programme, which focuses on important and neglected and controversial areas of reproductive health, and a broad range of natural and child health work, including the Safe Mother Initiatives.

HRP co-ordinates, promotes, conducts and evaluates international research in human reproduction. Activities cover biomedical research for the development of new and improved research of reproductive health with emphasis on potential and management of

Table 3 3.4 Intrauterine Devices

Method	Product	R&D Location	Status	Comments
FRAMELESS IUD	Flexigard 330 - Copper releasing IUD; six copper collars on nylon thread that is imbedded in the uterine fundus, also called CuFix 330	Developed in Belgium; WHO/HRP; GynoPharma to distribute in USA upon approval	Clinical trials in Europe and USA for more than 3 years by developer; WHO multicenter trials dropped due to high number of expulsions.	Significantly less removal for pain and bleeding reported
FRAMELESS POSTPARTUM IUD	CuFix PP330 - Same device as above, designed for postpartum insertion; polyacide coglycolide biodegradable anchor to the uterine muscle.	WHO/HRP	Phase II trials in Europe	CuFix is one device being tested with postpartum users; others also being tested
PROGESTIN-RELEASING IUD	Levonorgestrel-releasing IUD; a silastic collar containing levonorgestrel added to a Nova T-shaped IUD; release 20 mcg daily	Leiras Pharmaceuticals, Population Council, WHO/HRP	Approved for use in some European countries	7-year comparative study demonstrated that levonorgestrel releasing IUDs had equivalent efficacy to Copper T 380A; markedly reduces levels of bleeding

continued

Method	Product	R&D Location	Status	Comments
IMPLANTS	Implanon - single rod, expected effectiveness 2-3 years; releases 3-keto-desogestrel at daily dose of 30 mcg	Organon	Phase III studies ongoing	
BIO-DEGRADABLE IMPLANTS	Capronox-II - two implants, 4 cm capsule of polymer caprolactone filled with 18 mg levonorgestrel; effective for 1 year	CPR/NHCD, Research Triangle Institute	Animal studies	Some problems with biode-gradability experienced
	Capronox-III - possibly single implant, 4 cm co-polymer capsule (capro-lactone and trimethylene carbonate blend) filled with 32 mg levonorgestrel, effective for 1 year		May be available by the of the 1990s	The copolymer blend releases the drug more readily and also biodegrades more quickly than the single polymer as used in Capronox II

Method	Product	R&D Location	Status	Comments
	Annuelle (also known as NET implant) - 4-5 small pellets made of 90% norethindrone (NET) and 10% cholesterol; effective for 1 year; each pellet contains about 35 mg NET; 8 mm in length	CONRAD; Endocon, Inc.; FHI	Ongoing Phase II clinical trials comparing pharmacokinetics of various pellets	

Table 3.3.3 Long-acting Steroid Implants

Method	Product	R&D Location	Status	Comments
IMPLANTS	Norplant II - modified version of Norplant using 2 rods, expected effectiveness 3-5 years; contains levonorgestrel	Population Council/Leiras Pharmaceuticals	Phase II studies ongoing; widely dispersed in pre-introduction trials	May reduce incidence of removal problems experienced with 6-capsule system; appropriate for breastfeeding women
	Single ST 1435 rod implant - modified subdermal implant, expected effectiveness 2 years; releases the progestin ST 1435 at daily dose of 100 mcg	Population Council	Prototype devices tested in 3 countries with 12 volunteers (1991); dose finding studies planned	Appropriate for breastfeeding women (since ST 1435 does not act orally, safe if passed through breast milk); ST 1435 has been evaluated since 1976 for subcutaneous implants; human trials reported since at least 1981
	Uniplant - single, silastic implant, releasing nomegestrol acetate; releases approximately 100 mcg per day of progestin; effective for 1 year	South-to-South (Rockefeller), Thermex, Brazil, Chile, China, Dominican Republic, Egypt, Nigeria	Phase II studies planned	Inhibits ovulation in about 50% of cycles; peripheral action account for remainder of contraceptive effect. Good bleeding control is reported compared to Depo Provera or Norplant. Reported pregnancy rate is 1.1 (Pearl Index)

continued

Method	Product	Mode of Action	R&D Location	Status	Comments
INJECTION	HRP 002 - intramuscular injection of progestin (levo-norgestrel butanoate) size of crystals modified to produce more effective, slow release of drug	Thickens cervical mucus; may also inhibit ovulation	CPRN/NCHD, WHO/HRP	Tested in Phase II comparative clinical trials at four international sites; pharmacokinetic studies of new formulation ongoing. Metabolic studies will be undertaken.	
	Progesterone macrocrystals		Aplicaciones Farmacéuticas, CONRAD, Mexico	Under investigation	Also being considered in combination with estradiol macrocrystals

Table 3.3.2 Long-lasting steroid injections

Method	Product	Mode of Action	R&D Location	Status	Comments
INJECTION	Cyclofem - (Cyclo-provera, HRP 112) monthly injectable; progestin combined with estrogen (25 mg DMPA + 5 mg estradiol cypionate)	Inhibits ovulation	Upjohn, WHO/HRP	Extensively tested in multi-national clinical trials for introduction in Chile, China, Egypt, Indonesia, Jamaica, Mexico, Thailand and Tunisia. Registration and sale begin in 1993.	Good cycle control, rapid return to fertility; production scheduled to begin in Mexico, Indonesia and Thai-land in 1993
	Mesigyna (HRP 102) - monthly injectable; progestin combined with estrogen (50 mg NET-EN + 5 mg estradiol valerate)		Schering AG, WHO/HRP		Good cycle control, rapid return to fertility
	NET-90 - Intramuscu-lar injection of nor-ethindrone in semiper-meable biodegradable capsules; provides 3-month protection	Thickens cervical mucus; may also inhibit ovulation	CONRAD, FHI, Medisorb, Ortho, Stolle Research & Development Corporation	Injectable microspheres of NET have been tested in nearly 200 women; more extensive clinical trials under way (1990)	Slow release from microcap-sules allows greater control over drug compared with standard injectable delivery. Technology being investigat-ed for release of progesterone and norgestimate.

Method	Product	Mode of Action	R&D Location	Status	Comments
Weekly pill + Prostaglandin	Single dose of mifepristone followed 36-48 hours later by prosta-glandin, given shortly before or at time of expected menses	Endometrial and decidual effect; disruption of implantation when conception has occurred	WHO/HRP, Sweden	Pilot phase studies	
Menstrual Regulator	Single dose of mifepristone followed 36-48 hours later by prostaglandin, given within 7 days after missed menses	Endometrial and decidual effect. Termination of very early pregnancy if conception occurred	WHO/HRP	Multicenter Phase II study completed	
OTHER ANTIPROGESTINS	Several hundred antiprogestational compounds	Similar to mifepristone i.e. blockage of progesterone (and often also glucocorticoid) receptors	Jenapharm, Organon, Schering, private institutions (eg, Research Triangle Institute)	In vitro and animal studies; Phase I or II studies on a few selected compounds	

Table 3.3.1. Antiprogestins for women

Method	Product	Mode of Action	R&D Location	Status	Comments
MIFEPRISTONE Sequential Pill (antiprogestin + progestin)	Mifepristone followed by progestin (such as medroxprogesterone acetate) in a sequential regimen	Ovulation inhibition	Population Council (discontinued) WHO/HRP	Pilot phase studies	
Antiprogestin-only Pill	Continuous, daily low-dose regimen of mifepristone	Endometrial effect	WHO/HRP	Pilot phase studies	
Emergency Contraceptive	Single dose of 600 mg mifepristone given within 72 hours of unprotected intercourse	Ovulation inhibition; endometrial effect	WHO/HRP	Promising results in two completed trials; multi-center trials planned	Mifepristone has fewer side effects but causes delayed menses more often than Yuzpe regimen (combined estrogen/progestin)
Monthly pill	Single dose of 200 mg mifepristone given two days after urine LH peak	Ovulation inhibition; endometrial effect	WHO/HRP, Sweden	Phase II efficacy trial nearing completion	Necessity of accurate timing of drug intake relative to ovulation may prevent routine use until simple marker of ovulation has been identified

continued

In India, contraceptive R&D is carried out by a network of government-sponsored research institutes. A national committee sets priorities for research and the Indian Council for Medical Research (ICMR) monitors the progress of approved projects.

China's government has also supported contraceptive R&D which led to major innovations such as the no-scalpel vasectomy technique. Research is being conducted on other sterilization techniques, new male methods, contraceptive vaccines, antiprogestins, various types of IUDs and a two-rod implant system.

* * *

ANTIPROGESTINS FOR WOMEN (table 3.3.1.)

Depending on the stage of menstrual cycle and dose used, these compounds can suppress follicular development and prevent ovulation or disrupt the process of implantation. Also used in confirmed pregnancies for termination of pregnancy (in combination with prostaglandin), cervical ripening, and induction of labor. Mifepristone is the most widely studied antiprogestin and the only one registered for clinical use.

LONG-LASTING STEROID SYSTEMS - Implants, Biodegradable Implants, Injectables, Vaginal Delivery Systems, Transdermal Delivery Systems

Designed to provide slow release of steroids over time resulting in suppressed ovulation and reduced cervical mucus permeability to sperm. Injectables are the most commonly used method of this group.

RESEARCH OBJECTIVES - Develop more effective and acceptable means of hormonal contraceptives that would reduce risk of patient error, increase compliance and reduce necessity of repeated contacts with medical personnel while still being reversible.

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LONG-LASTING STEROID INJECTIONS (table 3.3.2)

LONG-LASTING STEROID IMPLANTS (table 3.3.3)

* * *

INTRAUTERINE DEVICES (IUD) - Frameless, Postpartum, Chemical Releasing, Fixed-Shape (table 3.3.4)

The IUD can be a highly effective method for long-acting reversible contraception. First described in 1909, IUDs have been made in many shapes and sizes. More than 85 million women around the world use an IUD. Nearly 60 million Chinese women use the IUD; most use a stringless stainless steel ring. Outside of China, the IUD most commonly inserted is the Copper T 380A.

RESEARCH OBJECTIVE - Reduce side effects, such as bleeding and pain, and modify existing devices for postpartum insertion.

* * *

FEMALE BARRIER METHODS - Sponge, Diaphragm, Cervical Cap, Spermicides

Vaginal barrier methods have been described for more than three centuries. Their popularity has been limited primarily by acceptability and accessability issues. Vaginal methods have received renewed attention because spermicides and vaginal barriers, along with condoms, are the only available contraceptive products that may help reduce STD transmission rates.

RESEARCH OBJECTIVES - Improve user acceptability by developing a range of products that are effective and easy to use.

* * *

FEMALE MECHANICAL BARRIERS (table 3.3.5)

SPERMICIDES (table 3.3.6)

VAGINAL RINGS CONTAINING LONG-LASTING STEROIDS (table 3.3.7)

* * *

FEMALE STERILIZATION - Ligation, Cautery, Clips, Plugs, Chemical Occlusion (table 3.3.8)

Voluntary female sterilization is the most widely used family planning method in both developed and developing countries; it is also one of the fastest growing methods. Female sterilization works by blocking the fallopian tubes thus preventing passage of the egg to the uterus. The fallopian tubes are reached through a minilaparatomy or laparoscopy procedure. The most common techniques for blocking the tubes are ligation, clips, and cautery. ith minilaparotomy, each tube is brought to a small incision in the abdomen where it is tied and a segment of the tube is removed. Laparoscopy consists of using a laparoscope to apply clips, rings, or heat to block the tubes.

RESEARCH OBJECTIVES - To discover safe, simple, effective, non-surgical means for sterilization; preferably reversible; and to make sterilization available to larger numbers of women at lower cost.

* * *

IMMUNOLOGICAL CONTRACEPTION - ANTI-hCG, - ANTI-TROPHOBLAST, - ANTI-SPERM, ANTI-OVUM (table 3.3.9)

The most advanced vaccines are those based on human chorionic gonadotrophin (hCG), the principal hormone product of the preimplantation blastocyst. Other studies are focusing on vaccines based on molecules expressed on the surface of the blastocyst and on the gametes (sperm and ova). May take several months for antibody response to develop during which another method must be used. Some women's groups are concerned about potential for abuse of method.

RESEARCH OBJECTIVES - To prevent fertilization or implantation. Ideally these vaccines would produce an antibody response in at least 95% of women, would be administered at 12-18 month intervals, and would be free of side effects. Various groups are working on these vaccines, with collaboration among the groups at many levels.

Method	Product	R&D Location	Status	Comments
FIXED SHAPE IUDs	CuSafe 300 - Copper-releasing IUD; variation of the Copper T with the arms bent downward	Developed in Germany, private sector funding	In clinical trials in Germany	Efficacy rates promising; expulsion rates very low; in trials by developer
	Mark II and MLCu-375 SL - modified Multibad IUD with shorter, more flexible arms and shorter IUD stem	Organon	MLCu-375 SL marketed in Finland	Designed to reduce problems with insertion/ removal
	Ombrelle-250 - flexible, designed to move toward fundus during uterine contractions	Organon	Being studied in Europe; marketed in France since 1986	Designed to reduce problems with insertion/removal
	Chinese researchers have developed various IUDs; 2 examples are the TCu-188 and the Shanghai V-200	China	Available in China	Devices designed to reduce pain and minimize expulsion

Table 3.3.5 Female mechanical barriers

Product	Mode of Action	R&D Location	Status	Comments
FemCap - over-the-counter; silicone rubber device shaped like sailor's cap; dome covers cervix; potential for use with or without spermicide	Mechanical barrier between sperm and cervix	CONRAD	Phase I study ongoing	Silicone rubber is non-reactive, non-allergenic, durable, heat stable, and can be sterilized; one size fits all; may need medical fitting
Lea's Shield - oval-shaped, silicone rubber device inserted in upper vagina, covering the cervix; reusable		CONRAD; Yama, Inc.	Undergoing Phase II clinical evaluation	Has the potential for being used continuously for 48 hrs., possibly without spermicide; designed to be supplied over-the-counter; one size fits all
Female Condom - several devices being developed, most widely tested is Reality™ (WPC 333), an over-the-counter barrier contra-ceptive; poly-urethane sheath with flexible ring at either end (also called Femidom)		CONRAD, Chartex, Ltd., Family Health International; WHO/HRP; Wisconsin Pharmacal	Approved for use in France, Switzerland and England	Over-the-counter device designed to reduce transfer of virus, bacteria and sperm between partners

continued

Product	Mode of Action	R&D Location	Status	Comments
Disposable diaphragms - non-metal rim devices with controlled release of spermicide designed for one-time use only: poly-urethane and silastic devices being tested	Mechanical barrier with spermicide	CPR/NICHD		May be more effective than the Today™ contraceptive sponge as it may provide more of a barrier; no need to add spermicide, so may be more acceptable to users

Table 3.3.6 Spermicides

Method	Product	R&D Location	Status	Comments
SPERMICIDES	Long-acting spermicide suppository, designed to release nonoxynol-9 over long periods of time	CPR/NICHD		May eventually provide long-term STD and pregnancy protection
	Propanolol - widely used in treatment of cardiovascular disease, spermicide research has focused on the inactive enantiomer. Concentrates in cervical mucus.	CPRN/NCHD, Family Health International	One study in 1990s involving 198 volunteers found a pregnancy rate of 3.9 per 100 woman years of use	Research discontinued
	C31G - Originally developed as an oral disinfectant; virucidal/ spermicidal compound similar to nonoxynol-9 but potentially less irritating	Biosyn, CONRAD, CPR/NCHD, WHO	Animal studies near completion; Phase I human studies may begin 1993	May have spermicidal, virucidal, and bacteriocidal properties similar to nonoxynol-9

continued

Method	Product	R&D Location	Status	Comments
	Screening of new compounds and formula-tions such as chlorhexadine	CONRAD, CPR/NCHD, Population Council		Emphasis is on compounds with virucidal and bacteriocidal properties
PLANT EXTRACTS WITH SPERMICIDAL ACTIVITY	Triterpene saponins - steriod glycosides derived from Acacia Auriculifonis	Indian Institute of Chemical Biology	In vitro testing for spermicidal activity. Animal tests for toxicity irritation.	This plant is widely distributed throughout India; effective dose is low (ED = .35 mg/ml); through higher than nonoxynol-9 (ED = .125 mg/ml), it is lower than gossypol (ED - .40 mg/ml)
	Neem Oil - purified NIM-76 fraction	INI, South-to-South (Rockefeller)	Animal studies ongoing	
	Gossypol	South-to-South (Rockefeller)		Other researchers also looking at gossypol as a virucide

Method	Product	R&D Location	Status	Comments
POTENTIAL RESEARCH AREAS	Nonochlonal antibodies of the IgM class, anti-sperm antibody, could be applied topically or used with a vaginal device	CONRAD, Johns Hopkins University		May eventually provide women with continuous long-term STD and pregnancy protection; monoclonal antibodies are 1,000 times more effective at immobilizing sperm than nonoxynol-9,; could be used in a vaginal ring or in a diaphragm-like device

Table 3.3.7 Vaginal rings containing long-lasting steroids

Method	Product	Mode of Action	R&D Location	Status	Comments
Vaginal Rings	Progestin (levonor-gestrel)-releasing ring; releases 20 mcg/day of levonorgestrel; can be left in place for 3 months	Thickens cervical mucus; may also inhibit ovulation	Roussel Labs (UK), WHO/HRP	Extensively tested at 19 centers; ready for production and registration	Appropriate for breast-feeding women
	Progestin (ST 1435)-releasing ring - can be left in place for 3 to 5 months		Population Council	Small scale trial in France and Finland	
	Progesterone-releasing ring - can be left in place for 3 to 5 months		CONRAD, Population Council, WHO/HRP	Phase II clinical studies completed at 11 clinics	
	Megestrol acetate - can be left in place for 12 months		China	Phase II studies completed	

Table 3.3.8 Female sterilization

Method	Product	R&D Location	Status	Comments
CLIPS	Cambridge Clip - modification of existing clip designs (Hulka and Fitshie); hinge pin is made from titanium and lubricated with silicone, audibly snaps when clipped properly	Private sector funding	Ongoing clinical trails in UK; patented in several countries, including Bangladesh, Canada, China, Pakistan and U. S.	Designed to have fewer operator failures; may have good prospects for reversibility; plastic parts may make clip less expensive than metal devices
PLUGS	Ovabloc™ (now Alphatron) - silicone plugs	WHO/HRP	Available in Canada, Netherlands and Switzerland	May improve prospects for reversibility
CHEMICAL OCCLUSION	Quinacrine pellets (quinacrine hydrochloride) - delivered transcervically using an IUD inserter; two insertions are necessary, one month apart, other contraceptive method required between insertions	Chile, FHI	Introduced in 1970 in Chile; also studied in Indonesia, India, Pakistan, Malaysia, Mexico, Vietnam and U. S.	Family Health International has initiated study of long-term safety of quinacrine; potential cancer connection

continued

Method	Product	R&D Location	Status	Comments
	Methyl cyanoacylate (MCA) - like quinicrine, this is a phenol-based compound; used as a tissue adhesive in humans since 1950s; delivered to the uterobal junction by means of a balloon-like catheter.	Brazil, Columbia University, CONRAD	Studies in many countries since 1990; various protocols used	Results from 3 Latin American study sites; bilateral tubal closures in 70% of women after one MCA application and 90% of women after two applications. Few complications reported.
	Iodine compounds - inserted through cervix in fallopian tubes	FHI		
	PAP (phenylatabrine) - a paste that is inserted through the cervix into fallopian tubes	China	Available in China	Studies to date report similar efficacy and rates of complication to mini-lap: but duration of complications was shorter

Table 3.3.9 Immunological contraception

Method	Product	Mode of Action	R&D Location	Status	Comments
Anti-HCG Vaccine	Whole ß-hCG vaccines - ß unit of the hCG linked to tetanus toxoid; could also be conjugated to diphtheria or cholera toxoid	Antibodies block action of HCG (hormone necessary for maintenance of pregnancy)	Indian National Institute of Immunology (INI), Population Council	Phase II studies of Indian vaccine almost completed as of 1993. Phase I studies of Population Council vac- cine completed in 1991.	80% of immunized women achieved effective levels of immunity; among these women there was one pregnancy in more than 900 cycles of exposure. Mag- nitude and duration of immune response varies by individual. Several months required to reach sufficient antibody response.
	Prototype consisting of synthetic peptide of hCG-specific portion of ß-hCG linked to diphtheria toxoid		WHO/HRP, Australia WHO/HRP, Sweden	Phase I trials completed 1988 Phase II trial planned to start in 1993	Dose-dependent response in 30 women lasted 3-9 months above estimated efficacy threshold

continued

Method	Product	Mode of Action	R&D Location	Status	Comments
	Advanced prototype (C-terminal peptide ß-hCG) - same as prototype by formulated in polymer delivery system		WHO/HRP	Pre-Phase I: toxicity studies planned to start in 1993-94	Formulation designed to provide 12 mos. protection from single administration of vaccine
ANTI-TROPHO-BLAST VACCINE	Vaccines based on molecules found on surface of pre-implantation embryo	Antibodies interfere with implantation		Animal studies	Research uses a combination of molecular gene- tics and monclonal antibodies to identify molecules of interest
ANTI-SPERM VACCINE	Vaccines based on sperm specific proteins (e.g., LDH-C_4, SP-10, PH20)	Antibodies interfere with fertilization	CONRAD, CPRNN/NICHD, INII, Fopu- lation Council and many others	Laboratory and animal studies complete	Advantages of pre-fertilization effect and high immunogenicity but problems of heavy antigen load and possible need for mucosal immunity

continued

Method	Product	Mode of Action	R&D Location	Status	Comments
ANTI-OVUM VACCINE	Vaccines based on zona pellucida show most promise		CONRAD, CPRN/ NICHD, INI, Population Council and many others	Animal studies	Advantage of pre-fertilization effect and high immunogenicity but problems of heavy antigen load and possible need for mucosal immunity

4. INDUSTRIAL TECHNOLOGIES

4.1 Pharmaceutical Preparations for Analysis

The latest List of Essential Drugs of the WHO contains the following hormonal contraceptives tablets:

ethinylestradiol + levonorgestrel	tablet	30mcg + 150mcg
ethinylestradiol + levonorgestrel	tablet	30mcg + 250mcg
ethinylestradiol + norethisterone	tablet	35mcg + 1mg
norethisterone	tablet	350mcg

Other patent-expired products -which have been used for a long time and may also be considered for local production- include:

ethinylestradiol + levonorgestrel	tablet	50mcg + 250mcg
ethinylestradiol + levonorgestrel	tablet	30mcg + 50mcg
ethinylestradiol + levonorgestrel	tablet	40mcg + 75mcg
ethinylestradiol + levonorgestrel	tablet	30mcg + 125mcg

The combination of the above compositions increases the choice and permits the manufacture of biphasic and triphasic oral contraceptives, as well.

levonorgestrel	tablet	30mcg
norethisterone + mestranol	tablet	1mg + 50mcg

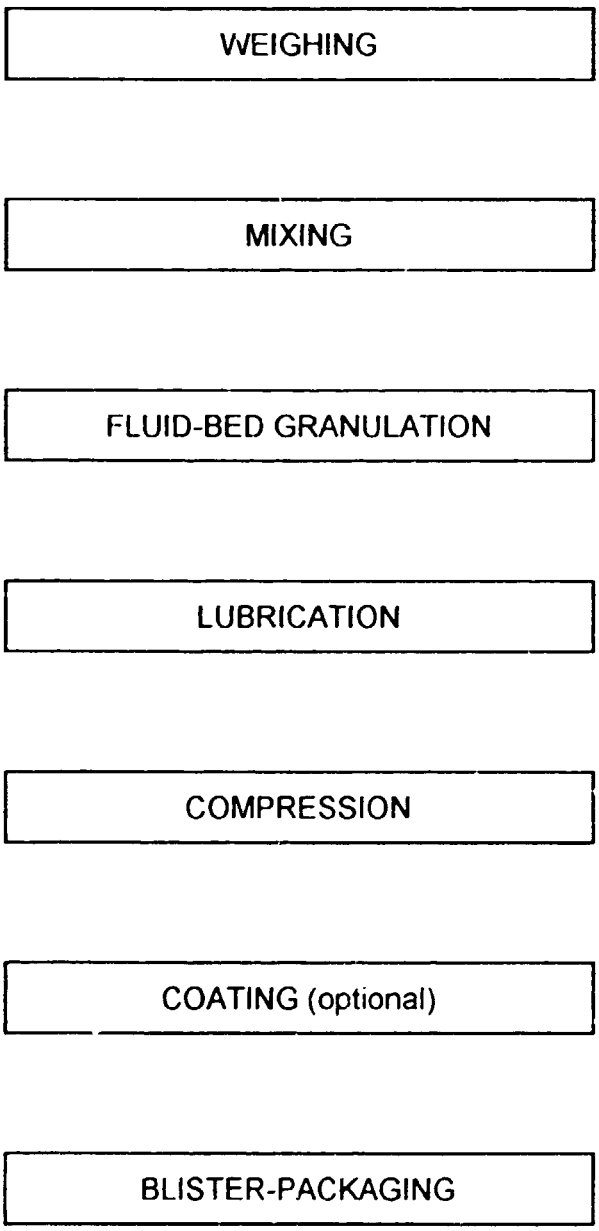
4.2 Contraceptive Steroid Sources

Table ..... presents data on the sources of supply. Governments supply more than 90% of all users of modern methods. Governments provide 95% of all users of modern methods of sterilization and IUDs, but only 57% of pills and 47% of condoms.

The active ingredients of essential contraceptive hormones -included in the List of Essential Drugs of the WHO- are available at competitive prices in international free trade.

4.3 Manufacture of Hormonal Contraceptive Tablets

The following general techniques are used typically in the manufacturing process:



Large-scale production methods of clinically effective formulations of all hormonal contraceptive tablets are fundamentally the same. An inert substance must be added during the development of the formulation to make tableting possible because the

quantities of the active ingredients are small in each of the above described compositions. The small amounts of potent drugs should be homogeneously distributed -frequently with the application of an organic solvent (mixture)- during the preparation of the tablets in order to reduce variations among dosage units of a given batch as well as batch-to-batch differences to a statistically acceptable minimum.

The operations of the above simplified flow sheet can easily be optimized since excipients dominate the physical properties of the formulation; therefore, the manufacturing process is considered technically simple. The good quality of the finished product depends on the quality of the active ingredients and excipients (which should preferably be purchased from approved vendors), facilities, personnel, validated processes and equipment, packaging and the controls (in-process methods, good manufacturing practices and chemical analysis) used during and after preparation of the tablets.

Hormonal contraceptives are very potent biochemicals. The major difficulties in the manufacture of anticoncipient tablets are: material handling, airborne dust problem, residual quantities of the medicinal chemical(s) remaining in equipment after cleaning and the associated labor safety and environment protection problems.

Special attention should be paid to the control and elimination of dust generated during the manufacturing process. Active substances should be weighed under negative pressure in laminar flow. The granulation should be carried out in a completely closed system and the fine powder exhausted from the tableting and coating machines should be trapped in dust separators. If airborne dust contaminates the production facilities or the area surrounding the factory, serious health problems may occur among the workers and in the population living around the factory. Therefore, the manufacture of tablets must be completely sealed off from the outside environment, making external contamination impossible.

The design and construction of the production facilities should prevent cross contamination and the polluted air to enter a zone of higher cleanliness level. There are usually five zones of cleanliness which are separated by air-locks from each other and the pressure difference between each two neighboring zones guarantees full safety of the external environment.

The cleaning of dust separators and the safe change of HEPA filters should be described in a special standard operating procedure. Staff carrying out these activities should be trained and should successfully pass the exam.

It should also be secured that technological waters are treated to remove biologically active chemicals before they are let into the municipality canalization system.

Standard operating procedures should be prepared for the incineration of the contaminated production wastage and packing materials.

For the same reason, labor safety regulations are very strict. The whole body surface of the production workers must be protected. Scafanders supplied with fresh air are the most suita _ protective garments. Personnel not in direct contact with steroid hormones may also use washable or disposable hooded dust-protected overalls and respiratory masks together with gloves and shoes. Protective devices should washed and dried inside the production facilities and the wash water should be treated before it is let into the municipality canalization system.

Workers in hormonal contraceptive tablet-plants usually work six hours per shift without interruption.

Sugar- or film-coated tablets can be packed under general conditions. The size of the blister pack may be particular to accommodate 21 or 21+7 tablets (possibly of different strength and color).

Due to the complexity of the manufacture of hormonal contraceptive tablets, extensive laboratory analysis is required to determine if local produced pills are safe and effective.

Good maintenance and efficient operation -as well as continuous improvement- of manufacturing processes are essential for good quality, competitiveness and productivity.

4.4 Manufacture of Hormonal Contraceptive Injections

medroxyprogesterone acetate	depot injection	150 mg/ml in 1-ml vial
medroxyprogesterone acetate	depot injection	50 mg/ml in 3-ml vial

norethisterone enantate	oily injection	200 mg/ml in 1-ml ampule

4.5 Good Manufacturing Practices and Training

Any company that wants to compete on the domestic and export markets must comply with the requirements of international current GMP standards. Enforcement of such requirements assumes the knowledge of these standards and the efficient operation of a GMP compliance inspection system by the government. It should also be understood and accepted that GMP is not testing the quality of the finished product but a management system of doing business according to the state of art, or -in other words- producing a good product by intent with the aid of validated processes. A batch which passes final physical and chemical analysis in all respects might be rejected because the GMP requirements had not been met or the good housekeeping methods had not been observed.

GMP training and total employee commitment in day-to-day operations, together with upgrading the factories, plays a decisive role in the success of the manufacture of hormonal contraceptive tablets. Top management must be committed to quality assurance. A well-trained GMP internal inspector should be on the staff of every factory and should report any violation of the GMP rules to the Quality Assurance Manager.

A UNFPA evaluation mission looked into the production of pills in a developing country and found that GMP -as part of an overall management programme- needed considerable improvement while the content uniformity of the tablets did not meet U.S.P. requirements.

4.6 Chemical Synthesis of Contraceptive Steroids

Steroid biochemicals that keep the human species alive by controlling the reproductive system are called sex hormones, namely estrogens (female hormones), androgens (male hormones), and progestogens [hormones that regulate pregnancy (gestation) and the female cycle]. Steroid biochemicals that help to regulate metabolism are called adrenocortical hormones, or corticosteroids or corticoids.

Multinational companies in the USA and the European Union dominate sales all over the world including intra-firm transactions and exports. India and Mexico are the two

developing countries that both produce and export bulk steroid medicinal chemicals.

Contraceptive steroid	Producers of bulk medicinal chemical
ethinylestradiol	Diosynth, Schering
levonorgestrel	.....
medroxyprogesterone acetate	Antibióticos, Cesquisa, Diosynth, Schering and Upjohn
mestranol	Diosynth, Schering
norethisterone	Diosynth, Schering
norethisterone enantate	Diosynth, Schering

The problems of contraceptive syntheses can be separated into two main fields, namely:

- choice of starting material, and
- selection of chemical steps.

Both topics have technical and economic features. The major, techno-economically feasible industrial scale approaches are the partial and the total syntheses.

4.6.1 Starting materials

Between 1950 and the early 1980s the main starting material for the chemical synthesis of steroid hormones was diosgenin, obtained by extraction from a Mexican species of the plant Dioscorea called locally *barbasco*. Diosgenin is still an important source material for the production of corticosteroids but its importance has diminished considerably since about 1984, when new starting materials -androst-4-ene-3,17-dione (AD) and androst-1,4-diene-3,17-dione (ADD) became available on the world market at very competitive prices with respect to diosgenin. While the new starting materials required the development of new synthesis methods, AD and AAD provide a shorter and more economic route to bulk medicinal chemicals than the methods starting from diosgenin or its upstream intermediate dehydroepiandrosterone acetate. Cholesterol, sitosterols and phytosterols are the source materials for the biochemical synthesis of AD and AAD.

Starting materials for commercial scale steroid synthesis are extracted mainly from vegetal

but also from animal sources. The most important compounds are listed in table ...

Table ...: Starting materials for industrial scale synthesis of steroid hormones

Sterol	Principal sources
Diosgenin	Dioscorea deltoidea or floribunda
Solasodin	Solanum species
Hecogenin	Agave species
Stigmasterol	By-product from the alkaline refining of soybean oil
Sitosterols	Widely distributed plant sterols; principal sources of beta-sitosterols are soybean oil, cotton seed oil, tall oils, sugar cane oils, etc.
Cholesterol	Sheep wool grease and cattle spinal cord
Desoxycholic and cholic acids	Bile of ox or pig

Various other sources of sterols exist but have no industrial application as of today.

4.6.2 Partial synthesis of contraceptive 19-norsteroids

Principal attention is paid to the synthesis of 19-norsteroids since well over 90 percent of all oral contraceptives used throughout the world pertain chemically to this class of compounds. The partial synthesis of 19-norsteroids (with the exception of norgestrel) from naturally occurring starting materials is exemplified in Figure .. through the key steps in the synthesis of norethisterone (9) -the first synthesized steroid oral contraceptive- from diosgenin (1).

Figure ..: Key steps in the synthesis of norethisterone from diosgenin

Source. Djerassi, Miramontes and Rosenkranz [1, 2]

The most cumbersome step on an industrial scale was the metal-liquid ammonia reduction {5(R=CH_3)→ 6} of estrone methyl ether [3] and many attempts were made to circumvent it. Figure .. illustrates a general solution to this problem, namely the functionalization of C-19 as the cyclic oxide 12 via lead-tetra acetate oxidation of the halohydrin 11.

Figure ..: Chemical conversion of Δ^5-3β-acetoxysteroids to 19-nor-Δ^4-3-ketosteroids

Source: Djerassi

Zinc treatment leads to a 19-hydroxy steroid (compound 13) which can be transformed readily into 19-norsteroids such as the key intermediate 6 in Figure ... The process outlined in Figure .. can replace steps 3 to 6 in Figure .. in the industrial scale synthesis of most 19-norsteroids.

Figure ..: Chemical structure of sitosterol and cholesterol

Microbiological degradation of the side chains of other naturally occurring starting materials such as sitosterol (14) and cholesterol (15) into 1,4-androstadiene-3,17-dione (4) [4,5] made possible the use of these starting materials in the synthesis of 19-norsteroid oral contraceptives -for example, norethisterone- according to the scheme in Figure .., since intermediate 4 can be pyrolized with high yield in one step to estrone (compound 5, R=H) and the latter can be converted to estrone methyl ether (compound 5, R=CH_3).

4.6.3 Total synthesis of norgestrel and 19-norsteroids

An enormous amount of work had been carried out between the 1940s and 1970s on the total synthesis of steroids [6]. The discovery of the high oral contraceptive activity and the commercial introduction of norgestrel (24) -a compound whose angular ethyl group precludes its partial synthesis from naturally occurring starting materials- immediately raised the question of an industrially feasible total synthesis. Extensive work in France, Germany, USA and the former USSR [7] had led to practical syntheses of norgestrel as well as the more conventional 19-norsteroid intermediate 19-norandrost-4-ene-3,17-dione (compound 6). The total synthesis of 19-norsteroids -such as norgestrel or the various advanced intermediates (for example, compound 5 with R=CH_3, or compound 6) for norethisterone and related oral contraceptive derivatives- represents one of the most complicated and lengthy synthetic processes employed anywhere in the chemical industry.

In view of its enormous complexity and need for a large variety of reagents and fine chemicals, production sites will only be located in centers of major chemical industries. Both the capital and manpower investments are high and a relatively large-volume manufacture is the key to economic success by this route. Once a company made this investment, then it is unlikely to switch to another starting material, especially one whose availability may depend on agricultural or political factors. The key steps and intermediates of norgestrel or norethisterone and related 19-norsteroid contraceptives is outlined in Figure ...

Figure ..: Key steps in the synthesis of norgestrel and norethisterone derivatives

4.6.4 Synthesis of progesterone-group contraceptives

This group of (oral and injectable) steroid contraceptives are based chemically on progesterone (33):

Convenient starting materials for the syntheses of progesterone-group contraceptives are diosgenin (1) or stigmasterol (34), from which the Upjohn Group in the USA has developed a process which is cost-wise competitive and even superior to the alternative one from diosgenin (1) via 16-dehydro-pregnenolone acetate (35) or solasodine (36) -the nitrogen analogue of diosgenin- which can also be degraded easily to 16-dehydro-pregnenolone acetate (35). This compound, in turn, constitutes the starting material of steroid contraceptives belonging to the progesterone group. While representing only a small proportion of the contraceptive market, medroxyprogesterone acetate (37), megestrol acetate (38) and alphasone acetophenide (39) are produced industrially by this route [8].

The principal contraceptives used in the last decade of this century or beyond will be identical or very similar to the prevailing ones.

The current regulatory climate in the USA and other technologically advanced countries is such that the time lag between the initial chemical discovery and biological tests and the final approval approaches 20 years. The potential return on the large financial investment by one of the pharmaceutical multinational companies for developing a fundamentally new steroid oral contraceptive is small and risky.

State-owned or private enterprises in developing countries, even if they were provided with the necessary resources, have no incentive to develop a basically new steroid contraceptive. Even the People's Republic of China -which is totally self-sufficient in this field- is not doing so. They are interested in producing steroid contraceptives which are known to be safe and effective rather than to develop new ones.

The patents of practically all oral contraceptive have already expired. Nevertheless, most developing countries do not synthesize their own active ingredients because of the technical difficulties involved in the chemical processes.

Currently only a few European pharmaceutical companies are responsible for the bulk of the totally synthesized steroid contraceptives in the world, namely Schering (Germany), Roussel (France) and Gedeon Richter (Hungary). Even the complete partial synthesis of

19-norsteroids is sufficiently complicated so that only about half a dozen companies in North America, Western and Eastern Europe and the People's Republic of China supply the world's current demand for oral contraceptives.

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4.7 Production of Condoms

4.7.1 Manufacture and Distribution

There are a few manufacturing countries in the world in spite of the high global requirements. The overall capacity of condom manufacturers was estimated at about 4,960 million units per year. The production of consistently high-quality condoms was considered complicated and difficult.

Today's condoms are manufactured from natural rubber latex, a milky liquid in a 60% concentration. Other elastomeric materials can also be used in principle as the starting material. The manufacturing of condoms consists mainly of the following five processes: compounding, molding, pinhole testing, packing and inspection.

The cost of investment -excluding buildings- for the Indonesian project was about USD nine million for a production capacity of 900,000 gross (= 129,600,000 pieces). The investment costs for the Vietnamese project with an annual capacity of 625,000 gross (= 90,000,000 pieces) were estimated at approximately USD four million.

Several countries -Denmark, France, Sweden, Switzerland, Thailand- installed packaging facilities with a quality control laboratory, when the consumption of condoms had reached 100,000 to 200,000 gross (14,400,000 to 28,800,000 pieces) per year.

Various international donor agencies -such as UNFPA, WHO, USAID, SIDE, IPPF and others- had supplied condoms free of charge to the family planning activities in developing countries for almost 20 years.

Whether commercially purchased or supplied by donor agencies, it was recommended to test deliveries at the time of acceptance. Approximately 30 m^2 space is required for a quality control laboratory and investment cost amounted to about USD 46,000 in 1985.

ISO 4074 International Condom Standard series specifies the sampling plan and the quality requirements as well as the test methods for rubber condoms.

4.7.2 Feasibility of local production in Bangladesh

All condoms were supplied as a commodity aid by USAID until 1993 and the aid programme has been continued by the European Union. This assistance was to be extended till the end of 1997 and the Bangladesh Management Development Corporation decided, therefore, to prepare a study on the local production of condoms. The main objective of the UNIDO project was to contribute to the assessment of the economic and financial feasibility of such a project. As a commodity aid, condoms were imported duty-free and any local production would have had to face international competition.

There were essentially two sources of supply of condoms in Bangladesh. The Government provided about 40 percent of the total demand through NGOs at a highly subsidized price, whereas the remaining 60 percent was packed and distributed through retail outlets by the Social Marketing Company (SMC). About 60 percent of the overheads of SMC were subsidized which allowed the company to sell condoms at an internationally low price.

There was no commercial source of supply for condoms. This situation is not likely to change after the expiry of the commodity aid programme because valid social reasons justify the subsidy of consumption. The main implications for local production can be summarized, as follows:

- a local manufacturer will depend on a few buyers and may be effectively restricted to supply one buyer, the Government;

- the total volume of sales will be determined by the pricing and promotional policies of the bulk purchasers rather than by the manufacturer's decisions which means, in practical terms, that ex-factory prices have little effect -if at all- on consumption.

The alternative of creating a competitive market for condoms would probably increase social costs since a local manufacturer with monopoly power would still have to be subsidized.

The total demand for condoms was about 348 million pieces in 1991 as compared to 264 million in 1985. Forecasts of demand suggest a further growth to reach 440 million by 2000.

For the purposes of feasibility study, a plant capacity of 160 million per year -to cover only Government supplies- was assumed.

The internationally competitive c.i.f. prices of condoms was USD 0.0174 or about 0.7 Taka per piece for Government supplies while condoms were imported by the SMC at a c.i.f. price of USD 0.0454 or Taka 1.6973 per piece. Landed costs can be taken equal to the c.i.f. unit prices for all practical purposes.

Product quality is a key element in production (and sales). Price is also a crucial variable because condoms can be readily purchased at free international trade. The ability to deliver continuously on time is a third critical element of success. As regards investment risks, the monopsony or duopsony puts the manufacturer in the hands of the buyer(s); for example, if the Government or the SMC decides to place purchase orders elsewhere, then local production capacity becomes vastly underutilized.

The three offers for machinery and equipment -for a plant capacity of 160 million condoms per year- ranged from USD 4.2 to 30.0 million duty-free and tax-free.

The technical expert advised that all three types of equipment were likely to provide a similar product quality, consequently the fixed capital costs were calculated with USD 4.2 million for machinery and equipment to arrive at a total of USD 7.3 million.

Manpower was estimated to cost about USD 350,000 per year for a total workforce of 203 persons.

At full production, variable operating costs at constant prices amounted to about USD 1.5 million per year while factory and administration overheads were estimated to be around USD 230,000.

Working capital requirement would be about USD 400,000 at local interest rates of 14 percent for long-term loans and 16 percent for short-term loans.

Projected sales revenues, at full capacity utilization, would amount to about USD 2.8 million per year.

The study considered five scenarios for the economic feasibility of local production.

The pessimistic scenario assumed competition against the lowest available world-market c.i.f. price of USD 0.0174 per piece of condom, a 100 percent capacity utilization (sales of 160 million per year) and commercial funding with no exemption from duty on the imports of machinery and equipment. The project was found to be a poor investment opportunity at constant prices under the above terms and conditions.

The optimistic scenario (machinery and equipment given as aid duty-free and tax-free, and ex-factory sales price of about USD 0.0199 per piece of condom) met all the normal requirements for feasibility, offering an overall internal rate of return of about 40 percent (over 10 years) and an internal rate to equity investment of 27 percent at constant prices.

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4.8 Manufacture of Intrauterine Devices

5. RECOMMENDATIONS AND PROJECT OPPORTUNITIES FOR UNIDO

5.1 Recommendations

UNIDO should provide technical assistance only for such countries where a policy supports local manufacture, including leadership in improving technical and managerial skills at the factory level, and there is a:

- national market of sufficient size to support profitable operation,
- adequate facilities and experience, and

- favorable family planning policy regarding the accessibility and use of contraceptives.

Government policies should lead to commitment for purchasing only safe and effective products for family planning programmes.

Projects should also be sustainable on economic grounds. Pricing should allow for investment in process controls, maintenance, improvement of facilities and equipment, and employee training.

UNIDO should provide technical assistance only for such projects where the local manufacturer has properly designed and constructed production facilities and can demonstrate the potential of achieving international standards of safety, efficacy and consistently high quality of the finished products as well as proper environment protection management. Compliance with the WHO draft Good Manufacturing Practices for Pharmaceutical Products should be considered as a minimum requirement for quality assurance.

Technical cooperation should be offered only on the basis of comprehensive feasibility studies. The cost of local manufacture should be compared with the landed costs of imported hormonal contraceptive tablets of the same composition.

5.2 Project Opportunities for UNIDO

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Endnotes

1. INFECUNDIN was registered by G. Richter in Hungary in ....., with the following composition: