

Commission on Intellectual Property Rights, Innovation and Public
Health

**What has been achieved, what have been the constraints and
what are the future priorities for pharmaceutical product-
related R&D relevant to the reproductive health needs of
developing countries?**

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March 2005

Disclaimer: The views and opinions in this paper are solely those of the author. Some of them are based on observation, experience and “insider” knowledge from a thirty year career in WHO and the NGO sector; as such some can be referenced and some can not. While most statements are based on factual evidence, some are subjective, some anecdotal and some opinionated but are included to stimulate the debate on the role of intellectual property, innovation and public health and, in particular, how intellectual property and innovation can be harnessed to ensure equitable access to affordable, quality drugs and other health products to those that require them in the less developed areas of the world.

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Executive summary

The Commission on Macroeconomics and Health stated that “Investments in reproductive health, including family planning and access to contraceptives, are crucial accompaniments of investments in disease control. The combination of disease control and reproductive health is likely to translate into reduced fertility, greater investments in the health and education of each child and reduced population growth.”. These were sentiments echoed recently by the Global Forum for Health Research which stated “Given the interrelationships between sexual and reproductive health and rights and the conditions that are addressed by the Millennium Development Goals (MDGs) will not be achieved without much greater attention to sexual and reproductive health, including research in the biomedical, health systems, and social sciences domains and the translation of that research into policies and programmes.”

Research and development in the private sector has been responsible for significant advances in both the fields of contraception and medical abortion. Without the pharmaceutical industry there would not be so many women of reproductive age in the world using modern methods of contraception. However, even in the early 1970s, it was perceived by the international donor agencies that the major pharmaceutical companies were not interested in developing contraceptives that met the needs of those in developing countries. It was felt that the private sector considered that the cost of R&D and potential liability risks did not justify developing other products. As a consequence, the donors established three public sector organizations for the R&D of contraceptive methods.

This paper addresses the role and achievements of the public and private sectors in the development of contraception, as well as other specific pharmaceutical products for reproductive health, such as microbicides and drugs used for medical abortion, as well as some of the obstacles to availability in developing countries. Finally, it looks at research needs.

Availability of products worldwide

Contraception

At the end of the 1990s, the percentage of married women of reproductive age worldwide using any method was 60.9% while those using a modern method was 54% made up of sterilization, 24.1%; oral contraceptives, 7.3%; injectables and implants, 2.9%; intra-uterine devices, 14.1%, condoms, 4.9%, other methods, 0.6%.

Despite the growing private sector, the public sector remains the principal supplier of contraception in most developing countries. However, the use of contraception is dependent on affordability, donors and/or governments must be able to purchase product for the public sector or social marketing programmes at the lowest possible price. Western donor agencies have purchased a large proportion of contraceptives in the developing world but this assistance has become more tenuous over recent years. As such, demand for contraceptives exceeds supplies in many countries and is increasing. Furthermore, the population of reproductive-age couples in developing countries is expected to increase by 23% between 2000 and 2015.

In most countries in the developing world, male condoms, intra-uterine devices (IUDs), oral contraceptives, injectable contraceptives and to a limited extent, implants are the non-permanent contraceptive methods available. In the developed world, in particular, western Europe and the USA, couples have access to condoms, a wide variety of oral contraceptives, the copper-T IUD, emergency contraception and in

recent years have begun to access an expanded choice of contraception including a vaginal ring, contraceptive patches, a levonorgestrel-releasing IUD, and implants.

In financial terms, the worldwide contraceptive product market, was estimated to be \$7.84 billion in 2002 and is projected to increase to \$10.3 billion in 2010. Of these estimates, oral contraceptives account for almost 50%. In 2002, the 16% married women of reproductive age who live in developed countries, spent/received \$42.20 worth of contraceptives per capita, while the other 84% of women in less developed regions of the world spent/received \$0.75 per capita!

Medical abortion

It is estimated that there are some 26 million legal abortions a year worldwide. Half of these are in China (around 8 million abortions per annum) and India (up to 6 million). It is not known how many of these are undertaken using medical abortion but in China, there are three manufacturers of mifepristone, which meet national needs as well as provide raw material to other countries and in India, four of the biggest pharmaceutical companies are marketing mifepristone.

Outside China and India, there are probably no more than 450,000 medical abortions undertaken each year using the anti-progestogen, mifepristone, in combination with a prostaglandin, usually the off-label use of misoprostol. Outside the USA and three western European countries, where costs are paid by the healthcare system or through health insurance, the cost of the product has been prohibitive to most women wanting access to this drug and no alternative anti-progestogens are available. Moreover, mifepristone is not registered in most developing countries. Even in China and India, the cost of mifepristone is \$7-8.

Microbicides

There are currently no microbicides on the market, however, they represent one of the drugs and vaccines areas for which R&D is being funded through and organized around public-private partnerships. There are currently some 17 products at various stages of clinical trials, five of which are in, or close to, Phase III clinical trial.

Impact of the public sector R&D programmes

Funding from bilateral aid agencies or foundations to public sector R&D programmes has resulted in the development of products which have expanded contraceptive choice for many people in the world. These have included development of two implantable contraceptive devices releasing levonorgestrel, a six-rod device, Norplant and a two-rod device, Jadelle; and two intrauterine devices (IUDs), the Cu-T 380A and the levonorgestrel-releasing IUD, Mirena, by the Population Council; and the once-a-month injectable contraceptives, Cyclofem and Mesigyna, and levonorgestrel emergency contraception by WHO/HRP. However, some of these products, particularly the levonorgestrel-releasing implants and IUD, have not benefited as many people as they should have done because of inadequate protection of cost and availability when licensing the pharmaceutical company responsible for manufacture and distribution.

The impact of clinical and epidemiological studies undertaken to investigate the safety and efficacy of products developed by others, by these public and philanthropic-funded programmes is extremely high. WHO/HRP has undertaken studies on, for example, Depo-Provera, Norplant and the Cu-T 380A. Data from these studies have helped make products affordable in developing countries; allowed guidelines for optimal use to be developed; and informed both providers and users of the relative safety and use characteristics of these products.

WHO/HRP has also, along with the Population Council played a major role in the use of mifepristone for medical abortion. CONRAD and FHI (another USAID collaborating agency which undertakes clinical trials) have played a significant role in making barrier methods available for the prevention of sexually-transmitted diseases and of pregnancy, such as the female condom; two intravaginal devices, Lea's Shield and FemCap; and new non-latex condoms for men. CONRAD and the Population Council, and to a lesser extent WHO/HRP, are also involved in the development of microbicides.

The pharmaceutical industry

Since the 1950s, R&D in the private sector has been responsible for many of the significant advances in both the fields of contraception and medical abortion. There has, however, been a significant reduction of the number of major pharmaceutical companies in the field, primarily because of mergers and acquisitions. Of the four major pharmaceutical companies, Organon, Ortho, Schering and Wyeth, with major contraceptive sales, three still have R&D programmes.

Oral contraceptives have been the major contraceptive products for these companies in terms of sales, however, in the west this market is changing because of the market penetration of generic manufacturers. While the "big four" will continue to have significant, albeit reduced, revenue flows from oral contraceptives, this is making them reinvest in R&D on, or to license in, technologies which will give them replacement revenue flows. It is unlikely that cost, which is always stated as an inhibiting factor in developing new entities, will prevent new R&D to be undertaken by the few remaining companies in this field.

In recent years, we have seen a vaginal ring, contraceptive patches and implants and a levonorgestrel-releasing IUD become available in Europe and the USA. These new products are unlikely to be available to the majority of people in the developing world and, even if they were, they are likely to be unaffordable, despite several having been developed with public funding.

With regard to the inhibiting effect of law suits and product liability in the USA on the willingness of companies to undertake R&D on new products, there is strong evidence that there is a decreased credibility of class action suits based on ill-defined symptoms and the causal effects on contraceptives; negligent design or manufacture; or inadequate warning of documented side-effects. Certainly, liability insurance is still hard to obtain, as some of the microbicide developers are finding, but it need not be the excuse for not undertaking R&D it was previously said to be.

With regard to products for the less developed world, there is little incentive for western pharmaceutical companies to participate in "difficult" developing world markets, when the "accessible" developed world is purchasing products with a total sales value that is more than 50 times greater! However, where companies have benefited from products having been developed with public funding, mechanisms should be instituted to ensure that this is reflected in availability and affordability in developing countries.

It has not only been the big pharmaceutical companies that have influenced the availability of reproductive health products in developing countries, small single product companies, have had significant impact. Finishing Enterprises have been the champion of widespread and affordable access to the Cu-T 380A IUD, even supporting transfer of technology to what are now competitors in developing countries. On the other hand, Exelgyn has been a significant constraint to worldwide

access to mifepristone. It had exclusive rights from Roussel Uclaf for worldwide manufacture and distribution, excluding the USA. The product is now off patent, making it possible to break this monopoly.

No major pharmaceutical company is currently involved in the development of drugs for medical abortion and opposition from the pro-life movement is likely to keep them out of research on medical abortion. Schering did have a major R&D programme on anti-progestogens for many years. It would be a significant gesture for the company to donate these products and related intellectual property to a public sector agency for continuing development, with all the provisos needed to protect them from possible liability, to serve women in developing countries.

With regard to microbicides, most of the advanced products are being developed by small biopharmaceutical companies with public sector and some venture capital funding. However, several big companies would enter rapidly the field if there were signs of success.

The role of developing countries

Except for Brazil, China and India, there has been little R&D of products for reproductive health in developing countries, other than participation in international, multi-centre clinical trials. Both India and China have major national (and China, regional) research institutes, involved in the R&D of new products, as well as in multicentred clinical trials. India and China both have the public sector R&D capacity to play a significant role in the R&D of products for reproductive health but both countries need to harness the potential of their pharmaceutical industry to complement this competence.

Hormonal contraceptives require special production facilities and significant health and safety precautions. As such there are relatively few, probably fewer than a hundred, companies in the developing world with the capacity to manufacture them and of those there few that can meet and maintain international GMP standards. There is a need to undertake a systematic study to address the capability and capacity of most of the developing country companies and how they could be used to provide quality, affordable products for reproductive health. This could lead to a network of qualified manufacturers of reproductive health commodities that would meet local and regional demand. It could also facilitate technology transfer of certain recently available products, such as the new implants and the levonorgestrel-releasing IUD.

Other potential uses of public sector funding to improve access to RH drugs

The international donors should establish a Global RH Commodity Access Facility (GRHCAF) to act as an International Financing Facility for reproductive health commodities and develop, maintain and survey a network of qualified manufacturers able to meet developing country and international donor needs. The GRHCAF should address all essential reproductive health drugs, such as mifepristone and misoprostol; and work with microbicide development groups in identifying and supporting the development of manufacturing sites for microbicides in certain countries, as they become available and more widely used. It would:

- Work with the international donor community to establish and implement an International Financing Facility for reproductive health commodities.
- Establish a qualified network of hormonal contraceptive manufacturers.

- Assist, where necessary, the transfer of technology from the major pharmaceutical companies for specific supply to the developing world
- Establish agreements which include preferential pricing for the public sector; and clear milestones for market access and quality manufacturing.
- Finance, through grants and loans, the upgrading of facilities to meet international GMP requirements.
- Establish a system of annual quality audits and an independent quality assurance programme.
- Provide assistance on regulatory issues and the introduction of the product in developing countries.

There is a critical role for the public funded R&D groups in product development to develop agreements to ensure protection of the cost of the product to the public sector of developing countries. This has been demonstrated by WHO/HRP, resulting in affordable prices for once-a-month injectables, emergency contraception and hopefully, medical abortion. Unfortunately, this has not been the route taken other groups which have made agreements with pharmaceutical companies which have not adequately protected the public sector price.

The expertise that public sector R&D groups have developed to conduct clinical trials and on the existence of clinical trial networks they have created must be built on. The funding of public sector R&D programmes to undertake clinical trials not only can reduce the overall costs of Phase III clinical trials; but also make people understand that clinical trial data is a critical component of the intellectual property relating to a product in its own right and can be used to control the price of the product.

What R&D is needed on products for reproductive health?

There remains a significant need for basic research, product R&D, and operational and health systems research in the field of reproductive health. Despite the pledges made at the International Conference on Population and Development held in Cairo in 1994, in recent years, there has been decreasing funding for R&D, other than for the prevention of HIV infection. Although there has been some resurgence of interest by the couple of R&D based companies remaining in the field, the overall funding for R&D in reproductive health looks bleak.

Product-related R&D that needs to be addressed includes:

- R&D on microbicides and barrier methods to prevent infection by sexually-transmitted infections, including HIV.
- Male contraceptive methods.
- Identification and development of new moieties which affect sperm maturation or capacitation, prevent fertilization or implantation of the fertilized egg.
- Development of anti-progestogens that are more effective and cheaper than mifepristone for medical abortion.

Other necessary research includes:

- The most appropriate ways of addressing acceptability in the process of developing new methods; and
- operational research to ensure that technologies meet peoples needs and can be delivered through weak service delivery systems, as well as being affordable, is paramount in any quest for new contraceptives, or other products for reproductive health, or indeed any drug for any purpose.

1. Introduction

WHO's Commission on Intellectual Property, Innovation and Public Health, stated that it is estimated that "truly" neglected diseases contribute only 1.2% to the disease burden in low income developing countries, whereas, sexual and reproductive ill-health contributes 19.5% of the global disease burden in women and 13.1% in men.

The 2002 World Health Report, from which these figures were taken, ranked unsafe sex as second highest risk factor contributing to 2.9 million deaths (5.2% of total) and 91.9 million disability-adjusted life years (DALYs) (6.3% of total). Lack of contraception ranked 19th, contributing to 149,000 deaths (0.3% of total) and 8.8 million DALYs (0.6% of total). It has also been estimated that the global burden of disease attributable to unwanted births amounts to 4.6 million DALYs (Collumbien et al., 2002). Hence, the use of contraception has had a significant, and could have an even greater, impact in decreasing the burden of ill-health, particularly in women.

The Commission on Macroeconomics and Health stated that "Investments in reproductive health, including family planning and access to contraceptives, are crucial accompaniments of investments in disease control. The combination of disease control and reproductive health is likely to translate into reduced fertility, greater investments in the health and education of each child and reduced population growth."

In the early 1970s, it was already perceived by the international donor agencies that, after a decade of use of modern contraception in developed countries, the major pharmaceutical companies were not interested in developing contraceptives that met the needs of those in developing countries. Even then, it was felt that the private sector considered that the cost of R&D and potential liability risks did not justify developing other products. As a consequence, the donors established three public sector organizations for the R&D of contraceptive methods.

Despite significant R&D programmes on the part of a few companies, until recently, oral contraception has tended to be the mainstay of the private sector, while the public sector has explored other approaches to fertility regulation.

So what has happened? Have the public sector programmes been successful? Has industry continue to hide behind R&D costs and liability issues? Have there been other approaches taken? Have developing countries benefited in terms of choice, cost and availability of products by any of these approaches?

This paper tries to address these questions, focussing primarily on the development of contraception. It also looks at other specific pharmaceutical products for reproductive health, such as microbicides and drugs used for medical abortion, since these provide examples of different approaches to developing and making products available to developing countries, as well as some of the obstacles to availability. Finally, it looks at research needs.

2. The current situation: availability and affordability of certain reproductive health commodities.

Contraception

Since the advent of hormonal contraception, nearly five decades ago, contraceptive use has increased dramatically. In the mid-1960s, contraceptive use in developing countries was limited to 10% of couples. At the end of the 1990s, the percentage of married women of reproductive age worldwide using any method was 60.9% while those using a modern method was 54% (United Nations, 2004). This is made up of sterilization, both male and female, 24.1%; oral contraceptives, 7.3%; injectables and implants, 2.9%; intra-uterine devices, 14.1%, condoms, 4.9%, other methods, 0.6%.

While it was estimated that there were some 1.553 billion women of reproductive age (15-49) in the world in 2000, unfortunately the United Nations figures only address women of reproductive age who are married or in union, a estimated total of 1,047 million women. They do not include the 0.506 billion unmarried women, most of who live in the developing world and of who we know very little. This major discrepancy must be borne in mind when we consider contraceptive usage here and in later chapters. However, it makes little difference to the overall conclusions except for making the gap between the developed and developing world even greater.

The distribution of use of contraception varies throughout the world, sterilization is widely used in many parts of the world, including many countries in the developed world, India and China. Condoms are now widely available. In some countries, particularly, China, Cuba, Egypt, Viet Nam and countries in eastern Europe and the former Soviet Union, the use of IUDs is high.

In most countries in the developing world, oral contraceptives, injectable contraceptives and to a limited extent, implants are the other non-permanent available methods by which women can postpone or space pregnancies. Most couples in a developing country would typically have access to condoms, two brands of oral contraceptives (one usually being a combined progestogen/estrogen product and the other, a progestogen-only pill), the copper-T IUD, and in some countries, a two or three monthly injectable contraceptive and the emergency contraceptive pill.

In the developed world, in particular, western Europe and the USA, couples have access to condoms, a wide variety of oral contraceptives, the copper-T IUD, emergency contraception and, as will be discussed in section 3.2, are now beginning to have an expanded choice of contraception including a vaginal ring, contraceptive patches, a levonorgestrel-releasing IUD, and a single rod implant.

In financial terms, the worldwide contraceptive product market, was estimated to be \$7.84 billion in 2002 and is projected to increase to \$10.3 billion in 2010. Of this, oral contraceptives accounted for almost 50% in 2002. The estimated sales value of oral contraceptives was US\$3.87 billion in 2002 and is forecast to grow at an annual growth rate of 3.4% to US\$5.09 billion by 2010. Condoms had a market share of 30.2% in 2002, estimated at US\$2.37 billion and also to grow at 3.4% to 2010. Implants and injectables had estimated sales of US\$0.67 billion in 2002, projected to increase to US\$0.86 billion by 2010 (Industry reports, 2004).

With regard to developing countries, the number of contraceptive users is projected to increase by more than 40% between 2000 and 2015 as a consequence of population growth and of an increase in the proportion of people who use contraception. UNFPA estimates that the cost of contraceptives (including condoms)

in the developing world in 2002 was \$657 million and that it will rise to \$1.03 billion by 2010 (United Nations Population Fund, 2005).

Although the above figures may not be exactly comparable, they do allow some generalizations to be made, such as sales in the developing world represent a staggering small 8.5% of the total world sales in 2002 and are unlikely to be more than 10% in 2010. This is despite some 84% of the world's women of reproductive age being in less developed regions of the world (United Nations, 2004) . Looking at it another way, in 2002, the 16% of women/couples in the more developed regions of the world, spent/received \$42.20 worth of contraceptives per capita, while the other 84% of women in less developed regions spent/received \$0.75 per capita.

Given these figures, there are two points that are glaringly clear:

- oral contraceptives will remain the major products from the pharmaceutical industry for contraception and, as such, the most competitive market for pharmaceutical companies; and
- there is little incentive for western pharmaceutical companies to compete for the \$0.75 per capita of women of reproductive age that is available in "difficult" developing world markets, when the accessible developed world is spending a whopping \$42 per capita and a total amount that is more than 50 times greater!

Medical abortion

In 2003, WHO in its landmark publication "Safe abortion: technical and policy guidance for health systems" stated that medical abortion using the pharmaceutical products mifepristone and a prostaglandin was one of the two preferred methods for early abortion (World Health Organization, 2003a).

It is estimated that there are some 46 million abortions per year worldwide, of which there are some 20 million illegal procedures, leaving a total of 26 million legal abortions worldwide. Two countries account for more than half of these, China for around eight million abortions per annum and India up to six million (although only one million legal abortions are actually reported). It is not known what proportion of these are undertaken using medical abortion but in China, there are three manufacturers of MF, which meet national needs as well as provide raw material to other countries and in India, there are four of the biggest pharmaceutical companies are marketing mifepristone.

Of the remaining 12 million abortions, about one quarter are being performed in the developed world in countries like the US and certain countries in the European Union. Currently about 15% of these abortions being undertaken by medical abortion using the anti-progestogen, mifepristone, totalling some 450,000 cases per year in the developed world. In the USA, it currently accounts for some 10% of all legal abortions and the proportion of users is increasing each year. It is also widely used in three European countries, France, Sweden and the UK.

Mifepristone is only registered in 29 countries. In western European countries, where product price is less of an issue to the women as costs are paid by the healthcare system or through health insurance, and even in China and India, where the cost of mifepristone is \$7-8, the cost of the product has been prohibitive to most women wanting access to this drug. This is because of its control by a small single product company, Exelgyn, in France, which until recently has been the sole provider of MF in the rest of the world, other than the USA. It had exclusive rights for MF from

Roussel Uclaf for worldwide manufacture and distribution, excluding the USA, where a separate agreement had been reached with the Population Council.

Misoprostol is marketed for the prevention of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs but is widely used off-label as the prostaglandin to be used in combination with mifepristone for medical abortion. Many drug regulatory agencies, including the USFDA, acknowledges its use in pregnancy and for medical abortion. It is widely available as Cytotec or as generic preparations and in many countries costs around US\$0.30 per 200µg tablet.

Microbicides

There are currently no microbicides on the market, however, they represent one of the drugs and vaccines areas for which research and development is being funded through and organized around public-private partnerships. There are currently some 17 products at various stages of clinical trials, four of which are in Phase III clinical trial. Another 45 are at earlier stages of development.

Access to products in developing countries.

It is acknowledged that in many countries contraceptives are available commercially through pharmacies and that there is a middle class able to purchase their contraceptive requirements. This group is increasing in large countries such as India and China, however, they remain a minority. Nevertheless, they will start to require products that are taken for granted in more developed countries. But inevitably, the majority of women are restricted to a limited contraceptive choice, some can afford socially marketed products, but these are limited by their very nature and require subsidizing by donors and/or governments and many women are dependent on what can provided free of charge through the public sector.

In most developing countries, the public sector remains the principal supplier of contraception, although in two of the smaller regions, the Arab world (Middle East and North Africa) and Latin America and the Caribbean, more than half the oral and injectable contraceptives are supplied by private providers (Curtis and Neitzel, 1996). The public sector in many countries supplies the poorest clients, although products such as condoms and oral contraceptives are also being supplied by social marketing programmes.

However, which ever sector is the supplier, the use of contraception is cost-dependent, donors and/or governments must be able to purchase product for the public sector or social marketing programmes at the lowest possible price.

It should be noted that a considerable proportion of contraceptives in the developing world have been purchased through western donor agencies but this assistance has become more tenuous over recent years. Donor support for contraceptives has varied over the past decade, dropping from 40% in the mid-1990s to 25% in the 1999-2000. In 2002, it amounted to \$197.5 million (30%) (United Nations Population Fund, 2005). While there is a major effort to try to maintain funding for reproductive health commodities this remains an uphill battle (Population Reference Bureau, 2004).

Several public sector agencies have been suppliers of reproductive health commodities to many countries in the developing world. These have included several bilateral donor agencies, UNFPA and IPPF (to its national affiliates). The two major

suppliers are currently USAID and UNFPA. USAID remains a major donor, spending some \$69 million on contraceptives in 2003.

Nevertheless, over recent years, the policy of USAID has been to push many countries towards self-sufficiency, while European donors, such as the British and Dutch aid agencies, as well as the European Union (EU), have shifted their support to UNFPA, which is now the largest supplier of reproductive health commodities, including contraceptives. In 2002 and 2003 it spent more than \$110 million, of which some 45% was on injectable contraceptives, 25% on oral contraceptives, 5% on IUDs, 3% on implants. In late 2004, the European Union pledged to fill the entire reproductive health commodities gap of \$75 million through a special contribution to UNFPA (Supply Initiative, 2004).

However, this is going to be a continuing and ever increasing gap in the future. Demand for contraceptives exceeds supplies in many countries and is increasing dramatically (PATH, 2003). Furthermore, the population of reproductive-age couples in developing countries is expected to increase by 23% between 2000 and 2015. The number of contraceptive users is projected to increase by more than 40% between 2000 and 2015 because of population growth and an increase in the proportion of people who use contraception (United Nations Population Fund, 2002). Failure to meet this need will result in unwanted pregnancies, unsafe abortions, maternal and infant mortality and diminished economic growth.

With regard to the other two products discussed in this paper, microbicides and drugs for medical abortion, microbicides are still under development and no product is yet available. Outside China and India, there are probably no more than 450,000 medical abortions undertaken each year using the anti-progestogen, mifepristone. Outside the USA and three western European countries, where costs are paid by the healthcare system or through health insurance, the cost of the product has been prohibitive to most women wanting access to this drug and no alternative anti-progestogens are available.

3. The development of products for reproductive health by the public sector; the private sector; and through public-private partnerships.

This section will review the development of pharmaceutical products for reproductive health and evaluate evidence on the achievements and lessons learnt from drug development for products developed by the public sector (contraception by WHO/HRP, the Population Council, CONRAD); the private sector (contraception and medical abortion); and through public-private partnerships (microbicides).

A 1996 Institute of Medicine report “Contraceptive Research and Development: Looking to the Future” classified the relative role of the different sectors as follows:

- Stage I: 1951-1972. The first contraceptive revolution and the primacy of industry.
- Stage II: 1973-1987. The rise of the public and non-profit private sector and a worldwide orientation.
- Stage III: 1987-present. The exodus of US industry and the entry of smaller firms.
- Stage IV: 1990s-present. The biopharmaceutical industry.

This classification summarizes the principal players involved in contraceptive development historically (Institute of Medicine, 1996). It still holds good, although as yet the latter stage has not contributed to contraception, it is, however, the principal source of products in the microbicide field.

This section will address the impact these different players have had on price of, and access to, these products in developing countries and of the inherently different mechanisms of funding of research and development on the number of products developed, costs of R&D and time to market. In particular, has public funding of R&D had any impact and, if so, how?

3.1 The public sector

There are three major public sector organizations involved in the R&D of contraceptive methods, these are: the Population Council, WHO/HRP, and CONRAD/CICCR.

The oldest of these is the Population Council, which was established some fifty years ago. It has its own R&D facility at Rockefeller University, New York which works with a clinical trial network under the auspices of the International Committee for Contraception Research (ICCR). The ICCR was established by the Population Council in 1970 to conduct clinical trials on the safety, efficacy, and acceptability of Council-developed products.

Also in the early 1970's, the Ford Foundation and SIDA assessed the feasibility of starting a public sector programme for contraceptive R&D at WHO. As a result, the UNDP/UNFPA/World Bank/WHO Special Programme for Research, Development and Research Training in Human Reproduction (WHO/HRP), WHO, Geneva. WHO/HRP was established in 1972 with the brief of developing new methods of fertility regulation and assessing the safety and effectiveness of existing methods, with particular relevance to developing countries.

A third group PARFR at Northwestern University, Chicago was established in the late 70s by USAID. This was superseded in 1986 by CONRAD of the Eastern Virginia

Medical School. In 1995, CONRAD established the Consortium for Industrial Collaboration in Contraceptive Research (CICCR) to revitalize the pharmaceutical industry's commitment to developing new contraceptives. In 2000, CONRAD established the Global Microbicide Project (GMP) to develop vaginal methods to protect women against sexually transmitted infections, including HIV/AIDS.

3.1.1 The Population Council

In terms of products reaching the market, the Population Council is arguably the most successful. It has developed four products which have been marketed: two implantable devices releasing levonorgestrel, a six-rod device, Norplant and a two-rod device, Jadelle; and two intrauterine devices (IUDs), one releasing copper, the Cu-T 380A (Paragard and generics) and the other, levonorgestrel (Mirena). Jadelle represents an improved, easier to provide version of the original Norplant device.

Of these four products, the Cu-T 380A is widely available throughout the developed and the developing world, Norplant is still being used in many countries worldwide but is no longer being marketed in the developed world, Jadelle is virtually unavailable anywhere and Mirena is only available in the developed world. So why after undertaking the considerable amount of R&D required to make these products available, and funded primarily through public funds, particularly from USAID, is there such a mixed picture on availability are the benefits of these products not

Box I discusses some of the issues around the development and use of the two implantable contraceptives, Norplant and Jadelle, developed by the Council. The first, Norplant, is still being used extensively - probably more than four million women, mainly in the developing world, currently have the implants. UNFPA spent some \$2.9 million on implants (mainly Norplant) and trocars in 2002, although this dropped to \$0.6 million in 2003. The current public sector price is \$23 (UNFPA, personal communication), nevertheless, together with the service delivery costs, this remains an upfront price unaffordable to many developing country health systems.

Norplant is one of the most researched contraceptive products, particularly, if you consider, the pre-introductory trials undertaken in many countries and the intensive five-year post-marketing surveillance study undertaken by the Council, WHO/HRP and Family Health International. While there has been significant demand creation undertaken in both developing and developed countries, this six-rod device has tested the skills of service providers in every country it has been used.

A recent WHO report states that "Existing contraceptive implants are highly effective and generally safe but their effectiveness and safety depend on the quality of the services through which they reach the end-user. ...Clearly, one criterion of a quality service is its long-term ability to ensure both the safety and satisfaction of users. Organizers and managers of country programmes would do well to learn from the mistakes made by some of the first programmes that introduced implants—mistakes due largely to inadequate attention to planning, sustainability, and quality of service. More specifically, there were problems of counselling, an inadequate response to requests by users for removal of their implants, insufficient attention to the prevention of infection, and insensitivity to the disruption that unpredictable vaginal bleeding can cause in a woman's life." (Meirick, Fraser and d'Arcangues, 2003).

Although the issue was clouded by claims of perceived lack of safety and links to Dow-Corning's subsequently disproved lack of safety of silastic (used to make the implantable rods), it was this inattention to quality service provision that was one of

Box 1. The implantable contraceptives, Norplant and Jadelle

The Population Council began the development of Norplant, a six-rod implantable contraceptive, in the late 1960s, undertaking Phase III clinical trials from 1975-1982. The R&D work was estimated to have cost some \$23.5 million, primarily from public sector funding (37.5% from USAID). The product was licensed to a Finnish company, Leiras OY, which invested some \$23 million into establishing manufacturing procedures. In the same year it was registered in Finland. A further \$16 million was spent on introductory and acceptability studies in numerous developing countries supported by several international donors (48% from USAID). The introduction of Norplant probably represents the most concerted effort to make a contraceptive product available widely throughout the developing world by the donor community. WHO/HRP supported one of the biggest post-marketing studies undertaken in developing countries on Norplant and also showed effectiveness for up to seven years.

Norplant was approved by the USFDA in 1990, which allowed its purchase by USAID for developing countries and its introduction in the USA by Wyeth-Ayerst. The company trained some 27,000 clinicians in insertion, removal and counselling. In the first year, sales in the USA reached \$141 million and by early 1993, over one million women had begun using the device. However, at a cost of \$365, the device was inaccessible to many women. The license agreement between Wyeth-Ayerst and the Population Council allowed a delay of five years after Norplant's introduction before making it available at a preferential price to the public sector, despite the significant public sector funding for its development, to allow the company to build private sector support and recoup its marketing and training expenses.

During this period, things turned sour in the USA. In early 1994, negative press stories began to appear in both the English and Hispanic press; the first lawsuit was filed in Chicago relating to problems of removal of the device; and a nationally broadcast TV programme covered the lawsuit. Despite USFDA support for the product in 1995, sales in 1996 dropped hugely and by mid-1997, lawsuits involving some 80,000 women were pending against Wyeth-Ayerst. The reasons cited included: problems of removal; possible levonorgestrel-related side-effects; and claims relating to the silastic used in the rods. While the major lawsuits did not result in a Dow-Corning or AH Robins (see section 3.2) corporate catastrophe, Norplant was withdrawn from the US market. While Wyeth had made a significant attempt to train providers, they did not appreciate that removal might become an issue. It has been well established that good insertion technique decreases removal problems, however, many physicians had considered insertion to be a simple operation and as such training was not as rigorous as required.

The Institute of Medicine's Committee on Contraceptive Research and Development supported a Workshop on Implant Contraceptives: An Illuminating Case Study in Current Dilemmas and Possibilities which reviewed the lessons learnt from the development and introduction of Norplant (Institute of Medicine, 1998).

The Population Council continued to develop a two-rod implant, Jadelle, which was also licensed to Leiras OY. Since 1996, it has been registered in: Finland, France, Iceland, Indonesia, Luxembourg, Netherlands, Norway, Spain, Sweden, Thailand, and the United States, originally for a duration of three years and now for five. However, it is only currently available in Finland.

Schering AG took over Leiras OY in 1996 and Schering OY is responsible for the continuing manufacture and marketing of Norplant and Jadelle (although it is impossible to find these products on the company's websites).

the issues in litigation against Wyeth on Norplant in the USA. Eventually this litigation resulted in the withdrawal of the product. It is a moot point whether this could have been avoided - certainly, greater awareness of the potential issues and tighter control over training of providers could have reduced problems experienced in the removal of the device. This was a lesson already learned in other countries but not understood by a major pharmaceutical company marketing the product in the USA.

The 2003 WHO report went on to say “Family planning programmes should move as soon as practical to the newer implant systems that use fewer capsules or rods and so are easier and safer to insert and remove, while remaining, as the evidence clearly shows, just as effective and safe as the original six-capsule Norplant system. There may be a period of overlap between the residual use of the older six-capsule system and the introduction of the newer methods. During this overlap period, dispensing more than one implant system may of course complicate training, counselling, logistics, storage, and reporting.”

However, Schering seems reluctant to make Jadelle widely available, perhaps because of the Wyeth’s litigation experience, perhaps because of the extensive support required to ensure appropriate service delivery (although this has often been funded by public funds, this is no longer a donor priority), or perhaps of its corporate product and country priorities (see section 3.1.2). Whatever, the reason, women in most developing countries are unable to access this product developed through public sector funding.

This raises the issue of a public sector R&D organization ensuring availability and protection of the public sector price in developing countries when licensing a product to a commercial pharmaceutical company. We shall return to this below with the case of Mirena, which together with Jadelle makes one feel that this critical area is not one of the Population Council’s strengths or priorities.

Two of the IUDs developed by the Population Council, the Copper-T 380A and the levonorgestrel-releasing IUD are discussed in Box 2. The Cu-T 380A has established itself as the most cost-effective, highly effective modern contraceptive and is available throughout the world. It is one of the most widely used contraceptive products in the world was developed in collaboration with a small, single product company based in the USA. The company, Finishing Enterprises, however, set itself the mission of making the device widely available at the lowest possible price.

The other, the levonorgestrel-releasing IUD, Mirena, is also highly effective and has other non-contraceptive characteristics that could provide health benefits to many women throughout the world, particularly those in developing countries Like the Cu-T 380A, it was also developed together with a small company, in this case Leiras OY in Finland. However, this company was subsequently bought out for its drug-releasing device expertise by a major pharmaceutical company, Schering AG. This expertise consisted of two components, the product research and development expertise developed by the Population Council with public funding, and the manufacturing expertise developed by Leiras. It included Norplant and Jadelle, discussed above.

While, as discussed above, Schering does not appear interested in implants, Mirena has become one of the company’s key products (see Box 2 and section 3.2). However, one consequence of Schering’s takeover of Leiras has been a lack of willingness on the part of the company to supply the product at an affordable cost to women in developing countries. The company has developed a public relations mechanism, the extravagantly-named International Contraceptive Access Foundation to appear to address this need. However, the levonorgestrel-releasing IUD is

Box 2. A tale of two intra-uterine devices

The Copper-T 380A

The Cu-T 380A intra-uterine device (IUD) was developed by the Population Council in the 1970s in collaboration with Finishing Enterprises Ltd (now FEI), a small, single product company which had set itself the mission of making the device widely available at the lowest possible price. It is registered in some 100 countries with a duration of action of 10 years, although a study by WHO/HRP shows that it could be used for 12 years. It was registered in the USA in 1984 and has become one of the most widely used contraceptives worldwide - FEI itself has manufactured more than 70 million devices and there are now several generic manufacturers, particularly in India and China (see section on WHO/HRP). In India, FEI assisted in the transfer of technology to other companies.

In 1988, FEI began supplying the product to GynoPharma, which was subsequently acquired by Ortho-McNeil (GynoPharma having initially been set up by an ex-executive of Ortho, because the company had stopped selling its the IUD it had developed itself!). It was marketed by Ortho-McNeil as Paragard at a cost of \$360 until the end of 2003. Following the sale of the NDA for Paragard to FEI (at an undisclosed fee) by the Population Council, FEI has taken over marketing and distribution (Population Council, 2003).

The public sector price of the generic Cu-T 380A is between \$0.25 and \$0.32, depending on volume, making it by far the cheapest modern contraceptive available (United Nations Population Fund, personal communication).

The levonorgestrel-releasing IUD

As part of its collaboration with Leiras OY on Norplant (see Box 1), the Population Council applied its expertise on the release of levonorgestrel through a silastic membrane to an IUD. The levonorgestrel-releasing IUD, Mirena, has been available in Europe for more than 10 years and was approved for sale in the United States in December 2000. Not only is the LNG-releasing IUD a highly effective contraceptive but it also has significant health benefits such as reduction of menorrhagia and anaemia and the treatment of endometrial hyperplasia.

Mirena is the most important Finnish pharmaceutical export product and is sold in some 100 countries. In the USA, it is priced at up to \$ 550 per unit and in Finland, \$220. There are some 3 million users worldwide and it is estimated that more than 1.1 million devices were sold outside the USA in 2003.

Despite being such a commercial success and having been developed with a significant contribution of public sector funds, there is little opportunity for poor women in the developing world (or even in the USA) to access this product. Although there is now a public sector price of \$40, this is an impossible up-front cost in most developing countries. However, to divert criticism and improve their public relations image, the manufacturer of the device and Population Council have recently established created the International Contraceptive Access Foundation to "provide selected public-sector organizations with Mirena on a not-for-profit basis to help serve the needs of women and families in resource-poor settings, primarily in developing countries" (Population Council, 2003). This year some 11,000 devices will be provided free and a further 33,000 at a cost of \$27. This will make a negligible contribution to the needs of poor women and will not provide sustainable access to this extremely important product.

destined to be a high-cost product only available to women in the developed world until a generic product becomes available. It must be re-emphasized that, like the implantable devices, both these IUDs were developed with a considerable amount of public funding, particularly from USAID.

While generic versions of the Cu-T 380A have now been developed, often with the technical assistance of the original manufacturer, FEI, the technology required to make a generic version of the levonorgestrel-releasing IUD means that an investment must be made through public sector funding to achieve this.

Hence, in the case of the two IUDs, one is accessible and affordable in the developing world, the other is not. Again, as an outside observer, there does not appear to have been sufficient desire or legal expertise to ensure that the Population Council protected the public sector investment in R&D that would have allowed affordable access to Mirena to women in the developing world.

The Population Council, like WHO/HRP, has also played an important role in the use of mifepristone and misoprostol for medical abortion, which is discussed in section 3.2. It also played a significant role in getting mifepristone registered in the USA. In 1994, Roussel-Uclaf donated rights to mifepristone for the USA to the Population Council. After a somewhat difficult attempt at getting a US licensee, the Population Council eventually licensed a newly-created, single product company, Danco, as the commercial entity to bring mifepristone to the US market, using bulk drug from China. Mifepristone costs \$250 for 600mg in the USA.

3.1.2 WHO/HRP

WHO/HRP has worked on many different approaches to contraception since its inception in 1972, ranging from the intranasal administration of hormones to immuno-contraception. However, the cost-effectiveness of development of products de novo has been low. Other than the once-a-month injectable contraceptives (one of which was a novel development by WHO/HRP) and the use of levonorgestrel emergency contraception, none of this research has led to products reaching the market. On the other hand, the Programme has made a considerable contribution to the availability of products developed by others (eg, Depo-Provera, Norplant, the Cu-T 380A, the use of mifepristone for medical abortion) and has pioneered once-a-month injectable contraception (Cyclofem and Mesigyna/Norigynon).

The impact of the clinical and epidemiological studies undertaken by the Programme on these products is extremely high. In some cases, such as emergency contraception, this has made products affordable to the public sector in developing countries. Moreover, the impact of the clinical research has been felt in both accessibility of products as well as providing the scientific data on which to build guidelines for optimal use and to inform both providers and users of the relative safety and use characteristics of specific methods and products.

With regard to its development of the two once-a-month injectable contraceptives, Cyclofem and Mesigyna/Norigynon, WHO/HRP spent an extremely small amount of money, which I once estimated to be in the order of \$5 million. While this expenditure did not include pre-clinical studies nor overheads, it did include dose-finding pharmacokinetic/ pharmacodynamic studies; metabolic studies; Phase III trials; and, in the case of Cyclofem, introductory studies in Brazil, Chile, Colombia, Indonesia, Jamaica, Mexico, Peru, Thailand and Tunisia. The development work began in 1979 and Cyclofem became available in Mexico and Indonesia in 1993.

The Mesigyna/Norigynon product was licensed to Schering AG, however the company found it difficult to get Board of Management approval to allocate the resources to be adopted as a product registered and marketed worldwide. However, the company approved its production in Mexico and Pakistan and sales groups to make the product available in those regions, where it was subsequently sold.

Box 3. Facilitating technology transfer: the Concept Foundation

WHO/HRP was instrumental in the establishment of the not-for-profit Concept Foundation in Bangkok which provides a model to ensure the availability of affordable reproductive health products to developing countries. The Concept Foundation selects pharmaceutical companies in developing countries as licensees for the manufacture, marketing and sales of drugs and diagnostics. It licenses out the intellectual property it holds and manages the downstream processes of technology transfer and capacity building to ensure the licensees meet international standards of GMP and can both commercialize the licensed products, as well as provide them to the public sector at the lowest possible cost.

The Concept Foundation was initially funded by WHO/HRP, using PATH/PIACT, and subsequently by UNFPA, the World Bank and several foundations to make a once-a-month injectable contraceptive, Cyclofem, available in developing countries. Concept received all IP for the product from WHO and undertook the responsibility of licensing manufacturers in Indonesia, Mexico and Thailand. It is presently negotiating agreements with companies in India, Oman, South Africa and Turkey. The license agreement with WHO required it to provide product to the public sector at a cost+ price as well as transferring the technology to developing countries. The agreement allowed royalties to be collected on private sector sales, these have allowed Concept to sustain its operations.

The Concept Foundation has assisted in developing manufacturing facilities for Cyclofem; established a network of distributors in collaboration with the manufacturers; assisted in registering the product in more than 30 countries; provided independent quality monitoring; protected trademarks; and assisted in product introduction. Cyclofem, has now been made available to the public and private sectors since 1993 and more than 150 million doses of Cyclofem have been manufactured and distributed by licensees worldwide, providing an additional choice that would not have been available to women in Asia and Latin America.

The Concept Foundation has developed a portfolio of other products, such as a HIV diagnostic test; emergency contraception; and drugs for medical abortion; and has transferred technology to nine manufacturing licensees in five developing countries, making products available in more than 30 developing countries. More than 50 million HIV rapid tests have been distributed by licensees to public sector health services worldwide.

However, the way that WHO/HRP made Cyclofem available was through a novel approach which involved the establishment of a not-for-profit organization, the Concept Foundation in Bangkok, which manages the downstream processes of intellectual property, out licensing, technology transfer and capacity building to pharmaceutical manufacturers for commercialization of the licensed products. The contractual framework of the license agreements with the pharmaceutical manufacturers ensures that the commercial rights to the products include a supply obligation to the benefit of the public sector in developing countries at the lowest possible cost. This is described in Box 3.

Being the first product to reach the point of commercialization, the development of Cyclofem made WHO aware of the need to develop licensing strategies and to assess its policies on intellectual property. WHO, as a public health organization, had

not considered the implications of having the responsibility for R&D programmes such as HRP and the Tropical Disease Programme (TDR), despite these programmes being the forerunners of what are now known as public-private partnerships (see section 3.3). Up until this time, WHO's Technical Service agreements with which it contracted its research partners, gave ownership of the data generated to the contractee!

At this point, WHO changed its agreements and understood its responsibility, as a public funded body, of developing and protecting product intellectual property to benefit the provision of products through the public sector of developing countries. All R&D information generated under contract with WHO is now the property of WHO. This allowed WHO to build the a body of intellectual property necessary to license products it develops, or contributes to the development of, to manufacturers and distributors.

Since the end of the 1980s, WHO/HRP negotiated several license agreements with companies, including the Concept Foundation which required them to:

- fix a public sector price based on a manufacturing cost plus;
- stipulate a requirement for technology transfer to developing countries; and
- provide a royalty on private sector sales (for which there is no controlled price).

WHO also requires the ability to audit manufacturing costs in order to get arrive at a public sector price before it will support Phase III clinical trials of a product it did not develop. This is a powerful tool to control cost through ownership of clinical trial intellectual property. It has been argued by some that it may be difficult to calculate manufacturing cost and/or these costs may not be stable. However, WHO believes, through the example of the Concept Foundation, that it is possible to audit costs at agreed intervals and that this has proven to be a viable approach.

The establishment of the Concept Foundation not only met WHO's licensing requirements but because it could levy a royalty on private sector sales, it also provides an example of a self-sustaining model for the management of intellectual property to ensure the availability of affordable reproductive health products to developing countries and a means of controlling the cost of products to the public sector (Oehler, 2004).

The other product success was on emergency contraception (EC). This was used as a case study as part of an External Evaluation of the Programme (World Health Organization, 2003b). Phase III clinical trials undertaken by WHO/HRP showed that levonorgestrel (LNG) in two doses of 750µg, twelve hours apart was more effective than a little used existing regimen using "high dose" combined oral contraceptives. The External Evaluation stated that "HRP wisely and skilfully used its research results, international prestige and credibility, and commitment of its staff to move EC from a method under study to an acceptable product available in 96 countries. HRP's estimated total costs on this effort from 1987 to 2002 are \$2.7 million."

The report went on to say "HRP now has data to infer cost-efficiency for its research contributions in terms of RH impact and global public goods. The \$2.7 million HRP spent on EC directly and indirectly contributed to approximately 2.9 million women in the USA being treated with the LNG product. For these women an estimated 200,000 abortions were averted from 1999-2002. Obviously many organizations contributed to EC policy and practice changes in the USA. However, there would be no LNG product without HRP's research and collaboration with registration. The registration dossiers of the two main manufacturers of the LNG Emergency Contraceptive were

based on the pivotal HRP study comparing LNG and the Yuzpe regimen. Quantitative outcomes of abortions averted can demonstrate RH impact, which is important for donors and the international health community. Current EC sales reflect only the beginning of RH impact of this rapidly expanding contraceptive technology. As EC sales and abortion statistics become available from the other 95 countries with registered EC products (particularly the 92 having LNG regimens), the costs of HRP's contribution will be much less than \$1 per abortion averted."

WHO/HRP is continuing to work on the development of a male hormonal contraceptive, in collaboration with Industry and CONRAD. According to its website, WHO/HRP has become a leader in the development and testing of male contraceptives by undertaking clinical, behavioural and basic science research in this field. It is also working on a new female progestogen-only injectable contraceptive with NIH and CONRAD; and the clinical trial of a microbicide with CONRAD. A collaborative initiative between the Rockefeller Foundation and WHO/HRP on basic research to develop an anti-implantation agent has just started (see section 3.1.3).

However, as stated above, it is the clinical and epidemiological studies undertaken by WHO/HRP on products developed by other public sector agencies or pharmaceutical industry that sets it apart from other groups in the field. The impact of these studies has been extremely high and they have certainly been instrumental in making several contraceptive products more widely available in many developing countries .

Following its in-depth evaluation of all available toxicological and other pre-clinical data and their value in predicting adverse effects when compared with findings from clinical and epidemiological studies, WHO/HRP proposed new toxicological requirements including dropping the inappropriate beagle dog model (World Health Organization, 1989). WHO's large case-control study on hormonal contraception and reproductive cancers, showed no overall relative risk of breast cancer with the injectable contraceptive, Depo-Provera, marketed by Upjohn. The outcome of this study, together with the conclusions of the toxicology evaluation, was responsible for the approval of Depo-Provera by the USFDA which then allowed USAID to purchase large quantities of the drug for supply to many countries worldwide.

Another large case-control study evaluate the risk of vascular disease from the use of oral contraceptives showed that the "third generation" pills had an increased risk of venous thrombosis compared with those containing levonorgestrel. The results of this study caused a furore with several pharmaceutical companies. However, this is exactly why WHO/HRP should continue to be funded to undertake such large comparative - there is no other body that has the independence and credibility to undertake such studies. Regrettably, this is not happening.

WHO/HRP has undertaken a large body of clinical trials on IUDs. One long-term trial has developed the data required for the USFDA to approve extension for the duration of use of the Cu-T 380A IUD to 12 years (see Box 1), it is probable that the study will have a sufficient number of users to provide evidence that the device can be used for up to 15 years. Another clinical trial has shown that pelvic inflammatory disease can be reduced to a very low incidence with appropriate selection of potential users of the Cu-T 380A IUD. These studies have provided data which allow the Cu-T 380A to be the most cost-effective method and provide both providers and users with the information needed for optimal and safer use.

The External Evaluation of the Programme also highlighted WHO/HRP's support of studies in collaboration with China's State Family Planning Commission comparing the widely used stainless steel IUDs with copper bearing IUDs. "The IUD conversion

study yielded evidence that the newer copper-bearing IUDs were more effective and safer than stainless steel ring IUDs. This led to a shift to copper devices in 1993. Through 2002, the estimates of health benefits for China are the avoidance of 55,600,000 pregnancies, 35,600,000 abortions, 16,300 maternal deaths, and 365,000 infant deaths. Similar benefits will occur in many other countries shifting to more effective copper IUDs, though the numbers may be less striking than in China.

Similarly, “HRP’s cost for IUD research in China was US\$1.4 million, including funds given to centres in China for research contracts to study stainless steel IUDs and copper IUDs during 1990-1997, capacity building country seminars, dissemination, and advocacy for policy change and new IUD practices. These actions were causally linked to making effective Copper IUDs available throughout China. The attributable reproductive health impact included 35.6 million abortions averted over 10 years, due to the change. HRP’s direct costs were about US\$0.04 per abortion averted over this period. Many local resources were also needed to change IUD practices; however HRP’s financial support, technical input and leadership effectively leveraged local resources to achieve substantial reproductive health benefits.” (World Health Organization, 2003b).

Another area that WHO/HRP has undertaken significant research is the use of appropriate strategies for the introduction of technologies (World Health Organization, 2005). Analysis of experiences with the large-scale introduction of new contraceptives into service delivery systems showed that the addition of a new method did not automatically lead to increased reproductive choice; and that service delivery systems do not always have the capacity to provide a new method with appropriate quality of care. Although small-scale studies and introductory trials of new contraceptives and other reproductive health products, usually offer high-quality services, weaknesses in training, counselling, supervision and logistics management often make it difficult to sustain quality service delivery when the method is introduced on a larger scale (Simmons et al., 1997). Unfortunately, these were not lessons learnt by Wyeth when it introduced Norplant in the USA (see Box 1). The development of appropriate strategies for the introduction of any contraceptive have a major effect on its accessibility and availability (see section 5).

3.1.3 CONRAD/CICCR

The priority areas in which CONRAD is working are: chemical barriers for women that prevent pregnancy and/or STIs; systemic hormonal methods for men; novel systemic non-hormonal methods for women and men; and mechanical barriers for women. CONRAD also supports projects that could likely lead to increase contraceptive use in developing countries, such as developing generic products for distribution by the public sector. It is funded primarily by USAID.

CONRAD has played a significant role in making barrier methods available for women for contraception and for the prevention of sexually-transmitted diseases available. It worked with the Female Health Company on the clinical trials necessary to get the female condom, Reality, approved by the USFDA in 1993. Similarly, it provided the necessary clinical trial data that allowed two intravaginal devices, Lea’s Shield, a single size device, and FemCap, which is available in three sizes, to be approved by the USFDA. According to its recent biennial report “CONRAD agrees with others in the field that the use of mechanical barriers that covers the cervix should enhance the potential effectiveness of a microbicidal product. CONRAD is, therefore, supporting several projects to explore the acceptability of using a diaphragm together with a microbicidal gel, as well as the feasibility of including these combined products in an HIV prevention trial.” (CONRAD, 2005)

CONRAD has also played a major role in the development of microbicides. In 2000, it established the Global Microbicide Project (GMP) with funding from the Gates Foundation. One of the products that it is developing, cellulose sulphate, has been shown to have some contraceptive efficacy, as well as protecting against STIs, including HIV. Cellulose sulphate is now undergoing a series of clinical trials: two Phase II trials on contraceptive efficacy began in 2004; a Phase III HIV prevention trial will begin in Nigeria in late 2004 and will be followed by a bigger Phase III trial in Benin, Burkina Faso, Uganda, South Africa, and India (see section 3.3.1). It is also working with other groups to identify and screen compounds for use as vaginal microbicides and/or contraceptives.

CONRAD and the Indian Council of Medical Research signed a Memorandum of Understanding in 2004 to cooperate in microbicide research, including drug discovery and formulation, preclinical screening, development of animal models, the preparation of clinical sites to conduct microbicide research, and also in the conduct of safety, effectiveness and acceptability studies. This is the first venture which may result in a research programme that involves a key organization in the developing world as an equal partner!

Together with WHO/HRP, CONRAD has been working on hormonal contraceptive methods for men using a progestin/androgen combination. CONRAD has undertaken a trial of the injectable depot medroxyprogesterone acetate plus testosterone pellets and showed it to be extremely effective. However, the delivery of this combination of hormones was not very acceptable. CONRAD and WHO/HRP have therefore planned to undertake an expanded multicentre trial of a different long-acting androgen and progestogen (norethisterone enanthate plus testosterone undecanoate) in 2005 (CONRAD, 2005).

The Consortium for Industrial Collaboration in Contraceptive Research (CICCR) was established with funding from several US foundations to help revitalize the pharmaceutical industry's commitment to developing new contraceptives. It encourages collaboration between industry and not-for-profit organizations by identifying potential leads under investigation in not-for-profit organizations, in both developed and developing countries; encouraging industry to collaborate with and provide support for these organizations; and providing additional funds to investigators at not-for-profit entities. CICCR, with funding from the Rockefeller Foundation and collaboration with WHO/HRP, has involved Schering AG in discovery phase research of both male and female contraception. This includes assessing compounds which can act between ovulation and implantation. Schering will have the right of first refusal to develop any entities arising out of this collaboration.

3.2 The private sector

3.2.1 Contraception

In considering the contribution of the private sector to research and development of contraceptive pharmaceutical products and to access to affordable products in the developing world, it is important to look at the impact of oral contraceptives on their contribution to companies' sales revenues and on companies' need or willingness to invest in research on alternative products.

There are several recent business reports on the global contraceptive market from market research companies such as, BioPortfolio (www.bioportfolio.com), the Business Communication Company (BCC) (www.bccresearch.com), Engel Publishing Partners (www.pharmalive.com) and Global Industry Analysts

(www.globind.com). A report from the latter states "In financial terms, the worldwide contraceptive product market, was estimated to be \$7.84 billion in 2002 and is projected to increase to \$10.3 billion in 2010. Of this, oral contraceptives accounted for almost 50% in 2002. The estimated sales value of oral contraceptives was US\$3.87 billion in 2002 and is forecast to grow at annual growth rate of 3.4% to US\$5.09 billion by 2010."

The oral contraceptive market

So let us look at this market more closely, where it is, what revenues it produces and what it means to the major companies, particularly in relation to their research and development and to making products available in the developing world.

Of the estimated \$3.87 billion sales of oral contraceptives worldwide in 2002, 46.5% of these sales, or \$1.8 billion were in the USA. Yet the prevalence of oral contraceptive use in the USA is only 15.6% - this represents some 5.9 million married women of reproductive age. Again, if we look at this globally, the 5.9 million women in the USA who represent less than 0.6% of married women of reproductive age worldwide (totalling 1.04 billion in 2000), purchased \$1.8 billion of the total worldwide expenditure on all contraceptive products of \$7.84 billion (or 23%!). This can be cross-checked by assuming that a monthly OC pill pack costs an average of \$25. One year's supply is \$300, which for 5.9 million women is just under \$1.8 billion per annum.

A very recent report states that there are some 11.66 million women using oral contraceptives in the USA, not the 5.9 million discussed above (Alan Guttmacher Institute, 2005). It also states that "The pill is the method most widely used by women who are in their teens and 20s, never married women and women with at least a college degree", which explains much of this discrepancy. While it makes the per capita expenditure discussed above less, it does not diminish the importance of the US market. In fact, another industry report recently stated "Hormonal contraception is a mature and overcrowded market, dominated by oral products, where high-levels of contraceptive efficacy are the norm. The market is worth \$4 billion, of which \$2.5 billion comes from the USA." (Industry reports, 2004, Bioportfolio). This is an even higher estimate of the value of the US market.

There are other regions of the world where oral contraceptive prevalence is 15% or more, eg, Europe at 17.4%, South America at 17.1%, North Africa at 17.7% (UN Population Division, 2003) but it would require the total sales in Europe, Asia-Pacific and Latin America of \$1.85 billion to match the value of US sales! This makes the USA, by far the most important market for any producer.

If we turn to Europe, the whole of Europe has about 10% of the world's women of reproductive age and sales of \$0.69 billion from a 17.4% oral contraceptive prevalence (about 19 million women), \$36 per capita per annum. However, of this France, Germany and the UK, represent about one-quarter of with a total of Europe's women of reproductive age but have some two-thirds of sales in Europe; other countries in western Europe have very high oral contraceptive prevalence, Austria, 30.8%; Belgium, 46.7%; Netherlands, 49.0%; and Switzerland, 34.1%. With France, Germany and UK, these seven countries represent less than 30% of Europe's women of reproductive age but sales of more than \$0.6 billion. Western Europe has lower oral contraceptive costs because of price controls, in UK most contraceptives are provided through the national health service which has moved significantly to generic pharmaceuticals, a move now occurring in other western countries, including the USA.

The 70 million women of reproductive age who live in the USA and the 31 million in the above 11 countries in northern and western Europe have unrivalled access to health care and they (or their governments or insurance companies) spend some \$2.4 to \$3.1 billion on oral contraceptives. Table I shows that the developing world has about 83.6% of the world's women of reproductive age (873 million) and sales of \$1.21 billion.

Table 1. Oral contraceptive prevalence and sales by region

Region	Married women of reproductive age (millions)*	Oral contraceptive prevalence (%)*	Estimated market sales in 2002 (\$ billion)
World	1,043.26	7.3	3.87
Less developed regions	873.22	5.8	1.21
USA	37.74	15.6	1.80
Europe (France, UK & Germany)	109.28 (25.68)	17.4 (39.8)	0.69 (0.47)
* UN Population Division, 2003			

To the marketing director, a group of 12 countries (or if we add the smaller Nordic countries, 17) represent a tightly grouped, well served nucleus of high value countries which purchase two-thirds of the world's sales. The remaining 180 or so countries in the world, many with less well served populations, more difficult access and limited resources, purchase one-third of the world's sales.

Why the focus on oral contraceptives?

So we have defined a small group of developed countries which provide an obvious market on which to focus but why do oral contraceptives represent 50% of the sales in the world's contraceptive market?

The development of the oral contraceptive pill fifty years ago was the turning point in the use of contraception and the beginning of true family planning. However, from a commercial standpoint, it has been a marketing manager's dream – a highly efficient, small oral pill which women need to take daily in monthly cycles for as long as they want to prevent pregnancy! Tablets are the one of most easily manufactured pharmaceutical preparations and even if the raw materials in current oral contraceptive products cost \$5,000/kg, they are used in 100µg quantities and the maximum cost is unlikely to be more than \$0.15 for a month's worth of 21 to 28 pills. Packaged in a foil strip in a box, they would have a maximum final product cost of \$0.20, or charitably, \$0.25 - representing 0.5 to 1% of the sales price in the USA!!

Product costs of \$18 million out of sales of \$1,800 million leaves substantial room for promotion, education, distribution, retailer's margins and all the other things that Martha Angell discusses in her book "The Truth About the Drug Companies: How They Deceive Us and What to Do About It" (Angell, M, 2004). It leaves an enormous amount to pay for liability insurance, or the usual out-of-court settlements and even research and development!

This leads us to research and development. Wouldn't a Board of Management want its company to do whatever was required to preserve their market share in what has been, and continues to be, a commercial cash cow? As a somewhat cynical

observer, why would any company wish to jeopardize this by spending money on R&D of other products that would probably be more expensive to produce or more difficult to use? This is now having to change, as discussed below, but until recently the major incentive for R&D based companies has been to protect this market by working on ways of getting new oral contraceptive patents.

While companies have definitely worked to improve the safety of oral contraceptive use and reduce the risk of side effects and other adverse reactions by significantly reducing the dose of both the progestogen and estrogen in oral contraceptives, there have also been two ways in which R&D has been undertaken to create continuing patent positions.

The first is to have a new progestogen to replace one coming off patent. Interestingly, there has been little effort to change from ethinyl estradiol as the principal synthetic estrogen to use for the pill, so the changes have only been in the progestogen. The second approach has been through “ever-greening”. When there have been gaps in patent protection before a new progestogen has become available, the major companies have surmounted this problem through development of different administration regimens, the biphasic and triphasic preparations, which provide different doses of progestogen and estrogen at different times of the monthly cycle. While there is little epidemiological evidence to show that they had any real advantage over standard monophasic preparations, which have the same progestogen/estrogen dose in each of the 21 active pills usually used in a monthly pill pack, they have bridged the gap before a new progestogen became available.

We are now into the fourth generation of progestogens (depending on who is counting). The third generation progestogens, gestodene and desogestrel were more controversial, some studies showing that these two products had a higher risk of venous thromboembolism (VTE) than the second generation levonorgestrel but it has been accepted that the risk of death from VTE is extremely low.

I must add that every time a product containing a new progestogen or presented in a new regimen is launched, there is a major marketing campaign claiming it to be “better” or “safer” than previous products. There are rarely any studies to back these claims up and there are never comparative trials to support them. WHO/HRP did a major comparative study on oral contraceptives and cardio-vascular effects but this remains a unique study and could only be done after long term use of products. It has never done comparative Phase III trials of new products, or comparison of a new product with those existing, although a Phase III study is ongoing comparing the two implants, Jadelle and Implanon. It is important to note that whenever a new product is registered with the USFDA, whether it contains a new progestogen or has a new regimen, no proof is required to show that is better or has real advantages than previous products. Comparative studies are not required.

So for nearly fifty years, a group of major pharmaceutical manufacturers have been able to grow and nurture a market for a product type which has been able to recover its R&D costs many times over, moreover, provisions for liability have been more than amply covered. However, although they are likely to maintain a significant share of the market for some time to come, the contraceptive market is changing.

The changing scene

The Bioportfolio report went on to say “Achieving success in this arena will depend on product differentiation, a factor that will become increasingly important as generic drugs flood into the market.While oral contraceptives are expected to continue

to dominate, product differentiation remains key in gaining a competitive edge in the market. Strategies for survival post patent expiry including product reformulation, geographical expansion and additional/non-contraceptive indications. Already a fragmented and poorly differentiated market, the spectre of genericization (!) and generic substitution is a growing threat to major players, particularly as managed care organizations are poised to exploit low-cost equivalents.”

The BCC report states, rather blithely, that “Contraception, although a mature market, has seen changes in existing product usage and the introduction of increasing contraceptive options and innovative products. New delivery systems, in particular, are making a significant impact on this market. Another “contraceptive revolution” is foreseen for the next decade, which will represent a quantum leap in approaches to birth control that include contraceptive vaccines.”

I personally feel that phrases like “contraceptive revolution” and “quantum leaps” are going too far. We’ve had the contraceptive revolution and there have been incremental but not quantum leaps in product development, moreover, it is highly unlikely that there will ever be a contraceptive vaccine. However, BCC is correct in saying that new contraceptive options have become available but it is important to consider why, where and to who.

The “why” is the rapidly growing impact of the generic manufacturers. The lucrative oral contraceptive market discussed above is extremely vulnerable, which is clearly spelt out in the statement from Bioportfolio above. As such, the major pharmaceutical companies do need new and different products to continue their major revenue flows from the contraceptive market in the USA.

As an example of what is happening in the US market, Barr Laboratories had by June 2004 become the largest suppliers of oral contraceptives in the USA. Sales in 2003-2004 were US\$0.40 billion from some 19 marketed products – some 20% of the US oral contraceptive market and a quadrupling of sales in three years. Until 2004, Barr had only one other generic competitor, however, two others recently entered the market. Nevertheless the company believes that its generic oral contraceptive sales will continue to grow (Barr Pharmaceuticals Inc, 2005) . This shows how the sales of the big pharmaceutical companies will continue to erode.

Another development is that the big pharmaceutical companies are either establishing, or developing agreements with, generic manufacturers to market their “older” off-patent products. For example, in 2004, Organon entered into an agreement with Prasco Laboratories to supply an “authorized generic” version of Organon’s Desogen (desogestrel, 150µg + ethinyl estradiol, 30µg) (Organon, 2004).

The “where” and “who” of availability of new options are related. It is ironic that during the 1980s and into the 1990s, concerns about litigation following the Dalkon shield and Copper-7 IUD episodes (see below), later compounded by Wyeth’s Norplant problems (see Box 1); as well as the desire to maintain the attractive oral contraceptive market, meant that women in the USA had the smallest choice of contraceptives than anyone else in the world. Now there is a vaginal ring, contraceptive patches, a levonorgestrel-releasing IUD, and soon a replacement implant. The “where” therefore is the USA and the other developed countries discussed earlier, where it is critical for the companies to come out with new, innovative products that will guarantee a continuing healthy revenue stream at a time the “traditional” oral contraceptive revenue flow is being whittled away.

However, the “who” in the USA remain the more affluent women and those who have got insurance programmes that will cover the cost of oral contraceptives at \$300 a

year (although these costs are now decreasing), the levonorgestrel-releasing IUD at \$550 and the CuT-380A IUD at \$240. Although contraceptives are the most widely used prescription drugs by women of reproductive age in the USA, only a third of private insurance plans cover oral contraceptives. There are public programmes which are intended to assist those who lack adequate private insurance but many low-income Americans do not qualify for Medicaid and Title X funding has not kept pace with inflation. Thus, many women, even those who are privately insured, face financial barriers to obtaining their chosen contraceptive methods. (Alan Guttmacher Institute, 2003)

Unfortunately, as we will see below, the new products are unlikely to be available to the majority of people in the developing world and, even if they were, they would be unaffordable.

The players

At the end of 2004, the worldwide hormonal contraceptive market was dominated by four major pharmaceutical companies: Akzo Nobel (Organon); Wyeth; Johnson & Johnson (Ortho); and Schering AG. Pfizer provides some products (through its acquisition of Pharmacia/Upjohn and Searle) and the remainder come from generic manufacturers (Barr and several other generic manufacturers). These are all traditionally R&D based companies but of the “big four” only the two European companies, Schering and Organon, and, to a lesser extent, Ortho, have retained a R&D effort in the field of contraception.

Hormonal contraceptives, primarily generic products, are manufactured in a handful of countries in the developing world: Africa, two companies in South Africa; the Middle East, Iran, Israel and recently Oman; South Asia, India and Pakistan; East and South East Asia, China, Indonesia, Taiwan and Thailand; Latin America, Brazil, Chile and Mexico.

The impact of litigation on R&D

The contraceptive revolution of the 1950s and 1960s was led by “big pharma”. But in 1974, AH Robins halted sales of the Dalkon Shield IUD because of reports of cases of septic mid-trimester abortion, and some deaths, in women who had become pregnant while using the IUD. The next decade saw conflicting reports on the issue. However, in 1984, the Chief Justice of Minnesota arraigned the executives of AH Robins and made a swingeing statement accusing them of planting “in the bodies of these women instruments of death, of mutilation, of disease...a deadly depth charge in their wombs, ready to explode at any time.” This was echoed in other countries, such as the UK. Approximately 2.2 million women were fitted with the device before its withdrawal. Thousands of lawsuits followed, forcing Robins into bankruptcy, the company collapsing under the weight of litigation. Ironically, a recent article recalled that in 1984 an analysis of 13,349 women using four types of IUDs in the UK and Ireland concluded that “reports that the Dalkon Shield was uniquely related to high levels of infection when compared to other IUDs was not substantiated” (Cox, 2003).

While this had little impact on IUD use in the rest of the world, major pharmaceutical companies pulled out of provision of IUDs in the USA. However, the IUD story continued with Searle and the Copper-7 IUD. By 1986, some 10 million women in the USA had used the Copper-7. When AH Robins’ 1984 bankruptcy halted the Dalkon Shield litigation, Searle became the target for lawyers who had developed expertise in IUD cases. By 1986, Searle had 500 IUD suits pending against it. Because it faced difficulties getting additional product liability insurance and because of the cost of

defending the existing lawsuits, Searle stopped selling the Copper-7 in the United States.

One law firm which had benefited by US\$37 million from its Dalkon Shield cases took on some 150 Copper-7 clients. Eventually in 1988, a Minnesota jury accepted the claim of one of them that the Copper-7 IUD had caused a pelvic infection, leaving her infertile. Although the jury rejected the claim that the company had negligently designed or manufactured the IUD and even though the IUD was only available through physicians and carried a warning clearly describing its risks, the judge still awarded compensation of US\$8.15 million! In 1985, Searle had been acquired by Monsanto and the two companies immediately began settling the 2,000 or so suits filed against Searle for nominal sums. Searle won 19 and lost five of the cases that went to trial. Four of them cost Searle a total of US\$689,000 in damages, the fifth being the US\$8.15 million claim. Overall, it cost the company around US\$10 million, the loss of its IUD business, and a significant reduction in share value for Monsanto (Arkin, 1999).

When Ortho withdrew from the IUD market, one of its senior executives decided to form a small company, GynoPharma, specifically to sell the Cu-T 380A (see Box 2). The company had no deep pockets and he ensured that there were no legal loopholes by which the company could easily be liable to litigation. A major irony is that Ortho eventually bought out GynoPharma and marketed the product themselves.

After the collapse of AH Robins, the contraceptive industry naturally became extremely conservative about any potential, perceived or imaginable exposure to product liability. It ensured it had adequate liability coverage and did not venture into what it could consider to be a "risky" area of activity. This stifled most of the R&D being undertaken by the companies in the contraceptive area. Whenever, legal challenges on remaining products, primarily oral contraceptives, arose they were rapidly settled out of court.

In the mid-1990s, litigation again reared its head in the case of Norplant (see Box 1), the legal battle was fought and the action resulted in the removal of the product from the USA for commercial, but not legal, reasons. The case against Wyeth was part of a repeat process - the same lawyers and medical experts who had obtained a US\$4 billion settlement against Dow-Corning on silicone breast implants, considered Norplant with its silicone rods, the next obvious target. Some of the lawyers were even involved in the Copper-7 IUD litigation!

There were cases involving some 80,000 women at the peak of the litigation. The claims were virtually the same, a range of symptoms attributed to an ill-defined array of auto-immune disorders but as the charges against silicone collapsed under the weight of developing scientific evidence, the plaintiffs' lawyers shifted to claims involving the more mundane, and well documented side-effects associated with hormonal birth control methods.

Wyeth-Ayerst reported in 1999 that 3,700 Norplant lawsuits remained outstanding but up to that point 14 cases were dismissed before trial and about 7,000 claims were dismissed, presumably through settlement, while many others were voluntarily withdrawn. There were only three trials, two ending in mistrials and the third in a defense victory. The litigation began foundering, having run into a host of unfavorable pretrial rulings and delays or denials of class certification; some law firms dropping out of the litigation altogether (Arkin, 1999).

According to Arkin “the Dalkon Shield affair remains the sole episode in which the American tort system gave an unambiguous verdict against a contraceptive product and its manufacturer. Subsequent experience with the Copper-7 IUD and recently with Norplant have given rise to decreased credibility of class action approaches to ill-defined symptoms and the causal effects on contraceptives; negligent design or manufacturer; or inadequate warning of documented side-effects” (Arkin, 1999). As such, while contraceptive manufacturers remain cautious, they are now beginning to venture back into the US market with new devices such as a vaginal ring, contraceptive patches, a levonorgestrel-releasing IUD and a new contraceptive implant (see section 3.2.1 above).

Perhaps this represents the end of a period which stifled contraceptive R&D, particularly in the USA. Certainly, while product liability insurance or other provisions for product liability will remain high and of major concern to all the major pharmaceutical companies, the US\$1.8 billion in sales of oral contraceptives in the USA should leave adequate margins for funding these costs as well as R&D of new products!

Recent outcomes from R&D

Research undertaken by Ortho has resulted in development of a once-a-week contraceptive patch which releases a new progestogen, norelgestromin, and ethinyl estradiol. According to the company, this has become the fastest growing hormonal contraceptive on the US market. However, let’s look at the two European big pharmaceutical companies involved in contraceptive development, Organon and Schering AG. Both these companies have invested in significant R&D programmes over at least the last three decades.

Schering has had a major R&D team in Berlin and acquired R&D capacity and technologies from its purchase of Jenapharm in the former East Germany and the takeover of Leiras OY in Finland. The company has had an independent R&D programme on a range of products for fertility regulation and during the 1980s, WHO/HRP had a close working relationship with Schering in research in several areas. The company developed several effective anti-progestogens (see section on medical abortion), a hormone-releasing vaginal ring, its two-monthly injectable was complemented by the once-a-month injectable, Mesigyna, through the work of WHO/HRP and various other innovative products were explored. Few ever reached approval by the Board of Management. It was not until Schering acquired Leiras OY that it moved beyond oral contraceptives and the injectable contraceptive, Noristerat.

In its recent Annual Report, Schering showed that in 2004, its fertility regulation products had total sales of Euro 1.49 billion (US\$1.92 billion) and that they represented 26.5% of the group’s sales. It is also relevant to note that 85% of the companies sales were in Europe, USA and Japan. Of its contraceptive sales, the levonorgestrel-releasing IUD, Mirena (see Box 2 under Population Council), yielded Euro199 million (US\$262 million), most of the remaining \$1.5 billion coming from oral contraceptives. However, Mirena is one of the two non oral contraceptive products that Schering is expecting to use to maintain contraceptive market share. The other is a progestogen/estrogen releasing patch which is expected to be launched in Europe in 2006 with anticipated sales \$130 million three years after launch. A lower dose version of its top selling oral contraceptive, Yasmin, is being launched in Europe and the USA with anticipated sales of \$260 million three years after launch (Schering AG, 2005).

Referring back to Box 1, the company appears to have abandoned the marketing of Norplant and Jadelle. Since Jadelle has now been shown to be effective for five years, there is no reason why the Norplant 6-rod implant should not be discontinued and the Jadelle 2-rod implant remain as a potential contraceptive option, particularly in developing countries. Both of these devices were developed with significant public funding and are no longer covered by patents. Even if the company is haunted by Wyeth's Norplant litigation in the USA, couldn't this technology be transferred to a developing country manufacturer? Again, like Mirena (see Box 2), the benefits of a significant R&D effort is not available to developing countries where there is demonstrable demand - but not at US or European prices.

As stated in Box 2, Schering and the Population Council have recently established created the International Contraceptive Access Foundation (ICAF) to "provide selected public-sector organizations with Mirena on a not-for-profit basis to help serve the needs of women and families in resource-poor settings, primarily in developing countries" (Population Council, 2004). This is unlikely to make a significant contribution to the needs of poor women, particularly those in developing countries or improve access to this extremely important product. The company is working on the development of male contraception and is collaborating on this and basic approaches to female contraception with CONRAD/CICCR (see section 3.1.3).

Although Organon has moved its headquarters to the USA, it has retained an active R&D facility in the Netherlands. The company has traditionally worked on its own leads, investing directly into research on new contraceptive methods through its own R&D teams. It has worked with local universities but has tended to shy away from partnerships with other groups such as public sector agencies. It has developed IUDs, oral contraceptives, a monthly vaginal ring, Nuvaring and a single rod implant, Implanon effective for up to three years. It developed desogestrel, a third generation progestogen, used in its oral contraceptives and more recently, etonorgestrel, used in its implant and vaginal ring.

Organon in 2004 had pharmaceutical sales of Euro 2.01 billion (US\$2.63 billion) of which contraceptive sales contributed some Euro 0.55 billion (US\$0.73 billion). Some 600,000 Nuvaring devices have now been sold, with sales of Euro 81 million (US\$107 million) in 2004 (Akzo Nobel, 2005). The company is also doing research on a hormonal contraceptive for men, trials of which are underway in the USA and Europe. Although Organon is launching the vaginal ring, and probably the implant, in India, it is likely that these will be priced at a level purchasable by women in India's middle class but unaffordable by government for the national programme.

3.2.2 Medical abortion

Mifepristone has been a key drug for medical abortion since the early 1980s. However, the story of its availability has been complex and convoluted. Box 4 describes some of the main elements of this story. Sadly, the secrecy and market protectionism behind the commercial exploitation of this admittedly difficult and politically charged product has limited its availability, particularly to women in developing countries.

There has been significant research undertaken on alternative anti-progestogens by both academic and pharmaceutical company research groups, such as the Research Triangle Institute in the USA and by Schering AG but no products completed testing. The latter had synthesized a promising range of products, which went through preclinical studies but this research effort was discontinued for non-scientific reasons.

Box 4. A brief history of mifepristone

In 1974 Hoechst AG purchased a majority share holding in Roussel-Uclaf, 40% being retained by the French government. Roussel-Uclaf synthesized and patented an anti-progestogenic steroid, mifepristone in 1980 and began studies on its use as a pharmacological abortifacient. The company collaborated closely with WHO/HRP on its clinical trials. However, in 1983, as part of studies supported by WHO/HRP, researchers at the Karolinska Institute, Stockholm showed increased efficacy when mifepristone was used in conjunction with a prostaglandin. This was deemed unnecessary by Roussel-Uclaf, which fought WHO on these findings! Coincidentally, in 1984, Schering patented the use of an anti-progestogen in combination with a prostaglandin, specifically citing mifepristone and misoprostol, as a more effective method of medical abortion!

As an important aside, there were uncompleted license negotiations between Roussel-Uclaf and China in 1986. The Chinese State Family Planning Commission immediately commissioned the synthesis of mifepristone by three companies in China and undertook clinical trials.

Subsequently the product, using a dose of 600mg of mifepristone, was approved in France and in September 1988, Roussel-Uclaf began marketing it in France. Within a month, the company withdrew the product because of pressure from the right-to-life movement. A week later, it was reinstated after pressure from the French government!

Roussel-Uclaf donated rights for the USA to the Population Council in 1994. At the end of 1996, Hoechst purchased the remaining shares of Roussel-Uclaf. Within a few months, Hoechst transferred the mifepristone patent and marketing rights, without remuneration, to a former executive of Roussel-Uclaf, claiming that it had been unable to find a partner or a buyer willing to invest in the product. Hoechst had a conservative, Catholic Board and was under continued pressure from right-to-life groups that were organizing a boycott of a new anti-allergy product, Allegra. A new single product company, Exelgyn, was then established to take over the worldwide manufacturing, marketing and distribution of the drug, excluding the USA.

Despite studies from WHO/HRP, published in 1993, which showed that 200mg of mifepristone was as effective as 600mg, Exelgyn jealously guarded their inflated cost structure in Europe, making them unwilling to consider registration of a 200mg product. However, in practice, countries like the UK are using 200mg. Despite it not being the registered dosage, it is the regimen recommended by the UK Royal College of Obstetricians and Gynaecologists (Royal College of Obstetricians and Gynaecologists, 2000) and was listed as a preferred regimen by WHO (World Health Organization, 2003).

The worldwide patent for mifepristone has now expired although Exelgyn retains rights for sale and distribution in France. The rights held by the Population Council for manufacturing and distribution in the USA were sub-licensed to Danco Laboratories Inc. Danco has been producing and distributing mifepristone, sourcing raw material from China. Schering's US patent for the use of mifepristone with a prostaglandin expired in October 2004, although Danco holds marketing exclusivity until 28 September 2005.

MF is currently registered in: Azerbaijan, China, 12 of the pre-May 2004 EU countries (all except Ireland, Italy and Portugal), Georgia, India, Israel, Moldova, Norway, New Zealand, the Russian Federation, South Africa, Switzerland, Taiwan, Tunisia, Ukraine, USA, Uzbekistan and Viet Nam.

Misoprostol has been widely used off-label as the prostaglandin to be used in combination with mifepristone for medical abortion. The product was originally patented by Searle, now part of Pfizer, which registered misoprostol, as Cytotec, in most countries in the world, except for those in Africa (other than South Africa or Ghana, where it is not marketed), India and several Middle Eastern and central Asian countries, for the prevention of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs. Use patents have now expired and it is widely available both as Cytotec or as generic preparations. Searle tried hard to fight its off-label use for medical abortion, however, many drug regulatory agencies, including the USFDA, acknowledges its use in pregnancy and for medical abortion

The Population Council, like WHO/HRP, has been involved in clinical trials of different treatment regimens for mifepristone and misoprostol. It obtained a license from Roussel to market mifepristone in the USA and has received substantial support from certain private US foundations for these as well as to undertake clinical studies in several developing countries with a view to subsequent registration. China accounts for some 8 million abortions per annum and India up to 6 million (although only 1 million legal abortions are reported). It is not known what proportion of these are undertaken using medical abortion. In China, there are three manufacturers of mifepristone, which meet national needs as well as provide raw material to other countries.

In India, four of the biggest pharmaceutical companies, Cipla, Nicolas Piramal, Sun Pharma and Zydus Cadila, all with international reputations and high GMP standards, are marketing mifepristone. They are supplying the local market at 350 rupees (approx \$7) for mifepristone and \$1 for misoprostol. Although the drugs are labelled "by prescription only" pharmacists often do not abide by this labelling and freely provide the product, something that most of the suppliers are trying to control. This is now creating a negative response both from women's groups as well groups involved in the rational use of drugs. Inadequate reporting makes it hard to know how much product is being used, although recent research in Tamil Nadu suggests that two out of three women in the study centres had accessed medical abortion (Sundari Ravindran and Balasubramanian, 2004).

The current price of mifepristone varies widely depending on the source. From Danco in the USA, it costs \$250; from Exelgyn, in Germany and Switzerland, \$US130-140; and in the UK, \$75 for 600mg; and from local suppliers in China, India and Viet Nam, it is \$7-8 for 200mg. As with contraceptives, in many western European countries, product price is less of an issue to the women as costs are paid by the healthcare or health insurance systems. In South Africa, mifepristone is registered and available from a Belgian company. The Department of Health would like to introduce medical abortion into the primary health care system, however, the total service delivery costs, including overheads, is estimated at Rand 266 (US\$46), with mifepristone representing Rand 137 (US\$24) or more than 50% of these costs (Cullingworth, 2004). Unless product cost can be reduced substantially, say to \$4, it is unlikely that public sector provision of this method will occur.

There are currently several major obstacles to wider access to drugs for medical abortion. The major international misoprostol manufacturer refuses to provide information on off-label use and has actively discouraged its use for gynaecological indications; mifepristone prices are too high to be affordable to most women; the drug is not registered or distributed in many countries; and there is a lack of interest or ability among current manufacturers to register an appropriately priced product in low-resource countries. Moreover, an opportunistic approach to the introduction of medical abortion through a limited investigational new drug registration for clinical

trials will not create a sustainable supply of affordable drugs; improve the health system's capacity to deliver quality medical abortion services; or increase women's awareness of this new method.

3.3 Public-private partnerships

3.3.1 Microbicides

There are currently no microbicides on the market, however, they represent one of the drugs and vaccines areas in which R&D is being funded through, and organized around, public-private partnerships.

Public-private partnerships (PPPs) became prominent on the international health agenda in the mid-1990s as one way to address health equity issues, and in particular, the needs of poor or disenfranchised populations in the prevention and treatment of infectious diseases. The Rockefeller Foundation and the Bill and Melinda Gates Foundation began initiating and supporting public-private partnerships to address these issues and there are now more than 90 PPPs. The term PPP is a new but somewhat artificial term since there has been a history of close collaboration between the public and private sectors, albeit under a different label. Certainly, the three programmes discussed in section 3.1, the Population Council, WHO/HRP and CONRAD, could all be described as PPPs.

There are currently some 17 microbicide products at various stages of clinical trials, four of which are in Phase III clinical trial: Carraguard (Population Council), Cellulose sulphate gel (GMP/FHI), PRO 2000/5 gel (Indevus, UKMRC) and Savvy (USAID, FHI, Biosyn Inc). Another product, Buffergel (ReProtect, NIH) is about to enter Phase II/IIb clinical trial. Waiting in the wings behind these 17 candidate microbicides are about 45 additional products that are still in pre-clinical testing (Alliance for Microbicide Development, 2005).

Most of the advanced products are being developed by small biopharmaceutical companies with public sector and some venture capital funding. None, as yet, have a major pharmaceutical company behind them. However, many big companies are holding a watching brief and some would enter rapidly if there were signs of success and in doing so would purchase or license all relevant intellectual property.

A 2004 factsheet (no longer on the website) from the International Partnership on Microbicides (IPM) stated that "With the exception of Gilead, no major pharmaceutical or biotech company is currently engaged in microbicide research and development. Indeed, the absence of pharmaceutical investment leaves a major gap in microbicide product development. The small companies and academic research organizations that are doing almost all of the work on microbicides lack the capacity and resources for testing, formulation, manufacturing, and packaging." Since then IPM has agreed with Tibotec, a subsidiary of Johnson and Johnson, and GlaxoSmithKline to develop certain antiretroviral drugs as microbicides. In addition, IPM has recently opened a manufacturing facility for the production of products for Phase I and I clinical trials, for use by both IPM and other development groups.

A recent preliminary report on Public and Philanthropic Investments in Preventive HIV Vaccines and Microbicides by the HIV Vaccines and Microbicides Resource Tracking Working Group, showed that the total investment by these two sectors in microbicide R&D increased from US\$66 million in 2000 to US\$140 million in 2004. The public sector contributed some 85% of the 2004 investment, of which 75% came from the USA. The National Institutes of Health accounted for about 70% of the US

public sector funding (HIV Vaccines and Microbicides Resource Tracking Working Group, 2005). In a forthcoming presentation to the G8, IPM together with other groups state that “Microbicide research and development are severely under funded. For example, only US\$140 million was committed to microbicide research, development and advocacy in 2004, despite the fact that the science is advancing rapidly. An additional US\$100 million per year investment will be needed to significantly accelerate the research and development of microbicides.” (IPM, 2005)

What is going to be more problematic is funding large scale clinical trials. IPM stated that “Making the leap from pre-clinical to clinical trials depends not only on the success of the product, but also the availability of resources to conduct clinical trials. The established pharmaceutical companies foresee little profit potential from microbicides because most of the women who need them are poor and live in developing countries. Product development is expensive, with Phase III trials alone estimated to cost between US\$75 million and \$100 million, and the likelihood of finding an effective product remains uncertain.”

Despite the latter statement and significant discussion between the field players, little has been done between donors and developers to rationalize products and ensure “best use” of donor funding. This is particularly critical since, on current evidence, several of the first generation products, all gels, that have or are about to enter Phase III trials are unlikely to have an adequate efficacy to make them a viable product. Yet the Phase III costs will be enormous. This message was understood by the UK sponsors of Emmelle, a dextrin sulphate product, which was withdrawn from a comparative study with PRO 2000/5. Revaluation of laboratory studies showed Emmelle to be substantially less effective than PRO 2000/5 in blocking HIV infection. They also had concerns that the two substances were too similar to each other and to several other microbicides being taken into full-scale testing (Meldrum, 2004). The Phase III study will continue comparing two doses of PRO 2000/5. It's a pity that other sponsors are not taking such a critical approach!

The Alliance for Microbicide Development runs a Microbicide Research and Development database, which regularly updates the status of all clinical trials being undertaken on microbicide candidate products (Alliance for Microbicide Development, 2005). The Alliance database currently lists Phase III studies on: Carraguard, that is planning to recruit more than 6,000 subjects; PRO2000/5, with some 12,000 subjects; cellulose sulphate, with over 2,000 subjects; and Savvy, a Phase IIB and a Phase III study with more than 5,000 subjects - a total of some 25,000 people. There is also a Phase II/IIB clinical trial planned with some 3,200 subjects to compare another product, Buffergel, with PRO2000/5.

This is still an immense amount of work and funding for a group of products which several are expected to exhibit low efficacy. A similar justification is given to that on the testing of certain vaccines against HIV - the studies will give us a lot of information which can help in the development of subsequent products. In addition, defensive modelling studies showing the economic impact of a partially-effective product have been undertaken. Some people anticipate that most of these studies are unlikely to result in a suitably effective product, hence they are unlikely to be cost-effective - so are they ethical?

The earlier IPM document went on to say “The experience of the International AIDS Vaccine Initiative and the Global Alliance for TB Drug Development has demonstrated that investments from public-private partnerships can entice companies into the field. We believe that once public-sector funding provides proof of concept with a first generation product, private investment will follow. According to a

study commissioned by the Rockefeller Foundation, the cost for a first-generation microbicide will have to be borne by public-sector funding. However, the study projects that a second-generation product could get to market without a public-sector subsidy. A third generation of product offers the first potential for significant returns, estimated at up to US\$428 million, due to increased market size and lower development costs.”

As discussed in section 3.1.3, CONRAD and the Indian Council of Medical Research recently signed a Memorandum of Understanding to cooperate in microbicide research. This is important as most of the other PPPs are working on developed country driven approaches to microbicides, in which, as with most contraceptive development programmes, developing country investigators are involved at the time of conducting clinical trials.

4. What is the role of developing countries in the development and manufacture of low cost reproductive health drugs?

Firstly, we need to ask whether the existence of generic or R&D-based pharmaceutical companies in developing countries has improved, or can improve the cost of, and access to, reproductive health commodities.

As mentioned in section 3.2.1, oral contraceptives, are manufactured in a handful of countries in the developing world: Africa, two companies in South Africa; Middle East, Iran, Israel and recently Oman; South Asia, India and Pakistan; East and South East Asia, China, Indonesia, Taiwan and Thailand; Latin America, Brazil and Mexico. There are an even smaller number manufacturing injectable contraceptives, these are in China, Mexico, Indonesia, South Africa and Thailand. In addition there are several manufacturers of copper-bearing IUDs in China and India.

Most of these manufacturers are making generic products. Certainly the availability and affordability of contraceptives and other reproductive health drugs, such as mifepristone, have improved dramatically through local production. As discussed in section 3.2.2, mifepristone is widely available in India and China at a cost of US\$7-8, still high but significantly less than the price in the USA and Europe. In Indonesia, the cost of the once-a-month injectable contraceptive, Cyclofem produced locally is US\$0.65 for the public sector and US\$0.93 in pharmacies. In many countries oral contraceptives are available for less than US\$0.50 a month, whereas the branded imports can cost many times more.

However, there are still major issues to be addressed. The biggest one is quality, quality, quality. While standards of GMP inspection by national drug agencies have increased dramatically in the past ten years, there is still significant room for improvement. A decade ago, when I asked a visiting Australian FDA GMP inspector to summarize his findings of an inspection of a company producing a generic injectable contraceptive that was widely used in that country, his response was "close it down"! Another random quality assurance analysis of an Asian oral contraceptive showed that samples of pills with a stated ethinyl estradiol content of 30µg, actually showed a range of 4 to 400µg! (World Health Organization, 1994). Since then there have been major efforts to improve the quality of production by WHO, regional groups and national bodies. However, the problem remains and WHO intends to establish a pre-qualification programme for contraceptive manufacturers.

The other problem has been the choice of product to be manufactured. Obviously, many are generic versions of products developed by the major western pharmaceutical companies. But, in a few countries, the products have been developed locally and have not always undergone adequate pre-clinical or clinical testing. This is changing, although there are still products being produced in China and Latin America which could not be registered in many other countries because of lack of preclinical and clinical data.

A recent review of once-a-month pills in China showed that while there is a lack of data to assess the effectiveness and safety of the method, they appear to be less effective than daily pills and injectable contraceptives. The monthly dose of the estrogen in the pill is high, raising concerns about long-term safety. The available data on safety of quinestrol is inadequate and a substantial number of users have complained of nausea, vomiting, leucorrhoea, and increased blood pressure (World Health Organization, personal communication). Yet these pills are still being used extensively in China and are available in neighbouring countries.

Similarly, a comparative Phase III study on once-a-month injectable contraceptives, supported by WHO/HRP in China, showed poor efficacy of the Chinese Injectable No 1 when compared with Cyclofem and Mesigyna, yet this product is still manufactured (Sang et al, 1995)). In Latin America, another once-a-month injectable, Perlutal, is still manufactured despite the absence of adequate safety data. Even one of Concept Foundation's licensees for Cyclofem is still producing it after a decade of making Cyclofem, since they feel they can service a "cheaper" market!

Several companies in developing countries are supplying significant quantities of contraceptive products primarily within their own or neighbouring markets. Some of them have the potential capability of increasing their capacity to compete for international tenders or make inroads into the competitive western markets. However, many face the significant hurdle of upgrading their facilities to meet international GMP and adopt the standard operating procedures that will allow them to sustain quality manufacture on a continuous basis. Furthermore, there needs to be a major effort made to ensure that all products, even those intended solely for local markets meet international requirements for safety and efficacy.

Global trade agreements may well impact on drug pricing and technology transfer, which is why significant attention is being paid to the WTO's agreement on Trade-related Aspects of Intellectual Property (TRIPS). TRIPS establishes minimum standards for protecting and enforcing IP rights. This will impact on the provision of generic products to many countries. From 2005, major generic drug producing countries like India and China are required to protect and enforce patent and other IP rights and least developed countries from 2016. Countries with insufficient manufacturing know how or capacity will be able to use compulsory licences to import generic products from producer countries. As discussed below, while TRIPS is unlikely to affect access to the most important contraceptive and reproductive health drugs currently available, it may well affect access to affordable microbicides or other new products as they become available.

Since the next section will look specifically at India and China, it is worth looking at this point what contraceptive use is in India and China, since this obviously influences national production. This is shown in Table 2. The use of hormonal contraception is low but when you look at the large numbers of women of reproductive age in these two countries, 270 million in China and more than 200 million in India, it means that in both these countries some 5-6 million women are using hormonal contraceptives - similar to the number of women using oral contraceptives in the USA!

Table 2. Use of contraceptive methods in India and China

	Prevalence of use of modern contraception	Sterilization (male and female, % total users)	Oral pills	Injectables	Implants	IUDs
China	83.3	47.5		2.2	0.4	45.5
India	42.8	75.0	4.0		0.0	4.0

Pharmaceutical production in India and China

The situation is changing rapidly, as with other pharmaceutical products, the acceptance of generic products in western Europe and the USA has opened up huge new markets (see section 3.2.1). This is stimulating significant change in manufacturing, where companies, particularly in India and Mexico, and to a lesser extent in China, are complying with, and meeting, modern standards of GMP. They are requiring that API materials are provided with a drug master file and that the products show bioequivalence with existing western products.

This change will eventually have an impact on the production of all products, although even in India there remains an enormous range of companies, from those expanding dramatically their supply to the developed world to those that should be immediately closed down. The latter are mainly smaller companies that have major problems in maintaining quality and operating procedures. About 10% of all private pharmacies report quality violations and that smaller firms manufacture most of the “out of quality” drugs. This is compounded by the fact that each state is responsible for quality assurance and there is wide variation in implementation. A recent study undertaken by MSH’s Strategies for Enhancing Access to Medicines programme in Rajasthan, found that 10.4% of essential medicines samples collected failed assay analyses - 6% of those obtained from public-sector facilities and 14.1% of those obtained from private retail outlets (Management Sciences for Health, 2004).

The Indian pharmaceutical industry has about an eight percent share of global pharmaceutical production. It has about 300 large companies and some 10,000 smaller companies. These include both domestic manufacturers and companies having foreign control. The latter have mainly been aiming at penetrating the domestic market and import most of their bulk drug requirements. However, many domestic companies have built up, and others have started to build, both their R&D capacity and the ability to synthesize new and existing compounds, developing a major API capacity. Part of a recent article from www.in-pharmatechnologist.com, a pharmaceutical internet news site, is reproduced as Box 5, with permission of the Novis Group, Montpellier, France, since it gives a comprehensive, up-to-the-minute review of the Indian pharmaceutical scene (Novis Group, 2005).

Three Indian companies manufacture Cu-T 380A IUDs, and UNFPA can now buy these devices at between \$0.25 and \$0.32, depending on volume. This a quarter of the price that USAID can purchase the original product the USA for supply to developing countries. A small number of companies manufacture oral contraceptives but none, injectable contraceptives. Nevertheless, before long these companies will begin to enter the western generic markets One company recently won the World Bank tender for the supply of oral contraceptives to Bangladesh worth US\$80 million.

It is interesting to see that at a Global Investor’s Summit in January 2005, the State Government of Gujarat is planning to set up a manufacturing facility for oral contraceptives (including the manufacture of APIs!) and female condoms, in Ahmedabad (a city where there is at least one major producer of quality hormonal contraceptives), with a focus on meeting domestic needs. It claims that “there is only one domestic player in this segment”, which is not true, and estimates the project cost to be US\$5.56 million (www.vibrantgujarat.com/pp/ph005)!

Box 5. India's drug sector tackles new patent regime

(reproduced with permission, from www.in-pharmatechnologist.com, 14 February 2005)

As expected, around 12,000 patent applications have been filed by multinational pharmaceutical companies for their patented drugs that are sold in India as generics, and companies that have built their business on copying in-patent drugs for the domestic market are expected to be hit hard. But on a more positive note, India's top companies have welcomed the new legislation, and the international pharmaceutical industry looks like it may fulfil its promise of investing in India now that the country is compliant with World Trade Organization rules on intellectual property.

Generics make up about 15% of the Indian pharmaceutical market and, according to the WTO rules agreed to by India, any generic versions of drugs patented abroad after 1 January 1995 must be withdrawn from the market immediately. It seems likely that a large number of patent lawsuits will follow, according to local press reports, and there is also likely to be considerable debate about exactly what is and is not covered under the new scheme. For example, the large number of patent applications has led to speculation that international companies are trying to protect innovations - for example mixtures of drugs and new uses for established agents - that will not be deemed novel under India's interpretation of the WTO rules.

The big domestic players in India - such as Ranbaxy, Cipla, Dr Reddy's and Nicholas Piramal - say intellectual property protection laws are essential, a stance in keeping with their recent conversion to a big pharma model - development of a novel active substance pipeline and expansion of marketing into overseas markets. The top 10 Indian companies spent 15,000 crore (€2.6bn) on R&D in 2003/4, suggesting that they can start to compete with the established researched-based pharma companies, by taking advantage of India's lower cost-base and pool of research talent.

At a meeting in London recently, Shri Kamal Nath, India's Minister of Commerce and Industry, said the government has committed some \$46 million (€35m) to oversight of the patent system so that it can administer and police the new regime. And while the top Indian companies see the benefits of stronger intellectual property for their homegrown products, India's generic drugmakers are fully equipped to take advantage of the \$50 billion worth of drugs going off patent in the next five years. *"We'll grab a major share of this,"* he said. For example, Indian firms have on average accounted for about 35% of all Drug Master File (DMF) applications in the US in recent years - a DMF is required before a company can make a product for which the patent has expired - and ranks second only to US companies in this effort.

India has a combination of *"cost-effective manufacturing, well-developed chemical industry infrastructure, strong vertical integration, abundant scientific talent and technical skills and unique synergy in fields of information technology, biotechnology and medicine,"* he said, adding: *"our objective is not only to manufacture drugs, but also to make India a hub for medical research and clinical data management."*

India's \$10bn drug sector has 300 large and moderate-sized firms, plus 10,000 small companies, making 8 per cent of the world's drugs. 70 per cent of production is by the top 100 firms and about a third is exports, which are rising 25 per cent a year. Meanwhile, multinational pharmaceutical companies have been encouraged to introduce new drug products in India and invest in new facilities, according to a recently published report by McKinsey and Co. The report has a lower estimate of the Indian drug market (\$6bn) than the Indian government, but nevertheless agrees that it is due to grow enormously over the next five years, all because of patent protection.

Sankar Krishnan of McKinsey feels that R&D spending could leap from less than \$1.0 billion a year to perhaps \$6 billion in 2010 as international companies increase their spending in India on their own or partner with local companies.

As discussed in section 3.2.2, four of the biggest pharmaceutical companies are making mifepristone and misoprostol for the Indian market at a retail cost of US\$7-8. It is only a question of time before this product This is still a relative It is a Most of the mifepristone API is sourced in China, only one of the companies is meeting part of its needs by through synthesis of the API.

The ability to produce quality APIs is important in the field of reproductive health, since some compounds like mifepristone (see section 3.2.2) are expensive because of a relatively complex synthesis, giving a low yield. Although Chinese companies have been the principal manufactures of mifepristone, India could become the principal source of quality raw material. This also applies to hormonal contraceptives, where levonorgestrel, one of the most common progestogens in oral contraceptives, currently costs around US\$3,000/kg.

While there are significant concerns about the interpretation of TRIPS in India, fortunately they are unlikely to create difficulties for key reproductive health drugs, such as mifepristone, misoprostol and many of the progestogens, or devices such as the levonorgestrel-releasing ring or implant since they are no longer on patent. Moreover, the newer progestogens are unlikely to have significant health benefits over compounds like levonorgestrel and monthly vaginal rings or weekly patches are unlikely to be easily delivered at an acceptable cost through existing service delivery systems wherever they are made.

If we turn to China, the story is quite different. China meets most of its pharmaceutical requirements through domestic production. While the rapid expansion of the industry has increased the availability of low cost products and has reduced import requirements, most advanced products have to be imported. The focus of the industry has, unlike India, been on the domestic market. Almost all pharmaceutical production facilities, other than joint ventures, are small and use simple production methods. The quality of products has been extremely and very, very few companies meet international GMP standards.

A recent article in the Economist (06 January 2005) was entitled “China wants to build world-class companies. Can it succeed?” It went on to say that “China has so far failed to build world-class companies. Even the natural monopolies and resources companies are mostly just big rather than particularly efficient. In manufacturing, technology and consumer areas, a few companies are groping towards international competitiveness, but none are there yet.” This is certainly true of the pharmaceutical industry.

Recently, the government has been trying to increase the competitiveness of the pharmaceutical industry by persuading many of the small, unprofitable state-owned enterprises to merge to achieve economies of scale and increase investment in R&D and marketing. Most of the leading producers have expanded their production by acquiring smaller, or less profitable companies. The government is offering a package of incentives to the pharmaceutical sector to invest in key products that are competitive on the international market through technology transfer and R&D. In addition, government is pushing the industry to conform to international standards by establishing, implementing and policing national technical standards, equivalent to those in the developed world.

In the field of contraception and reproductive health, a large number of small pharmaceutical companies produce a wide range of oral contraceptives, once-a-month pills, once-a-month and two-monthly injectable contraceptives, IUDs, a generic levonorgestrel-releasing implant, barrier methods, mifepristone and

misoprostol, among others. Many of these producers began as small state-owned enterprises or offshoots of university research departments encouraged by the Chinese State Family Planning Commission (SFPC).

SFPC, the head of which is at ministerial level, has been working to encourage the availability and affordability of contraception in the country. It also has established a subsidiary which is promoting the export of Chinese contraceptive and other reproductive health products. Despite, the problems referred to above, China remains a major source of raw material, although to date, few companies have internationally approved GMP or can provide an adequate DMF. As mentioned It is a primary supplier of mifepristone to several companies in India, as well as Danco in the USA (see Box 4). With support of the Rockefeller Foundation, the Concept Foundation (see Box 3) was responsible for getting one company's bulk production up to USFDA approved GMP. However, to my knowledge, the final tabletted product has never been approved.

Research and development

Many developing countries have been involved in the development of the new drugs supported through the public sector (see section 3.1). Although they have been considered as "partners" in research, their principal role has been to undertake clinical trials directed from outside by the major public sector research programmes. This has changed in some areas of infectious diseases, including HIV/AIDS but in the reproductive health, and particularly the contraceptive field it has really only been China and India that been conducting independent R&D activities. There was a South-to-South research programme established in Brazil for R&D collaboration between developing countries which investigated a one-year contraceptive implant, male contraception among other things.

Both India and China have major national research institutes, such as the Indian Council of Medical Research (ICMR) and China's National Research Institute for Family Planning and the Shanghai Institute for Planned Parenthood Research. These institutions have been involved in the R&D of new products, as well as in multicentred clinical trials.

ICMR has an extensive network throughout India of academic groups supported to undertake clinical trials both on products developed locally and in other countries. India has a major pool of researchers which in general is highly qualified and proficient in R&D and in the rapidly developing biotechnology field. This is complemented by those in the public sector institutions, such ICMR, the Central Drug Research Institute (CDRI), the Council of Scientific and Industrial Research (CSIR), and numerous universities. Some of these institutions now have state-of-the-art equipment and facilities.

Researchers in the public sector have, for many years, been working on many basic science leads towards the development of methods of fertility control, ranging from the suppression of spermatogenesis to plant products to immunocontraception. A summary of these activities is provided in Sharma et al, 2002. As yet, in terms of products, little has come out of the public sector research. CDRI developed an anti-estrogen to prevent ovum implantation, a once-a-week pill marketed since 1991 as Centochroman. However, its efficacy is rather low.

The private sector has to date spent relatively small sums on R&D, although this is changing rapidly. In 2004, the sums spent on R&D as a percentage of total sales was 4% by Cipla; 8% by Wockhardt; 4.45% by Cadila; and 1.76% by Nicolas Piramal.

Recently the CEO of Biocon, a major Indian Biotech company, said that India enjoys a competitive edge in terms of low cost, quality of intellectual assets, biodiversity and clinical capabilities. "But we have to shift from imitative innovation to discovery-led innovation." She said that there is need to build the intellectual property rights regime, promote patenting culture, and encourage interface between academia and industry for commercialization of biotech products. As yet none of the private sector's growing R&D capacity appears to have oriented towards products for reproductive health.

In China, there is both a R&D and manufacturing capacity to develop drugs for reproductive health. Both the National Research Institute for Family Planning (NRIFP) in Beijing and the Shanghai Institute for Planned Parenthood Research (SIPPR), as well as other provincial research institutes have had significant research programmes. Several of these institutions have worked closely with WHO/HRP on post-ovulatory methods of contraception. A research network led by NRIFP, in collaboration with the Concept Foundation, WHO/HRP and the SFPC and funding from the Rockefeller Foundation, developed mifepristone (10mg) for use as an emergency contraceptive. As well developing a new emergency contraceptive pill, this project was responsible for getting the production of bulk mifepristone by one of the Chinese manufacturers approved by the USFDA discussed above.

Other outcomes of R&D are discussed earlier in this chapter, some of the R&D has been to produce generic copies of existing methods and some has resulted in inadequately tested products. However, both the objectives and standards of R&D are changing because of the input of the State Family Planning Commission, as well as the pharmaceutical manufacturer's standards of GMP because of government pressure. As such, China has the potential resources to play a role in product development in reproductive health.

5. What are the priorities for R&D of reproductive health products and for health service research on access to products?

The Institute of Medicine of the US National Academies, published reports on contraceptive development in 1990 and 1996. In 2003 it received funding from the Gate Foundation to continue its review of research needs in this area. This report was published in 2004 (Institute of Medicine, 2004) and as well as providing an update of the contraceptive field and proposals for research and development, it was also intended to inform the Gates Foundation in its development of issues for funding. A summary of its recommendations is attached as Box 6.

Since this a very recent report and involved a range of experts in the field of contraceptive development, I will address some of the issues identified in the report, as well as use them to raise my own priorities for R&D of reproductive health products and for health service research on access to products. IOM reports are influential but sadly this one really does not help the needs of those in developing countries.

Box 6. A blueprint for action, summary of recommendations.
(New Frontiers in Contraceptive Research, Institute of Medicine, 2004)

Identity and validate novel contraceptive targets

1. Generate a complete reproductive transcriptome and proteome, and define generic and protein networks.
2. Generate reproductive lipidomes and glycomes.
3. Validate existing and emerging contraceptive targets.

Enhance contraceptive drug discovery, development, and clinical testing

4. Develop high-throughput screening facilities.
5. Facilitate translational research.
6. Facilitate the development of appropriate drug delivery systems.
7. Develop new approaches to measure contraceptive efficacy.
8. Integrate behavioural research at an early stage of development.
9. Discover, enhance, and promote potential health benefits of existing and new methods, and intensify efforts to develop new contraceptive methods that are prophylactic for HIV infection and other STIs.

Facilitate and coordinate future implementation of contraceptive research and development

10. Expand public-private partnerships for contraceptive development.
11. Increase the participation of developing countries in contraceptive development.
12. Increase training and career development opportunities in contraception.
13. Establish an ongoing Forum on Contraceptive Research and Development and create an Alliance for Contraceptive Development.

A major part of the report represents “blue sky” brain-storming on issues such as, how the use of genomics and cell regulatory mechanisms could identify new leads that might be used for new approaches to contraception. This is basic research that would normally be funded by national Institutes for Health, Medical Research Councils and universities. It is extremely long term research, which is fine but it has little relevance to existing needs in developing countries. However, also under basic research, it also notes the need for continuing research on developing new entities which could affect sperm maturation or capacitation, sperm-egg interactions, and maturation of the egg and ovulation. This is important research, some of which has been going on for some years but, as yet, there are no compounds which could reach initial clinical trial.

The next section of the report on enhancing contraceptive drug discovery, development, and clinical testing is also long-term and somewhat theoretical. For example, it talks about the advances in drug delivery which we have seen in recent years, such as implants, patches, vaginal rings and drug-releasing IUDs. However, it is western-centric in its considerations. These products need not only to be cheap but able to be delivered through weak health delivery systems. In the late 1970s, we (WHO/HRP and NIH) worked on the cutting edge of pharmaceutical development, such as the use of biodegradable implants without considering the service delivery implications in developing countries. A biodegradable implant degrades at 37°C whether it is inside or outside the body!

The report states “All of these expanded activities will require additional expertise and an increase in the number of scientists focused on contraceptive research and drug discovery, which could be achieved through endowed professorships or chairs in contraceptive research, new multidisciplinary training grants, and courses or workshops.” Sure, but where, how and with who’s money? It certainly won’t be happening in many developing countries, except perhaps India and China, and certainly Mr Gates’ money would be better spent in getting what we’ve got to those that need it!

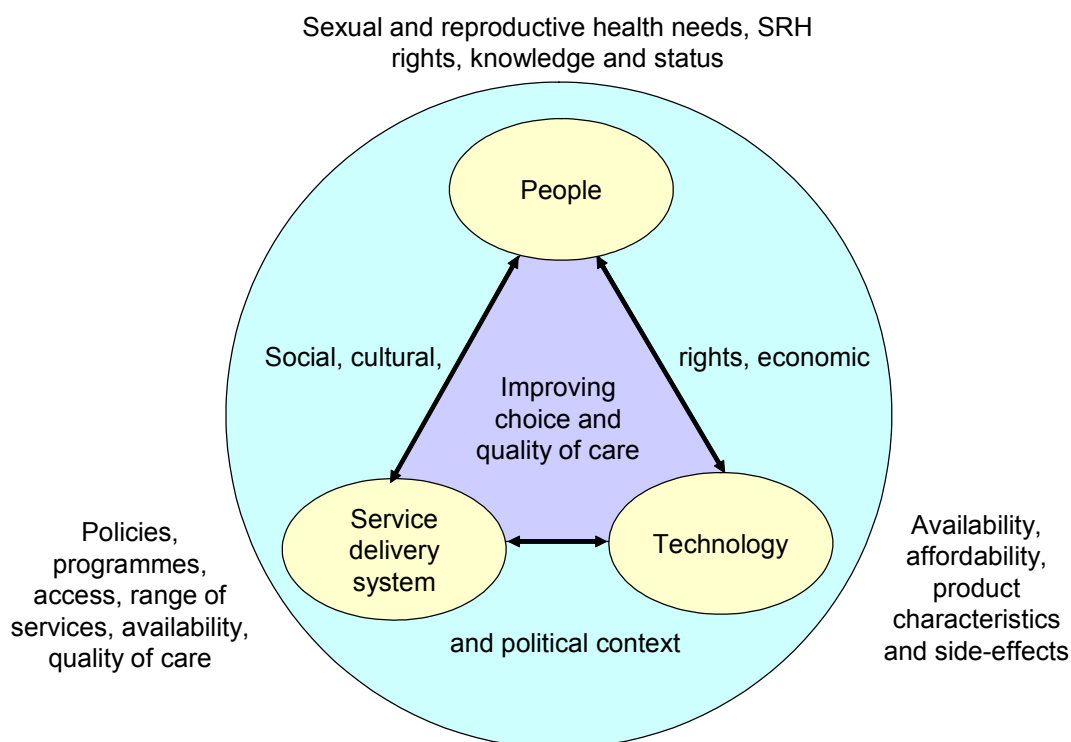
Despite the enormous profits that a small number of companies are making out of contraception (see section 3.2), the report thinks that “A number of incentives could be provided to the pharmaceutical industry for the development of new contraceptives for use in developing countries. For instance, some of the FDA processes could be fast-tracked to ensure that contraceptive products being developed for use in developing countries are approved in a timely manner. The patent life could be extended and liability relief could be provided for contraceptive products developed by the pharmaceutical industry for use in developing countries. Cost sharing through the codevelopment of contraceptive products by several pharmaceutical companies or through funding of initial research and development of low-cost contraceptive alternatives by establishing a central fund that would be supported by governments in those countries that would benefit from such contraceptives. Each contributing country would decide individually how to dispense the products developed. However, this would require a stable commitment of funds to the initiative from these countries and would require the countries to have clear knowledge and to accept that product development could take a rather long period of time (7 to 14 years).”

There is merit in considering establishing a central fund for reproductive health commodities as we will see in section 6.5 but not to fund R&D. What developing country governments could support the above proposals, given the little money going to health in those countries and, again except for India and China, the lack of R&D capacity; in which case, what developing country governments would contribute to a

fund for western researchers and western pharmaceutical companies? Extending patent life would continue the stranglehold of these companies and who would provide (or want to provide) liability relief to companies making hundreds of millions of dollars on contraception. There is a total lack of realism behind these proposals!

Admittedly, the short chapter on “Improving contraceptive use and acceptability” does return to real life. It does make the statement that “It is important to conduct research designed to understand and integrate the views of potential users, their partners, and their providers as early as possible in the development process. In this way, the views of users can influence decisions that must be made over the course of method development to ensure that the ultimate method will best meet user and provider needs. Such information will also be helpful in determining country-specific needs and in crafting the best ways to introduce new contraceptive technology.” This has been the philosophy developed in recent years by WHO/HRP (see section 3.1.2). Ensuring that technologies meet peoples needs and can be delivered affordably by service delivery systems is paramount in any quest for new contraceptives, or other products for reproductive health, or indeed any drug for any purpose. Taking a systems based approach to the development and introduction of appropriate technology is one area where we need to invest research funding. This is shown in Figure 1.

Figure 1. A systems framework for the development and introduction of appropriate technology (adapted from WHO/HRP) (www.who.int/reproductive-health/strategic_approach/methodology.en.html)



This chapter also states that “It is not easy to measure the acceptability of contraceptive methods to users, both potential and current (World Health Organization, 1997). Acceptability is determined by many factors, including inherent (and often unexplained) preferences regarding particular types of methods, the

perceived and actual risks and side effects, and the influence of other people and circumstances in a person's life, as well as how the methods are provided." This is certainly true and raises the question of what are the most appropriate ways of addressing acceptability in the process of developing new methods. This merits further social science research.

This chapter also briefly considers issues around service delivery and points out that there is a need for operational research and research on education and informational materials when introducing new methods of contraception into health systems. It endorses WHO/HRP's strategic approach to contraceptive introduction (World Health Organization, 2005). This certainly an area of research which needs to be promoted.

Unfortunately, this chapter then gets carried away with enthusiasm arising from other health benefits of the levonorgestrel-releasing IUD (see Box 2) and the potential of certain candidate microbicides also protecting against pregnancy. It states that "The development of drugs with two mechanisms and optimizing a single compound for both mechanisms is complex and time-consuming, so the task of developing products that have contraceptive and non-contraceptive effects will be challenging, both synthetically and clinically, but it is an achievable and worthy goal.....Strategies to combine a new contraceptive with some other agent that prevents a disease might be another more feasible approach to achieve the goal of dual activities in new contraceptive agents/devices." It is already difficult to purchase and deliver reproductive health drugs without going into extremely complex and expensive development work.

The research that is needed is in obtaining simple, affordable methods that are can be easily delivered through health delivery systems and other distribution channels. This is an issue that IPM is addressing through its country preparedness framework for microbicides (International Partnership for Microbicides, 2004). IPM is investigating all possible ways of making a microbicide accessible, including the possibility of using distribution channels outside the formal health delivery system should be explored in preparing for microbicide introduction. The specific channels that could be used will depend on the type of regulatory approval that has been granted. However, even for products registered as pharmaceuticals, agreement/approval could be sought for distribution outside the formal health delivery system. The types of distribution channels to be investigated include pharmacies, community-based distribution networks, social marketing, community groups, commercial outlets that sell personal hygiene and/or cosmetic products to women and other community gathering places for women, such as hair salons, markets, etc.

With regard to the development of new products, the three public sector agencies discussed in section 3.1, the Population Council, WHO/HRP, and CONRAD/CICCR are all agreed that one of the greatest needs in the reproductive health field is to prevent the spread of sexually-transmitted infections (STIs), including HIV. While a significant effort is being put into the development of vaccines against different strains of HIV, it is arguably more important to undertake research on microbicides and barrier methods, coupled with studies that address their use. Both the Population Council and CONRAD, as well as several other groups are involved in the development of microbicides (see section 3.3.1 and this will remain an area of intense research activity over coming years. Both CONRAD and FHI have been working on improved male and female barrier methods which can prevent the transmission of STIs as well as prevent pregnancy.

With contraception per se, many people and organizations like WHO/HRP and CONRAD, consider that male methods are a high priority. Hormonal methods using a

progestogen and an androgen are at a late stage of development. However, there are still problems of dosage and one of the critical needs is to develop an androgen that is several orders of magnitude more potent than testosterone and which would allow the development of a pill or injectable preparation that does not require the delivery of grams of steroid. In addition, there is a great need for additional safety studies on the continuous use of high doses of androgen; further studies on the behavioural aspects of high dose testosterone use; and attitudes and acceptance of women to men being the partner using a "spacing" method of contraception, particularly as a man would not get pregnant if he stopped taking or forgot his pill.

As stated in the IOM report, research is also required on methods that prevent maturation or capacitation of sperm, prevent fertilization or ensure that implantation of the fertilized egg does not occur. These are likely to be non-steroidal and as such represent the hope to get away from the side-effects experienced by many women on hormonal contraception, which are often the main reasons for discontinuation of the methods. WHO/HRP has undertaken a considerable amount of research in these approaches but no longer has funds to pursue new leads. CICCRR, has collaborated with WHO/HRP and has now developed a basic research programme together with the Ernst Schering Foundation and Schering AG (see section 3.1.3). The programme known as Application of Molecular Pharmacology for Post-Meiotic Activity has been funding research on novel epididymal and testicular targets and had recently funded projects on molecular mechanisms in the female.

In addition, there is a significant need to find easier to synthesize and more effective anti-progestogens than mifepristone for medical abortion. As discussed in section 6.2, perhaps these already exist in the vaults of certain major pharmaceutical companies.

I think that it is worth concluding this section with part of the statement generated at Forum 8 of the Global Forum for Health Research which was held in Mexico City, 16-20 November 2004

"Research is also needed on nutrition, pregnancy care and skilled care during and after delivery, to improve maternal and neonatal health and decrease maternal and neonatal mortality and morbidity; and to develop female controlled methods of protection, including microbicides and vaccines, for the prevention of HIV infection. Given the interrelationships between sexual and reproductive health and rights and the conditions that are addressed by the Millennium Development Goals (MDGs) will not be achieved without much greater attention to sexual and reproductive health, including research in the biomedical, health systems, and social sciences domains and the translation of that research into policies and programmes."

6. Reflections and conclusions

6.1 Achievements from publicly funded R&D

Section 3.1 discusses the availability and affordability of products, particularly in developing countries, emanating from R&D undertaken by publicly-funded agencies. We can see that there has been an impact from funding by the bilateral aid donors and philanthropic foundations of drug development programmes run by organizations such as the Population Council, WHO/HRP and CONRAD.

The successes have included development of two implantable contraceptive devices releasing levonorgestrel, a six-rod device, Norplant and a two-rod device, Jadelle; and two intrauterine devices (IUDs), the Cu-T 380A and the levonorgestrel-releasing IUD, Mirena by the Population Council; and the once-a-month injectable contraceptives, Cyclofem and Mesigyna, and levonorgestrel emergency contraception by WHO/HRP.

These programmes have also made a considerable contribution to the availability of products developed by others, WHO/HRP making a major impact through clinical and epidemiological studies on Depo-Provera, Norplant and the Cu-T 380A. WHO/HRP has also, along with the Population Council played a major role in the use of mifepristone for medical abortion. CONRAD and FHI (another USAID collaborating agency which also undertakes clinical trials) have played a significant role in making barrier methods available for the prevention of sexually-transmitted diseases and of pregnancy, such as the female condom; two intravaginal devices, Lea's Shield and FemCap; and new non-latex condoms for men.

CONRAD and the Population Council, and to a lesser extent WHO/HRP, are also involved in the development of microbicides. There are numerous candidate microbicide products at various stages of development. Most of the advanced products are being developed by small biopharmaceutical companies with public sector and some venture capital funding, as part of public-private partnerships.

There has been no attempt to analyse the funding that has gone into the public sector agencies to achieve these outcomes. All three R&D organizations have spent considerable sums in investigating potential new leads, many of which have not resulted in products. However this is no different from the process and funding of discovery programmes, preclinical and early clinical studies undertaken by the pharmaceutical industry that does not result in products. What is probably different is that the public sector has spent considerably less for the product gains in reproductive health than the private sector.

This is a subjective statement and it would be impossible to undertake a research study to prove it. It would be feasible to calculate the total funds expended by the major public sector agencies on all reproductive health product development they have undertaken in the past thirty years, which I propose should be done, but it would be impossible to obtain comparative data from industry, since few companies report their R&D expenditures by line item.

There are two clear conclusions:

- For contraceptives, funding from bilateral aid agencies or from philanthropic charities or foundations to the public sector R&D programmes has resulted in the development of some important products which have had the potential to expand choice to many people in the world. However, many people have not

had the benefit of affordable access to some of these products because of adequate protection of cost and availability as agreements have been developed with pharmaceutical companies for manufacture and distribution.

- The impact of clinical and epidemiological studies undertaken to investigate the safety and efficacy of products, by programmes such as WHO/HRP and FHI, is extremely high. Data from these studies have helped make products affordable in developing countries; allowed guidelines for optimal use to be developed; and informed both providers and users of the relative safety and use characteristics of these products.

6.2 What has happened in the private sector

Obviously, research and development in the private sector has been responsible for significant advances in both the fields of contraception and medical abortion. Without the pharmaceutical industry there would not be some 54% of the married women of reproductive age in the world using modern methods of contraception.

Although it is impossible to ascertain the level of funding that has been expended on R&D on new contraceptives in the pharmaceutical industry, it is obvious that, at least for the three of the “big four” pharmaceutical companies still conducting research, Organon, Ortho and Schering, it has been significant. However, this is likely to have been recouped more than adequately from sales of existing products, and especially of oral contraceptives, over the past few decades.

While, as discussed in section 3.2.1, oral contraceptives will remain the major pharmaceutical products for contraception in terms of sales and, as such, the most competitive market for the pharmaceutical industry. However, this market is changing dramatically with the growing influence and market penetration of generic manufacturers. While the major pharmaceutical players will continue to have significant, albeit reduced, revenue flows from oral contraceptives, it is making them return to their in-house R&D teams to develop, or to their licensing departments to find, technologies which will give them replacement, or preferably increased sources of revenue flows. It is therefore unlikely that the cost of R&D, which is always stated as an inhibiting factor in developing new entities, will prevent new R&D to be undertaken by the few remaining companies in this field. Moreover, costs have been mitigated for certain companies by licensing products from public sector R&D programmes.

In recent years, we have seen a vaginal ring, contraceptive patches, a levonorgestrel-releasing IUD and a new contraceptive implant become available in Europe and the USA. Unfortunately, these new products are unlikely to be available to the majority of people in the developing world and, even if they were, they are likely to be unaffordable, and this is despite several of these products having been developed with public funding.

I feel strongly that with products such as Schering’s levonorgestrel-releasing IUD and its two-rod contraceptive implant, the company has an ethical obligation to make it accessible to women in, or the public sectors of, developing countries at an affordable price. I mentioned that, in the case of the implant, Jadelle, Schering maybe reluctant because of a variety of factors such as Wyeth’s litigation experience, although this is hardly relevant outside the USA; or the extensive support required to ensure appropriate service delivery; or its corporate product and country priorities; or concerns of reimportation of product into its high-value countries. The latter is often raised as a reason for not having a cheaper price in selected countries, however, this can be overcome by adequate product differentiation.

One option is for the company to license the technology to a generic manufacturer with the specific purpose of serving developing countries. It would then be for that manufacturer to assess market segmentation which would allow it to make profits with the growing middle classes of the developing world while responding to government or international tenders to supply the public sector of the developing world (see section 6.4 below).

With regard to the inhibiting effect of law suits and product liability in the USA on the willingness of companies to undertake R&D on new products, there is strong evidence that this has very much diminished. It is worth reiterating Arkin's statements that "the Dalkon Shield affair remains the sole episode in which the American tort system gave an unambiguous verdict against a contraceptive product and its manufacturer. Subsequent experience with the Copper-7 IUD and recently with Norplant have given rise to decreased credibility of class action approaches to ill-defined symptoms and the causal effects on contraceptives; negligent design or manufacturer; or inadequate warning of documented side-effects". Certainly, liability insurance is still hard to obtain, as some of the microbicide developers are finding, but it need not be the excuse for not undertaking R&D it was previously said to be.

No major pharmaceutical companies are currently involved in the development of drugs for medical abortion and opposition from the pro-life movement is likely to keep them out of research on medical abortion. Schering did have a major R&D programme on anti-progestogens for many years. As such, the company is sitting on a treasure trove of potential competitors to mifepristone, several of which are well characterized and tested. It would be a significant gesture for the company to donate these products and related intellectual property to a public sector agency such as WHO/HRP, or a new public-private partnership, with all the provisos needed to protect them from possible liability so that one could be developed to serve the needs of women in developing countries.

Schering is not the only company to be sitting on a treasure trove of screened products. While this has immediate applicability as in the case referred to above, it would be important to develop a mechanism to identify and classify compounds that have already been developed by industry either as part of a discontinued drug development programme or as part of drug development in other therapeutic areas, but where they may have another potential disease or other health application. Some companies appear willing to allow access to these moieties as public goods so that they could be made available to other groups for further development.

But it has not only been the big pharmaceutical companies that have influenced the availability of reproductive health products. In the discussions in sections 3.2.1 and 3.2.2, we have seen examples of the opposite impact of small single product companies. Finishing Enterprises have been the champion of widespread and affordable access to the Cu-T 380A IUD. On the other hand, Exelgyn has been a significant constraint to access to mifepristone, the company appears to have had extremely conservative objectives but high financial expectations. Finishing Enterprises supported transfer of technology to what are now competitors to promote access for women in developing countries. While accepting that there is a quite different political environment around a drug like mifepristone, it is a pity that no company or public agency outside China or India did not take up the challenge of developing a generic product prior to mifepristone coming off patent. However, times are changing and I anticipate that the stranglehold on this product will soon be broken.

To conclude this section, I will stick with my previous observations:

- oral contraceptives will remain the major products from the pharmaceutical industry for contraception and, as such, the most competitive market for pharmaceutical companies; and
- there is little or no incentive for western pharmaceutical companies to compete for the \$0.75 per capita of women of reproductive age that is available in “difficult” developing world markets, when the accessible developed world is spending a whopping \$42.20 per capita and a total amount that is 53.6 times greater.

And add that:

- where companies have benefited from products having been developed with public funding, mechanisms should be instituted to ensure that this is reflected in availability and affordability in developing countries; and
- access should be given to public sector programmes, or a new public-private partnership, to compounds which could have significant benefits in developing countries.

6.3 The role of developing countries in the development of new drugs for reproductive health

Except for Brazil, China and India, there has been little R&D of products for reproductive health in developing countries, other than participation in international, multi-centre clinical trials. Both India and China have major national (and China, regional) research institutes, involved in the R&D of new products, as well as in multicentred clinical trials.

Recently, China developed mifepristone (10mg) for use as an emergency contraceptive but in the past it has produced generic copies of existing methods as well as several inadequately tested products. However, both the objectives and standards of R&D are changing because of the input of the State Family Planning Commission. This change in approach over recent years, coupled with the government’s desire to improve the quality of its pharmaceutical industry, makes China a potential major resource in the R&D of products for reproductive health, not just in contraception but in vaccines against HIV and in the field of medical abortion.

India has had a significant R&D programme, spearheaded by the Indian Council of Medical Research, however, this has not resulted in any breakthrough in product development. The Central Drug Research Institute developed a low efficacy once-a-week pill which has been marketed since 1991. However, as yet, little has come out of the public sector research. India is beginning to become involved in research on microbicides and the agreement between ICMR and CONRAD may well promote R&D in this area.

Indian industry has arguably some of the premier pharmaceutical manufacturers in the world. While they have built the capacity to challenge western companies on their home ground through the manufacture of high class generic products, it is only in recent years and partly as a response to TRIPS that several companies are building a strong R&D capability, although there appears to be little interest in drugs for reproductive health.

In summary:

- India and China both have the public sector R&D capacity to play a significant role in R&D of products for reproductive health. Both countries need to harness the potential of its pharmaceutical industry to complement this competence, China having more companies working in this area and India having some higher quality companies that should be involved.

6.4 The role of developing countries in the manufacture of low cost reproductive health drugs

Hormonal contraceptives require special production facilities and significant health and safety precautions. As such there are relatively few, probably fewer than a hundred, companies in the developing world with the capacity to manufacture them and of those there are not many that can meet and maintain international GMP standards. Except for China, all of these companies are manufacturing generic products. As described in section 4, there is tremendous change ongoing in India and China, and to a lesser extent in Brazil, Mexico and South Africa, both in improving drug production as well as broadening choice.

Manufacturers in the developing world are found in: Africa, two companies in South Africa; Middle East, Iran, Israel and recently Oman; South Asia, India and Pakistan; East and South East Asia, China, Indonesia, Taiwan and Thailand; Latin America, Brazil, Chile and Mexico. Only China and India are producing mifepristone although several are making generic misoprostol. These 13 countries are really the only ones that can be considered when addressing the role of developing countries in the manufacture of low cost reproductive health drugs and transfer of technology.

Since the issue of ensuring the continuing supply of reproductive health commodities has become a major crisis in the light of changing donor priorities (see section 2), a well qualified network of manufacturers in the developing world could be the best safeguard the international community has to achieve this. There are those that argue that adequate capacity exists in the world for production of contraceptives and other reproductive health commodities. While I would agree that there is little need to establish new companies, there is a need to have companies and facilities that can supply people in the developing world with products that are affordable and accessible.

Certainly the World Bank, UNIDO, certain bilateral donors and other organizations have been active in the area of so-called "local" production of pharmaceuticals and there are very mixed views of the feasibility and benefits in establishing of pharmaceutical production in developing countries. In a recent paper prepared for a World Bank meeting entitled "Is local production of pharmaceuticals a way to improve pharmaceutical access in developing and transitional countries? Setting a research agenda", Kaplan et al. (2003) put forward several cogent arguments why access may not be improved through "local" production. Some of these are:

- In many parts of the world, there is no reason to produce medicines domestically since it makes little economic sense.
- In the local pharmaceutical manufacturing sector, local production is often not reliable and, even if reliable, it does not necessarily mean that medicine prices are reduced for the end user.

- If local production is adopted by many countries, it may lead to less access to medicines, since there are no economies of scale in having a production facility in each country.
- It may be possible for small country markets to be coordinated or otherwise joined together to create economies of scale.
- For many countries, technical expertise, raw materials, quality standards, and production and laboratory equipment need to be imported so that foreign exchange savings may be small or non-existent.
- A research agenda should be created that is specifically designed to test assumptions about local production of pharmaceuticals. This agenda must be based on evidence and not just on post-hoc case studies.”

These points are certainly relevant, but I am not talking about trying to build capacity in all countries, rather harnessing the potential of a relatively small group of companies that have pre-existing manufacturing capability to ensure that the necessary capacities are available to meet the need for reproductive health commodities at an affordable cost. It would also allow “big pharma” access to qualified companies to which they could transfer technologies for use in developing countries (see section 6.2).

It must be appreciated that when trying to ensure increased availability of quality product at the lowest prices, competition in low-profit markets may not initially achieve this. Companies’ earnings potential in unit costs will initially decrease for those that will incur the increased manufacturing costs required to conform to international regulations. This could be averted in part with financial input from loans or grants and is a the way by which a secure network of approved suppliers could be developed. In addition, a developing country manufacturer cannot afford to participate in all markets at any cost if their earnings potential is not commercially interesting, moreover, competitive mechanisms do not always work in certain developing markets as seen in other product areas.

It is necessary to address the issues raised by Kaplan et al. However, there has been no systematic study undertaken to address the capability and capacity of most of the developing country companies and how they could be used to provide quality, affordable products for reproductive health that would meet local and regional demand. I would argue that this is necessary and should be undertaken.

As discussed in section 4, achieving and maintaining quality remains a major problem for many developing country manufacturers. Experience has shown that many require continuous quality surveillance, not just an initial prequalification visit, to ensure that product quality can be maintained to meet original specifications. While this is likely to change for those manufacturers which intend to compete in Europe and the USA and have to meet EMA or USFDA requirements, it remains a daunting task when working with many others.

There are three major issues that need to be addressed when considering the potential of developing country companies to become part of a network of qualified manufacturers of reproductive health commodities. These include:

- the extent to which their production facilities meet modern standards of GMP and the willingness of the company to achieve them;
- their ability to access or produce the active pharmaceutical ingredients (APIs) manufactured to accepted standards of GMP with fully documented drug master files;

- where necessary, their willingness and ability to take up new technology

The capacity exists to make many drug types, although surprisingly this is extremely limited for aqueous microcrystalline suspensions such as the injectable contraceptives, Depo-Provera and Cyclofem and for drug delivery systems, such as implants and the levonorgestrel-releasing IUD. Hence, there is a critical need to ensure that there is provision for the transfer of technology for manufacture in certain countries. This will eventually be the only way of ensuring widespread availability of many of the products that are available in western countries and which could provide substantial health benefits to people in the developing world.

In the past it was a requirement for registration of a product by the governments of India and Indonesia. However, the experience of WHO/HRP, when negotiating agreements with pharmaceutical companies, has been that it is often harder to reach agreement on the transfer of technology than on a cost+ price for the public sector. Companies express concerns about loss of control of IP, maintenance of quality of product and of liability. There is significant experience of technology transfer in the pharmaceutical industry, however, there is little on the transfer of products for which development has been supported through public or philanthropic funds, other than the not-for-profit Concept Foundation in Bangkok (see Box 3).

A recent development with vaccines has been the use of an International Financing Facility to ensure that countries can ensure access to key vaccines. In order to address the contraceptive and other reproductive health commodity needs of developing countries, and ensure access to products of appropriate quality as well as affordability, I would propose the development of a Global RH Commodity Access Facility (GRHCAF). The GRHCAF could fulfill the roles of an International Financing Facility for reproductive health commodities and develop, maintain and survey a network of qualified manufacturers able to meet developing country and international donor needs. Its specific objectives would be to:

- Work with the international donor community to establish and implement an International Financing Facility for reproductive health commodities.
- Qualify hormonal contraceptive manufacturers in developing countries and establish a network of producers.
- Assist, where necessary, the transfer of technology from the major pharmaceutical companies for specific supply to the developing world
- Establish agreements which include preferential pricing for the public sector; and clear milestones for market access and quality manufacturing.
- Finance, through grants and loans, the upgrading of facilities to meet EMA or USFDA GMP requirements.
- Establish a system of annual quality audits and an independent quality assurance programme.
- Provide assistance on regulatory issues and the introduction of the product in developing countries.

The GRHCAF could also address the other reproductive health drugs discussed in this paper, such as mifepristone and misoprostol and other drugs identified as essential for reproductive health. It could work with IPM and other microbicide development groups in identifying and supporting the development of manufacturing sites for microbicides in certain countries, as they become available and more widely used.

6.5 The potential of funding public sector R&D groups

While funding, whether it be through bilateral aid agencies or from philanthropic charities or foundations, should be maintained to the public sector R&D groups to allow the development of new methods of contraception and, in particular, barrier and other methods to prevent infection from sexually-transmitted diseases, we must capitalize on the expertise that these groups have developed to conduct clinical trials and on the existence of clinical trial networks they have created.

Since ownership of intellectual property relating to a new product would normally reside with its original developer, if a product is developed by a public sector R&D programme, ownership of that intellectual property would allow that programme to include safeguards in any subsequent license with a manufacturer that would protect availability and cost to the public sector of developing countries.

In the case where a small biotechnology company owns the intellectual property on a new product and is participating in a public-private development partnership, it is the funders that have the opportunity to ensure availability and protection of the lowest possible price for the product for distribution through the public sector in developing countries by including. Money can trump intellectual property in the development of a public good!

As an example, DfID is funding microbicide development groups using the UK Medical Research Council (MRC) as its executing agency. The MRC concluded an agreement on public sector price with the two companies which had developed products for testing should a marketable product emerge from the clinical trials. However, it should be noted that research groups and other organizations receiving US government funding cannot protect IP to leverage public sector benefits from commercial companies. This is something that WHO/HRP ran into when funding contraceptive development jointly with NICHD.

Even when there has been, or is a pharmaceutical company involved in the development of a product, if one of the public sector R&D organizations is responsible for clinical trials, it can develop agreements to ensure protection of the cost of the product to the public sector of developing countries (Oehler, 2004). This has been the approach taken by WHO/HRP and which has resulted in affordable prices for once-a-month injectables, emergency contraception and hopefully, medical abortion. Unfortunately, this has not been the route taken by the Population Council, which has made agreements with pharmaceutical companies which, as discussed in section 3.1.1, have not adequately protected the public sector price. This has left issues of cost and availability to be addressed by the public funded procurement agencies such as USAID and UNFPA.

It has been argued by some that the mechanism used by WHO/HRP to control public sector pricing described under section 3.1.2 is difficult to impose since it may be difficult to calculate manufacturing cost and/or these costs may not be stable. However, WHO believes, through examples, such as the Concept Foundation (see Box 3), that it is possible to audit costs at agreed intervals and that this has proven to be a viable approach.

Obviously, access to, and building the capacity of, competent clinical trial sites capable of undertaking trials to modern standards of Good Clinical Practice (GCP) is a critical step in product development. It is critical both in ensuring that products are tested in a timely and appropriate manner and, in the case of vaccines against HIV infection and other infectious diseases, in high-prevalence environments.

The pharmaceutical industry and others (see section 3.3.1) claim that a Phase III clinical trial costs between US\$75 million and \$100 million, meaning that it will be necessary to raise billions of dollars to fund the efficacy trials of microbicides and vaccines against HIV, let alone the drugs and vaccines against the many tropical diseases that industry is not interested in pursuing. Experience has shown that that clinical trial networks developed by the public sector R&D organizations in countries throughout the world, have the ability to undertake Phase III clinical trials at 5-15% of the costs claimed above. It is therefore essential that these networks are accessed and/or developed further in order to reduce the problems that will be faced in the future of raising sufficient funds.

The publicly funded R&D agencies, like WHO/HRP, the Population Council, CONRAD and FHI are groups with access to clinical trial sites throughout the world. For vaccines against HIV, there are, among others, the European Developing Countries Clinical Trials Platform, which is addressing trial capacity in sub-Saharan Africa; and the Gates Foundation's Global HIV Vaccine Enterprise, which has identified four areas of focus – scientific and human resources; clinical trial infrastructure; trial subjects; and policy maker/opinion leader support for clinical research. IPPPH organized a meeting on "Clinical trial capacity in low and middle income countries" which discussed all aspects of the conduct and organization of clinical trials and country capability needs (IPPPH, 2004).

The funding of public sector R&D programmes to undertake clinical trials, provides a potent mechanism for ensuring availability and affordability of any new drug or vaccine, not only products for reproductive health. They can do this in two ways:

- by reducing the overall costs of Phase III clinical trials; and
- by the generation of clinical trial data as a critical component of the intellectual property relating to a product.

I do not believe that to date this has been exploited to the extent it could or should be.

6.6 What R&D is needed to obtain necessary products for reproductive health?

There remains a significant need for basic research, product R&D, and operational and health systems research in the field of reproductive health. Unfortunately, with regard to the major bilateral or philanthropic donors, since the late 1990s, and despite the pledges made at the International Conference on Population and Development held in Cairo in 1994, there has been decreasing funding coming into this field, other than for the prevention of HIV infection. As such programmes like WHO/HRP have little money available for funding product R&D. So the caveat to the R&D needs discussed below, is that although there has been some resurgence of interest by the couple of R&D based companies remaining in the field, the overall funding for R&D in reproductive health looks bleak.

Some of the basic research mentioned in the IOM report is potentially important (Institute of Medicine, 2004). While the reproductive physiology is understood, as yet there are no new entities which could affect sperm maturation or capacitation, sperm-egg interactions prevent fertilization or ensure that implantation of the fertilized egg does not occur. This is important research, some of which has been going on for some years but, as yet, there are no compounds that have reached initial clinical trial. Such entities are likely to be non-steroidal and, if they had a high efficacy in preventing pregnancy, they would represent the hope to get away from the side-

effects experienced by many women on hormonal contraception, which are often the main reasons for discontinuation of current methods.

One of the greatest needs in reproductive health is to prevent the spread of sexually-transmitted infections, including HIV. While a significant effort is being put into the development of vaccines against different strains of HIV, it is arguably more important to undertake research on microbicides and barrier methods, coupled with studies that address their use. There has been significant investment in the development of microbicides and it is anticipated that, whatever the outcomes of ongoing Phase III clinical trials (see section 3.3.1), this will be an ongoing area of R&D for some years to come. The major donor has been the Gates Foundation and several bilateral donors have now made this a priority area.

With regard to contraception per se, many people and organizations like WHO/HRP and CONRAD, consider that male methods are a high priority. Hormonal methods using a progestogen and an androgen are at a late stage of development. However, there are still problems of dosage and one of the critical needs is to develop an androgen that is several orders of magnitude more potent than testosterone and which would allow the development of a pill or injectable preparation that does not require the delivery of grams of steroid. In addition, there is a great need for additional safety studies on the continuous use of high doses of androgen; further studies on the behavioural aspects of high dose testosterone use; and attitudes and acceptance of women to men being the partner using a “spacing” method of contraception. Although both Schering and Organon are now interested in developing a male contraceptive, I believe that these issues raised above will provide significant constraints to the final development of a hormonal product.

In addition, there is a significant need to find easier to synthesize and more effective anti-progestogens than mifepristone for medical abortion. As discussed in section 6.2, perhaps these already exist in the vaults of certain major pharmaceutical companies.

There is a real need to transfer the technology certain developing countries to manufacture some, but not all of the recent available products. For example the new implants and the levonorgestrel-releasing IUD, could play an important role in many countries, on the other hand the currently available patches and vaginal rings are expensive and would not serve poorer people in these countries but remain middle-class products. The research that is needed is how to obtain new and existing methods cheaply and deliver them easily through weak health delivery systems and other distribution channels.

There are still important questions to be answered around the acceptability of contraceptive methods. Although acceptability studies have been undertaken for years, the question remains as to what are the most appropriate ways of addressing acceptability in the process of developing new methods.

Finally, there is a need for operational research and research on education and informational materials when introducing new products into health systems. Ensuring that technologies meet peoples needs and can be delivered through service delivery systems, as well as being affordable, is paramount in any quest for new contraceptives, or other products for reproductive health, or indeed any drug for any purpose. WHO/HRP’s strategic approach to improving the quality of reproductive health service (World Health Organization, 2005) takes a systems based approach to ensuring that technologies meet with user’s needs and service delivery capability. This is where we need additional research funding.

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