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IMPROVING HORMONAL CONTRACEPTIVE SUPPLY

THE POTENTIAL CONTRIBUTION OF MANUFACTURERS OF GENERIC AND BIOSIMILAR DRUGS

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ABSTRACT

Research and development (R&D) companies dominate both the public- and private-sector markets in developing countries, despite the growing number of manufacturers able to produce low-cost generic and biosimilar products around the world. This paper describes the different types of hormonal-contraceptive manufacturers and opportunities for increased competition from generic and biosimilar suppliers in the procurement field, as well as the commercial sector. Barriers addressed in the paper include the difficulty of monitoring product quality and safety in developing countries, the limited sales and marketing capability of local manufacturers, unfavorable procurement policies, and market distortions caused by well-meaning donor-funded programs.

ACRONYMS

ARV	Antiretroviral
CBO	Congressional Budget Office
DMPA	Depot Medroxyprogesterone Acetate
EC	Emergency contraception
ECP	Emergency contraception pills
EGMA	European Generic Medicines Association
FDA	Federal Drug Administration
FHI	Family Health International
GMP	Good Manufacturing Practices
IC	Injectable contraceptive
IPPF	International Planned Parenthood Federation
ISO	International Organization for Standardization
JSI	John Snow Inc.
KfW	Kreditanstaldt für Wiederaufbau
MCG	Microgram
MG	Milligram
NRDA	National drug regulatory authority
OC	Oral contraceptive
PATH	Program for Appropriate Technology in Health
PSI	Population Services International
PSP-*One*	Private Sector Partnerships-*One* Project (USAID-funded, 2005-2009)
R&D	Research and development
SDO	Service delivery outlets
SMO	Social-marketing organization
UN	United Nations
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
WHO	World Health Organization

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GLOSSARY

Bioequivalent medicines

Two medicines are bioequivalent when they contain the same amount of an identical active substance and when their bioavailability (the rate and extent at which the body absorbs the active ingredients) is the same when administered in equal doses in equal conditions (EGA 2005).

Biosimilar/biogeneric product

An off-patent biological medicinal product produced by manufacturers other than the originator product and that is similar to the originator product. Biogenerics are sometimes also called biosimilar products (EGA 2005). Biosimilar/biogeneric products are not necessarily significantly different from the originator product in terms of quality, safety, and efficacy, but this has not been proven by clinical tests.

Contract manufacturing

Contract manufacturers focus on the production side of contraceptive supply. They manufacture products on a contract basis, while another entity does the marketing and distribution. Contract manufacturers are common in countries with large government-funded procurement programs that tend to favor local manufacturing over imports, such as India, and China.

Copy product

In the pharmaceutical industry, a copy product is a good that was developed while the innovator product was still protected by patents. Copy products are typically developed by illegally obtaining scientific dossiers from research and development (R&D) companies or through reverse engineering. Copy products are common in countries that have not adopted or do not enforce patent-protection laws. Biosimilar copies of off-patent products that have not undergone bioequivalence testing are sometimes also called copy products.

EU marketing authorization

A pharmaceutical product may only be sold in the European Union when a marketing authorization has been issued. Applications are submitted to the European Agency for the Evaluation of Medicinal Products and assessed by the Committee for Proprietary Medicinal Products.

FDA approval

Responsibility for drug regulation in the United States lies with the Food & Drug Administration (FDA). This agency has a mandate to ensure that drugs that reach the public in the United States are safe and effective. For a new drug the approval process involves filing an Investigational New Drug Application, which needs to be accepted before the drug can enter clinical trials. When clinical trials are successfully completed, the company submits its results as a New Drug Application to seek approval for marketing.

Generic medicine

Generic medicines are equivalent medicines demonstrating the same quality, safety, and therapeutic efficacy as the originator product. They contain the same active substance in the same pharmaceutical form as the originator and are marketed after patent expiry. A generic medicine is produced and marketed in compliance with international patent law. It is identified either by its scientific international nonproprietary name or, less frequently, by its own

brand name. In most countries with generic laws in place, these products must be bioequivalent to the originator product (EGMA 2005).

Good Manufacturing Practices (GMP)

GMP, also referred to as Current Good Manufacturing Practices (CGMP) ensure that pharmaceutical products are manufactured consistently and adhere to recommended practices established by governments or international regulatory institutions, such as World Health Organization (WHO). To be GMP certified, a company must show that its facilities and equipment are appropriate, its staff has the required training, it manufactures according to approved procedures, it maintains detailed manufacturing records, and it follows specific norms on storage and transport.

International Organization for Standardization (ISO)

ISO is a global network that identifies international technical standards in partnership with governments and the business industry, and technology sectors. Although ISO standards are voluntary, some countries adopt them as part of their regulatory framework and the standards have become a common requirement in international transactions. The most-common family of ISO standards is the ISO 9000, which focuses on quality management, expressed in customer expectations and regulatory requirements.

Originator product

The first version of a medicinal product, developed and patented by an originator pharmaceutical company, which receives exclusive rights to marketing the product in a particular market.

Patent

A document granting an inventor exclusive rights to exploit a creation for a period of time (typically twenty years for pharmaceuticals) in return for submitting to public access the information necessary to repeat the invention. The patent prohibits others from making, using, or selling the invention without the permission of the inventor in the territory where the patent was issued (EGMA 2005).

EXECUTIVE SUMMARY

Demand for hormonal contraceptives has been increasing consistently in developing countries. In the absence of affordable commercial products, commodity supply in those countries is often donor or government-supported. This paper explores the factors that affect the availability, affordability and/or sustainability of hormonal contraceptive supply, and suggests strategies to increase the participation of Southern-based manufacturers in international procurement programs as well as commercial markets.

WORLDWIDE AVAILABILITY OF HORMONAL CONTRACEPTIVES

Large multinational pharmaceutical manufacturers, commonly referred to as research and development (R&D) companies, are responsible for most new hormonal-contraceptive formulations, also known as innovator brands. As patents expire, other manufacturers around the world have the opportunity to develop and sell the same formulation as their own brand.

The most popular combined oral-contraceptive formulations are now off-patent and manufactured locally in several middle-income countries, as well as a few developing ones. The most widely available formulation is levonorgestrel 0.15 milligram/ethinyl estradiol 30 microgram, which is produced and marketed worldwide with more than 40 brand names, as well as in a generic form. Dedicated emergency-contraceptive brands also have become widely available in many countries, though mostly through the commercial sector. The most-commonly used injectable contraceptive formulation is Depot Medroxyprogesterone Acetate, known as *Depo-Provera*, which is manufactured by Pfizer, as well as a number of manufacturers in Thailand, Indonesia, and South Africa. Monthly injectables are increasingly popular in Latin America where several locally-produced formulations are sold commercially.

MANUFACTURERS OF BRANDED CONTRACEPTIVES

R&D companies (such as Schering, Wyeth, Organon, and Pfizer) have established a considerable worldwide presence and tend to dominate both the commercial and public sectors in developing countries. R&D brands sold commercially carry high margins to finance marketing activities and the development of new formulations. Selling products through donor or government channels is also an important strategic area for these companies because it allows for substantial economies of scale. Although R&D manufacturers share many characteristics, they often have different corporate strategies, particularly when it comes to investing in the development of new contraceptive products.

Manufacturers of generic contraceptive products developed from off-patent formulations have made considerable inroads in the North American and European markets. Because of the large investment required for bioequivalence testing, generic manufacturers tend to be based in developed countries. Generic manufacturers in India, China, and South Africa, however, also are competing increasingly in these markets. So-called biosimilar products, which are not bioequivalent but based on the same formulation as existing R&D brands, primarily are found in middle-income and developing countries.

DISTRIBUTION AND MARKETING

Contraceptive manufacturers tend to respond to business opportunities within the channels they have chosen to sell their products. R&D manufacturers that can invest in costly marketing activities, such as provider detailing, public relations, and continuing education, tend to dominate commercial channels. Both R&D companies and manufacturers of generic and biosimilar products can compete for government tenders in developing countries,

but development and donor organizations generally favor Western-based companies that can satisfy stringent prequalification requirements. Contract manufacturers that sell exclusively to government or social-marketing programs compete on the basis of price and usually have limited distribution and marketing capability.

Social-marketing organizations marketing their own brands use the same supply mechanisms as governments and donors (usually a competitive bidding process) or receive donated commodities. Prompted by dwindling commodities donations or changing donor policies, these organizations increasingly are purchasing products from Southern-based manufacturers. Social-marketing programs based on public/private partnerships use commercially available brands, but have traditionally involved R&D manufacturers with a history of supplying donor-funded programs.

EXPANDING THE SUPPLY POOL

Key Challenges

The most-significant barrier to expanding the pool of suppliers to the developing world appears to be the extent to which their products meet international quality standards. Although some countries have achieved acceptable levels of production quality, others have been found to lack adequate regulatory and manufacturing control. Assessing the quality and safety of products made in countries with less-than-stringent regulatory environments is a challenge for procurement and donor organizations. Despite established manufacturing standards, there is no centralized, uniform system to assess and monitor manufacturing facilities. Prequalification programs, such as those the World Health Organization developed for condoms and antiretroviral drugs, are still years away. As a result, international procurement tenders tend to favor companies that have obtained FDA approval or undergone an equally stringent certification process.

In the commercial sector, the presence of domestic contraceptive brands is subject to market potential and business strategies by local entrepreneurs. Manufacturers in Thailand, Brazil, and Chile market contraceptives commercially because there is high demand for affordable products and no large-scale subsidized program in those countries. Indian manufacturers on the other hand see limited opportunities on their market, which is dominated by R&D and subsidized brands. Exporting branded products is also difficult for small contract manufacturers, because of high registration costs and the lack of local representation. An increasing number of Indian suppliers, however, are developing the capacity to market products commercially both in and outside India.

Access to Procurement Programs

Contract manufacturers of off-patent hormonal-contraceptive products can compete in the international procurement business, provided they adopt quality-assurance systems that meet international standards. The fragility of the local regulatory environment in developing countries does not necessarily imply that products manufactured in those countries are unable to meet international quality standards. Procurement and quality-assurance experts report that reliable manufacturers can be found in India, Indonesia, Thailand, and South Africa. Increasing their participation in large procurement programs requires relaxing current prequalification requirements while developing cost-effective quality-assessment and monitoring systems. Recent collaboration between procurement organizations is expected to help promote information and cost sharing, as well as open up competition from new low-cost manufacturers.

Commercial Markets

R&D firms tend to see developing markets as divided between commercially sold private brands, targeting high and upper-middle income customers, and public-sector or social-marketing brands, targeting lower-income users. Multinational companies benefit from this type of segmentation because institutional contracts help develop economies of scale and maintain brand loyalty, while private markets contribute to profits.

A middle-market approach, consisting of affordable commercial brands targeted at average users in low-income countries potentially can increase the sustainability of the product supply, but its viability in highly subsidized markets remains to be tested. Attracting new commercial suppliers willing to market lower-priced products requires freeing up a market segment that is occupied by free and subsidized contraceptive brands. Planned phase-outs of donated commodities in some countries may provide an opening for these suppliers.

Manufacturers of generic and biosimilar products are promising partners for interventions designed to increase the sustainability of product supply because they are able to generate profits while targeting low and middle income consumers. Thus, public/private partnerships may involve these suppliers, as long as they are willing to develop and support their own brands. Contract manufacturers that only supply government programs, however, are least likely to enter commercial markets and most likely to pursue new opportunities in the tender business. A few appear to be receptive to other approaches, but may need to partner with organizations with strong marketing capacity. Their capacity and willingness to support extensive marketing and demand-creation activities, however, are unlikely to match those of R&D companies.

Bioequivalence-testing programs, which can improve the affordability and safety of the drug supply in developing countries, remain too costly and politically sensitive. As a result, R&D companies, suppliers of untested biosimilar brands, and contract manufacturers serving the public sector will continue to dominate emerging pharmaceutical markets. A growing number of entrepreneurs, however, understand that bioequivalence testing is the cost of doing business in an increasingly regulated pharmaceutical environment. The combination of generic substitution programs, market-building policies, and competitive forces can ultimately bring users in the developing world a choice of sustainable, high-quality products at prices they can afford.

1. INTRODUCTION

Worldwide contraceptive use has been increasing consistently in the past few decades. By 2015 the developing world alone may have 217 million more contraceptive users than in 2000 (UN 2002). Much of the demand for contraceptive supplies will involve hormonal methods. Oral contraceptives (OC) are already the most-popular modern method in Middle and Western Africa, whereas injectable contraceptives (IC) are used widely in Eastern and Southern Africa, as well as in Southeast Asia (UN 2003). While a wide range of commercial products is available in developed and middle-income markets, commodity supply in developing countries is often donor or government-supported. The following examples illustrate this disparity:

- In the United States a woman whose doctor prescribes *Mircette*, a combined OC marketed by the pharmaceutical company Organon at an average retail price of $40 per cycle (one month's supply), will find that a generic brand (*Kariva*) with the same formulation is available at her pharmacy for about $26. If the customer carries insurance, she may see a 50 percent difference in her co-payment between the two brands.

- In Brazil, where *Mircette* is not available, the same woman may use instead another Organon brand, *Mercilon,* which sells for the equivalent of $10 per cycle, or a copy of it (*Minian)* made by Libbs Farmaceutica, a local Brazilian manufacturer, for about $6.50.

- In India, this woman may not be able to afford commercial brands (which start at about $1.25). She is likely instead to buy one of fourteen socially marketed brands for less than $0.10 per cycle.

- In Nigeria, this woman may be able to obtain free OCs at a public sector clinic, or may purchase a social-marketing brand for $0.30 at a neighborhood pharmacy. If she finds any commercial brand of OC, it is likely to cost her more than $3.80.

Contraceptive users in developed countries have the widest range of hormonal products at their disposal. In Western Europe, Canada, or the United States, women can choose from multiple brand names or purchase bioequivalent generic copies of off-patent brands at reduced prices. Users in middle-income countries, such as Colombia and Thailand, also have access to a wide range of contraceptives made in the United States or Europe or produced in their region. The further down one goes on the development scale, the scarcer contraceptive options become. In some sub-Saharan African countries, only one brand of OC or IC may be available and a person may have to travel far to find it.

Experience in developed markets has shown that increasing the number of manufacturers of a drug, particularly if generic manufacturers are included, can lead to more affordable drug options for consumers. For example, the U.S. Congressional Budget Office (CBO) estimated that substituting generic prescription drugs for brand-name ones saved purchasers at retail pharmacies $8 to $10 billion in 1994. Although the introduction of generic options in the United States does not always influence the price of brand-name products (CBO 1998), it has resulted in greater product choice and a wider range of consumer prices.

In many middle-income countries, such as Argentina, Mexico, and Thailand, bioequivalent generic contraceptives are still uncommon, but local manufacturers often market lower-priced versions of U.S. or European name brands, commonly referred to as *biosimilar products*. In most low-income developing countries, however, generic and biosimilar products are not commonly available. This paper explores opportunities for improving the contraceptive supply in developing countries by increasing the number of low-cost suppliers to these countries, using both public and private distribution channels.

2. WORLDWIDE AVAILABILITY OF CONTRACEPTIVE BRANDS

Large multinational pharmaceutical companies are responsible for most new hormonal contraceptive formulations, commonly known as *originator* or *innovator* brands. Patent legislation gives an inventor the exclusive right to market such brands for a number of years (typically twenty). As patents expire, manufacturers around the world have the opportunity to develop and sell the same formulation under their own brand. This section provides an overview of the worldwide availability of common formulations of OC and ICs.

2.1 ORAL CONTRACEPTIVES

First introduced in the 1960s, OCs have evolved through different dosages and combinations of active pharmaceutical ingredients, which are tiny amounts of male and female hormones, mainly progesterone and estrogen. Three major types of OCs can be found around the world:

- *Combined pills* provide progestin and estrogen in a fixed dosage (except for the seven placebo pills). There are forty-eight different formulations of combined OCs marketed worldwide with more than 300 brand names.

- *Phasic pills* have a combination of estrogen and progestin that varies throughout the cycle. There are twenty-four formulations of phasic pills sold worldwide with nearly one hundred brand names.

- *Progestin-only pills* contain a low, uninterrupted daily dose of a progestin and no estrogen. The latter generally are recommended for women who are breastfeeding or who cannot take combined pills. Eleven formulations of progestin-only pills are sold worldwide with thirty-five brand names.

According to industry experts, monophasic combined OC formulations—and mostly those containing less than 50 micrograms (mcg) of ethinyl estradiol—account for nearly 90 percent of the global market in units sold (Pritchard 2005). The most-common OC formulation worldwide is levonorgestrel 0.15 milligram (mg)/ethinyl estradiol 30 mcg, which is marketed under more than 40 brand names (see table 1). It is also the formulation of *Microgynon*[1] and *Lo-Femenal*,[2] the brands commonly purchased by donors and governments, and distributed through public clinics in many developing countries.

A slightly different formulation (norgestrel 0.30 mg/ethinyl estradiol 30mcg) is available as *Duofem*, a product created by Wyeth for social-marketing programs that is widely marketed under various local brands. Products based on this formulation also are manufactured in India and Thailand.

Biphasic, triphasic, and progestin-only formulations have a smaller market share. The most-recent OC formulations using new progestins and lower doses of estrogens are popular in developed markets, but rarely are produced in generic form outside the United States, Western Europe, and Latin America. At least two Indian manufacturers, however, claim to have developed these formulations and secured the necessary license to produce them, possibly in anticipation of entering developed markets.

[1] Manufactured by Schering AG (Germany).
[2] Manufactured by Wyeth (United States).

TABLE 1. BRANDS AND MANUFACTURERS OF LEVONORGESTREL 0.15 MG/ ETHINYL ESTRADIOL 30 MCG OC[3]

Brands	Manufacturer	Country	Availability
Nordet, Nordette, Stediril, Follimin, Gynatrol, Lo-Femenal, Lo-Gentrol, Lo-Ovral, Monofeme, Neomonovar, Norvetal, Ovoplex 3, Ovranet, Ovranette	Wyeth	United States	Worldwide
Microfemin Cd, Microgest, Microgyn, Microgynon, Microvlar, Minigynon, Minivlar, Levlen, Neovletta	Schering	Germany	Worldwide
Ciclo 21	União Quimica	Brazil	Brazil
Gestrelan	Biolab Sanus	Brazil	Brazil
Nociclin	EMS Sigma Pharma	Brazil	Brazil
Norvetal	Gynopharm (Recalcine)	Chile	South America
Anovulatorios Microdosis, Innova CD	Laboratorios Chile	Chile	Chile
Anulette	Laboratorios Silesia	Chile	Chile, Paraguay
Microfemin CD	Grunenthal GmbH	Chile	Colombia, Chile
Norgylen	Laboratorio Gutis	Costa Rica	Costa Rica
Duo Ri Na	Zizhu Pharmaceuticals	China	N/A
Ludeal G	Laboratoires Pierre Fabre	France	N/A[4]
Rigevidon	Gideon Richter	Hungary	Worldwide
Oralcon	Famy Care	India	N/A
Ovipause	Phaarmasia	India	India
Planotab	PT Triyasa Nagamas Farma	Indonesia	Indonesia
Lorsax	Pfizer	Mexico	Mexico
Famila 28	Zafa Pharmaceuticals	Pakistan	Pakistan
Ologyn Micro	Labatec-Pharma SA	Switzerland	N/A
Anna	Thai Nakorn Patana	Thailand	Southeast Asia
Riget	Biolab Co.	Thailand	Malaysia
Portia	Barr Laboratories	United States	United States
Levora	Watson Pharmaceuticals	United States	United States

In addition to these brands, which are marketed directly by their manufacturers through mostly commercial channels, many brands have been developed in the context of donor or government-funded social marketing programs. These programs receive donated commodities or procure them through competitive tenders, and market those products under their own brand names in more than 45 countries (DKT International 2004). Major suppliers of social marketing programs include Schering, Wyeth, and several India-based manufacturers.

Both progestin-only pills (containing levonorgestrel) and combined estrogen-progestin pills can be used safely and effectively as emergency contraception (EC). Dedicated products that are specially packaged and labeled for this

[3] IPPF 2005, Martindale 2005, and company websites.

[4] This information is not publicly available.

purpose also are available in many countries. There are two formulations of emergency contraception pills (ECPs) marketed worldwide, with more than forty brand names (table 2). Dedicated EC brands have become widely available in developing countries where they are sometimes the only contraceptive product marketed by a local manufacturer. This trend may be explained by the high profitability of ECPs, and better sales potential, as this product is less likely to be donated or subsidized than regular OCs.

TABLE 2. BRANDS AND MANUFACTURERS OF ECPS[5]

Levonorgestrel 0.75 mg	Manufacturer	Country	Availability
Inmediat N	Gador	Argentina	South America
Pilem	União Quimica	Brazil	Brazil
Pozato	Libbs Farmaceutica	Brazil	N/A
Tace	Gynopharm (Recalcine)	Chile	N/A
An Ting	Shenyang No.1	China	N/A
Hu Ting	Beijing Zong Hui	China	China
Yu Ting	Zizhu Pharmaceuticals	China	N/A
Duofem EC, Norlevo, Pronta, Vermagest, Vika, Vikela,	HRA Pharma	France	Worldwide
Levonelle, Levonelle-2	Schering	Germany	Western Europe
Escapel, Escapelle, Levogynon, Postfemin, Postinor, Quenz	Gideon Richter	Hungary	Worldwide
Pill 72 Levonorgestrel 0.75 mg	Cipla	India	India, Madagascar
Pregnon	Famy Care	India	India
Preventol	Hindustan Latex	India	India
Ovistop	Phaarmasia	India	India
Estinor	Duopharma	Malaysia	Malaysia, Singapore
Glanique	Asofarma	Mexico	Latin America
Postday	IFA	Mexico	N/A
PPMS	Laboratorios Panzyma	Nicaragua	Nicaragua
ECP, Emkit, Emkit Plus	Zafa Pharmaceuticals	Pakistan	Pakistan
Madonna	Biopharm Chemicals	Thailand	N/A
Secufem	Urufarma	Uruguay	Latin America
Plan B	Paladin Laboratories Duramed (Barr)	United States	United States, Canada
Levonorgestrel 0.25mg and ethinyl estradiol 50mcg			
Neo-Primovlar, Tetragynon, PC-4, E-Gen-C	Schering	Germany	Western Europe
Preven	Gynetics Inc.	United States	United States, Canada
Inmediat	Gador	Argentina	South America, DR
Fertilan	Gideon Richter	Hungary	Eastern Europe

[5] IPPF 2005; International Consortium for Emergency Contraception, Office of Population Research Emergency Contraception 2005; Consorcio Latinoamericano de Anticoncepción de Emergencia 2005; and company websites.

2.2 INJECTABLE CONTRACEPTIVES

Approximately 25 million women, mostly in developing countries, use ICs and the number of users is increasing (Affandi 2002). The most-common IC formulation is Depot Medroxyprogesterone Acetate (DMPA), developed by the Upjohn Company and marketed as *Depo-Provera* by Pfizer and *Megestron* by Organon. Other formulations available around the world are Norethisterone Enanthate, a two-month injectable developed and sold by Schering as *Noristerat,* and the monthly IC *Cyclofem,* developed by Upjohn and marketed in various countries through manufacturers licensed by the Concept Foundation. As is the case for ECPs, the limited range of injectable formulations marketed by research and development (R&D) firms appears to have stimulated the emergence of locally developed formulations and brands in Latin America and Asia, particularly monthly IC formulations (tables 3 and 4).

TABLE 3. BRANDS AND MANUFACTURERS OF TWO- AND THREE-MONTH ICS[6]

DMPA	Manufacturer	Country	Availability
Megestron	Organon	Netherlands	Worldwide (mostly developing countries)
Contracep	Thai Nakorn Patana	Thailand	Cambodia, Laos, Myanmar, Vietnam
Depo-Gestin, Depo-A	ANB	Thailand	Nepal, SE Asia
Depo-Progesta	General Drugs House	Thailand	N/A
Depo-M, Pheno M	Vesco Pharmaceutical	Thailand	N/A
Depo-progesno	Milano Lab.	Thailand	N/A
Medeton	TP-Drug	Thailand	Cambodia, Laos, Myanmar, Sri lanka
Deponeon	Triyasa Nagamas	Indonesia	N/A
Depo-Progestin	Harsen	Indonesia	N/A
Famila, Roxyprog-Depo	Zafa Pharmaceuticals	Pakistan	N/A
Non-Preg	LBS labs	Thailand	Malaysia
Petogen	Fresenius Kabi	South Africa	Cambodia
Depocon, Depo-Provera, Depo-Clinovir, Depo-Progevera, Depo-Prodasone, Depo-Ralovera, DepoCon, Dugen	Pfizer	United States	Worldwide
Norethisterone Enantate 200mg			
Depocon	Duopharma	Malaysia	Malaysia
Noristerat, Nur-Isterate	Schering	Germany	Worldwide
Doryxas	Gideon Richter	Hungary	Eastern Europe, Malaysia

[6] Sources: Sources: IPPF Directory of Hormonal Contraceptives http://contraceptive.ippf.org/; Lande, R. E. New era for injectables. Population Reports, Series K, No. 5. Baltimore, Johns Hopkins School of Public Health, Population Information Program, August 1995.; Martindale Complete Drug Reference - http://www.medicinescomplete.com/mc/martindale/current/; and company websites.

TABLE 4. BRANDS AND MANUFACTURERS OF MONTHLY INJECTABLE CONTRACEPTIVES

Brand name	Manufacturer	Country	Availability
Norethisterone Enanthate 50 mg and Estradiol Valerate 5 mg			
Mesigyna, Norigest, Norigynon	Schering	Germany	Worldwide
Dihydroxy Progesterone Acetophenide 150mg and Estradiol Enanthate 10mg			
Atrimon	Ivax Argentina	Argentina	N/A
Femineo	Lab. Ducto Ind. Farm. Ltda	Brazil	N/A
Agurin	Laboratorios Recalcine	Chile	Chile
Proter	Laboratorios Gutis	Costa Rica	Costa Rica
Deproxone	Laboratorios Arsal	El Salvador	Central America
Nomagest	Laboratorios Vijosa	El Salvador	Central America
Novular	Laboratorios Paill	El Salvador	Central America
Ovoginal	Guayaki	Paraguay	Paraguay
Dihydroxy Progesterone Acetophenide 75 mg and Estradiol Enanthate 5 mg			
Yectames	Laboratorios Grossman	Mexico	Central America
Anafertin	Armstrong Laboratorios de Mexico	Mexico	El Salvador
Medroxyprogesterone Acetate 25 mg and Estradiol Cypionate 5 mg			
Cyclofem, Ciclofemina	Millet Roux , Master SA, PT Tunggal, Carnot Laboratorios	Brazil, Chile, Indonesia, Mexico	Mexico, Central America, Peru, Southeast Asia
Novafem	Laboratorios Silesia SA	Chile	Chile
Cyclo-Geston	PT Tunggal	Indonesia	Indonesia
Algeston acetophenide 150 mg and Estradiol Enanthate 10 mg			
Perlutal, Perlutan, Topasel	Boehringer Ingelheim	Argentina, Brazil, Mexico, Spain	Central and South America, Spain
Uno Ciclo	Instituto Biochimico Ltda	Brazil	N/A
Gynomes	Laboratorio Ancalmo-Hessel	El Salvador	Central America
Ginoplan	Carnot Laboratorios	Mexico	N/A
Patector	Aplicaciones Farmaceuticas	Mexico	N/A
Hydroxiprogesterone Caproate 250 mg			
Progestin Depot	Laboratorios Vijosa	El Salvador	Central America
Unbranded	Shanghai Xudong Haipu (Sunrise)	China	N/A

3. TYPES OF CONTRACEPTIVE MANUFACTURERS

Hormonal contraceptives are ethical products that are subject to worldwide trends observed in the pharmaceutical industry. European, Japanese, and U.S. companies dominate this industry, which is concentrated—ten companies control an estimated 40 percent of the worldwide market (Abrol 2004). Similarly, a handful of multinational companies account for the majority of hormonal contraceptive brands registered around the world.

3.1 R&D MANUFACTURERS

Western-based pharmaceutical companies have a long history of scientific innovation, product development, and sophisticated marketing. Most dedicate a substantial percentage of their sales revenue to research and development, which is why they often are called R&D companies. Products these manufacturers develop and launch are submitted to stringent and costly clinical tests, as required by U.S. and European regulations. Their products typically are branded, registered, and marketed through commercial supply networks that include distributors, retailers, and private clinics. Major R&D manufacturers of hormonal contraceptives include Schering (Germany), Wyeth (Untied States), Ortho-McNeil (United States), Organon (Netherlands), and Pfizer (United States).

Worldwide Presence

R&D companies have established a worldwide presence through local affiliates, partner organizations, and, when necessary, manufacturing facilities. In developing countries, these companies tend to dominate both the commercial- and public-sector markets. Selling products through donor or government channels allows for substantial economies of scale through high-volume production of a single formulation. R&D companies refer to this type of business as *institutional*.

Some R&D companies also have developed a strong presence in countries that favor developing local industry instead of importing goods, such as India and China, by licensing local manufacturers or entering into joint ventures with them. Schering, a leading marketer of OCs and ICs, has production sites in several countries, but also licenses manufacturers around the world to produce its brands.

The Importance of Brands

For R&D manufacturers, high-margins are necessary to finance developing new products. The patent-expiration cycle creates a need for the regular introduction of innovative products that can be patented and enjoy a monopoly until a competitor introduces a cheaper generic equivalent. As a result, the hormonal-contraceptive market has a plethora of brands with similar active ingredients and therapeutic indications, but slightly different formulations.

R&D companies produce and market most OC brands, though manufacturers often market the same formulation with different brand names. For example, *Femovan* a combined OC formulation Schering developed for the German market is registered as *Gynera*, *Gynovin,* and *Femoden* in other markets. Other manufacturers also market off-patent formulations with their own brand names. The Wyeth equivalent of *Femovan* is *Minulet* and biosimilar versions of that product are found in Latin America with the names *Ciclotab, Feminol,* and *Gestodeno.* Some R&D manufacturers also like to use different brand names for products sold to donors and governments to distinguish them from their commercial business. For example, Wyeth supplies governments with a dedicated brand (*Lo-Femenal)* that is bioequivalent to *Nordette*, a combined OC sold in commercial markets.

Corporate Strategies

Although R&D manufacturers share many characteristics, they often have different corporate strategies. Organon, Schering AG, and Ortho McNeil, which derive a large part of their revenue from their contraceptive lines, are the most innovative. Schering is developing a new contraceptive product for women over thirty-five years old and Organon launched a hormonal-releasing vaginal ring and a new formulation of implants in the last two years. Ortho McNeil has invested in the development of *Ortho Evra*, a trans-dermal hormonal patch that has become the most-prescribed contraceptive brand in the United States (Ortho McNeil 2005).

In contrast, some manufacturers prefer to invest R&D resources in other therapeutic classes deemed more profitable, such as anti-depressants, hypertensive drugs or hormonal replacement therapy. Successive waves of consolidations in the pharmaceutical industry have led to disinvestment or product discontinuations in the contraceptive area. Pfizer, in particular, has absorbed more than 60 contraceptive brands as a result of merging with Pharmacia and GD Searle but most of these brands are off-patent and eventually may be discontinued. Recent R&D projects at Pfizer have not included contraceptive-product research and it is unclear whether the company intends to invest future resources into this therapeutic area. Although a company may choose not to invest in contraceptive R&D, it invariably applies R&D margins to all contraceptive products.

3.2 NON R&D MANUFACTURERS

This category includes manufacturers that do not develop their own formulations, but instead copy existing products to market them with a different brand name or sell them unbranded. These products are typically off-patent, though in some countries that do not recognize or enforce patent protection, local manufacturers have been copying R&D formulations for decades. The pharmaceutical industry often calls such products *copy products*. Legitimate copies of off-patent drug formulations come in two categories: those that have demonstrated bioequivalence with the original formulation, and those that have not. The latter are often referred to as *biosimilar* because they are not strictly identical to, but similar to the originator brands.

Manufacturers of Bioequivalent Generics

Two medicines are bioequivalent when they contain the same amount of identical active ingredients, and when their bioavailability (the rate and extent at which the body absorbs active ingredients) is the same when administered in equal doses in equal conditions. Strict scientific studies, including clinical trials, are necessary to determine bioequivalence (EGA 2005).

A growing number of manufacturers worldwide are producing bioequivalent formulations of off-patent drugs that are in high-demand. Generic manufacturing is subject to the same technological and scientific requirements and stringent regulations as R&D manufacturing. Because of the considerable investment required for bioequivalence testing, these companies tend to be based in the United States, Canada, Western Europe, Israel, and South Africa. Establishing bioequivalence for their products allows generic manufacturers to gain acceptance in the healthcare community without the considerable costs involved in marketing name brands. Regulatory institutions have an important role in legitimizing generic companies and encouraging providers and consumers to switch to generic formulations. For instance, the U.S. Food and Drug Administration (FDA), which regulates generic drugs, has stated that "it is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a determination of therapeutic equivalence for the drug products under consideration" (FDA 1998).

A few generic manufacturers are producing a wide range of OC formulations for the United States, Canadian, and European markets (see table 5). Barr Laboratories, the second largest developer, producer, and marketer of OCs in the United States, produces generic versions of twenty-two formulations at lower prices than the original name brands (Barr 2005). Another U.S.-based generic manufacturer, Watson Pharma, markets eleven OC formulations with its own trade names. These two companies focus on the North American market and have not attempted to make inroads in other countries.

Large generic manufacturers based outside the United States and Western Europe also have their sights on lucrative developed markets. Teva Pharmaceutical Industries Ltd., headquartered in Israel, is among the top twenty-five pharmaceutical companies and one of the largest generic manufacturers in the world. Teva markets OCs in the United States and was granted FDA approval to market the first generic version of Pfizer's IC brand *Depo-Provera*. Gideon Richter, a major generic manufacturer based in Hungary, is the main supplier of affordable hormonal contraceptives in Eastern Europe. Gideon Richter has developed the capacity to conduct bioequivalence testing and now supplies the United States, Western European, and Japanese markets with OC and ECP formulations.

TABLE 5. MAJOR MANUFACTURERS OF GENERIC HORMONAL CONTRACEPTIVES

Country	Manufacturer
Hungary	Gideon Richter
Israel	Teva Pharmaceutical Industries
U.S.	Andrx Corporation
U.S.	Barr Laboratories
U.S.	Watson Pharmaceuticals

Generic markets in the United States and Europe also are expected to be the main engine for growth for major South African, Indian, and Chinese pharmaceutical companies that have the capacity to conduct bioequivalence studies. In those countries, however, manufacturers may choose to invest in those studies and seek access to developed markets only for products that have the highest potential for sales and profits. For example, while several antiretroviral (ARV) drugs and numerous other therapeutic formulations produced in India have undergone bioequivalence testing, contraceptive products have not yet benefited from such investment.

Manufacturers of Biosimilar Products

The introduction of legislation that favors the use of generics in public-sector or managed-care programs is linked to bioequivalence regulations. In most developing countries, however, such regulations do not exist. Bioequivalence programs are costly, time-consuming, and many nations do not have the resources or trained staff to manage these programs. Hormonal contraceptives manufactured in these countries reflect a pattern observed in the rest of the pharmaceutical industry: There are many biosimilar copies of R&D brands, but few bioequivalent generic products. Manufacturers of branded biosimilar products are found in several middle-income countries and a few developing countries (see table 6).

Many manufacturers of biosimilar products are found in South America (Brazil, Chile, Uruguay, Paraguay, and Argentina), where protectionist policies favored the development of a local manufacturing base in the 1950s and 1960s. These companies, some of which are very large, have substantial therapeutic portfolios, and use the same marketing techniques as R&D companies, though their prices are typically lower. Some local manufacturers also have developed close relationships with local governments by bidding on public-sector procurement tenders.

Legislation facilitating generic substitution and bioequivalence is making its way to Latin America, where it threatens many of the smaller domestic producers (IMS 2005). Analysts estimate that all major pharmaceutical markets in Latin America eventually will consist solely of original brands or bioequivalent generics. In Brazil unbranded generics already are subject to bioequivalence testing and many locally produced formulations are to be tested as part of a ten-year program that started in 2004. It is estimated that at the completion of the program, all products on the market will have proven bioequivalence, and untested products will no longer be on the market (Sanduro 2005).

Many OC and IC manufacturers also are found in Asia. In China, India, Vietnam, and Indonesia, where laws favor local production over imports, hormonal products are manufactured at a low-cost for national family-planning programs. In Thailand and India, some local manufacturers also have made inroads into commercial markets, either

by marketing their own brands or by supplying social-marketing programs. Injectables are produced primarily in Thailand and Indonesia where DMPA was registered more than 30 years ago and is among the preferred methods of contraception.

TABLE 6. MANUFACTURERS OF BRANDED BIOSIMILAR HORMONAL CONTRACEPTIVES

Country	Manufacturer
Argentina	Gador S.A, Laboratorios Elea, Roemmers
Brazil	Aché Lab Farmacéuticos S.A, Biolab-Sanus, Cifarma, EMS-Sigma Pharma, Eurofarma, Haller, Medley, Libbs Farmacêutica, União Quimica
Chile	Corporación Farmaceútica, Gynopharm (Recalcine), Laboratorio Chile, Grunenthal Gmbh, Laboratorios Silesia
China	Zizhu Pharmaceuticals
Costa Rica	Gutis S.A.
El Salvador	Ancalmo-Hessel, Arsal, Laboratorios Vijosa, Paill
India	FamyCare, CIPLA, Hindustan Latex
Indonesia	PT Triyasa Nagamas Farma
Malaysia	Duopharma
Mexico	Aplicaciones Farmaceuticas, Armstrong Laboratorios, IFA Mexico, Laboratorios Carnot, Laboratorios Grossman, Productos Cientificos SA
Pakistan	Zafa Pharmaceutical Laboratories
Nicaragua	Panzyma Laboratories
South Africa	Fresenius kabi
Thailand	Biolab Co., Thai Nakorn Patana, ANB
Uruguay	Urufarma

Contract Manufacturing

Branded commercial contraceptives represent only a fraction of the total hormonal-contraceptive supply. The IPPF Directory of Hormonal Contraceptives, the most-comprehensive directory of hormonal contraceptive products, does not list manufacturers of unbranded products (IPPF 2005). There is no publicly available list of generic contract manufacturers and information about these companies is difficult to obtain outside of industry circles. Contract manufacturing is an important aspect of the pharmaceutical business because it allows companies with different capabilities to join forces, as illustrated in the following examples:

- Teva Pharmaceutical Industries and Andrx Corporation, a local U.S. manufacturer, signed an agreement in 2003 to develop and market generic OCs in the United States and Canada. Andrx is responsible for all formulations, U.S. regulatory submissions, and manufacturing of products while Teva markets the brands to major clients.

- In 2004, Prasco Laboratories, another U.S.-based manufacturer, partnered with Organon to produce *Solia*, a generic equivalent of Organon's *Desogen*. This partnership allows Organon to market its own generic version of *Desogen* and compete with another generic brand (*Apri*), marketed by Barr Laboratories (Prasco 2005).

- Gideon Richter, the Hungarian-based manufacturer, produces OCs, ECPs, and steroid active agents for pharmaceutical companies with a large market presence in Europe and the United States, such as Pfizer, Duramed, Woman's Capital Corporation, and Schering AG.

Contract manufacturing is common in developing countries where contraceptives are produced for national family-planning programs or exported to countries with government-procurement programs. Indian and Chinese generic-contraceptive manufacturers in particular derive the bulk of their business from government tenders. In China, Beijing Zizhu Pharmaceutical Co. is the most-important production base for the state Family Planning Committee (Chambers 2004); and in India, five domestic manufacturers compete for India's large government-funded social-marketing program. Table 7 lists prominent contract manufacturers of hormonal contraceptives.

TABLE 7. MAJOR CONTRACT MANUFACTURERS OF HORMONAL CONTRACEPTIVES

Country	Manufacturer
China	Shanghai Xudong Haipu Pharmaceutical Co. (Sunrise) and Beijing Zizhu-Pharmaceutical Co.
Egypt	Chemical Industries Development
Hungary	Gideon Richter
India	FamyCare, Hindustan Latex, Indian Drug, and Pharmaceutical, Phaarmasia
Indonesia	PT Tunggal
Oman	Oman Pharmaceuticals Products Co.
Thailand	Umeda (Ponds Chemical)
United States	Andrx Corporation, Prasco

4. DISTRIBUTING AND MARKETING CONTRACEPTIVES

Manufacturing is only the first stage in the supply process. The following section examines the three main channels through which hormonal contraceptives are made available and promoted to providers and consumers. Contraceptive manufacturers differ in their approach to domestic and international markets and tend to respond to business opportunities within the channels they have chosen to distribute and market their products.

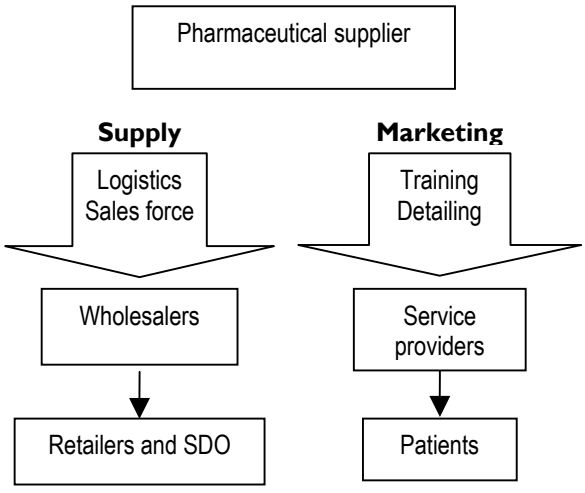
4.1 COMMERCIAL CHANNELS

Hormonal contraceptives are marketed like other so-called ethical pharmaceutical products dispensed by prescription. Commercial distribution channels for these products include licensed pharmacies and service delivery outlets (SDO), such as public and private clinics and hospitals. To distribute their products, manufacturers may develop their own sales force, transportation system, and fleet, or partner with a distributor. Pharmaceutical distributors are sophisticated operations that typically carry hundreds of products from different companies in order to spread fixed costs and build clout with trade partners.

Ethical products rarely are promoted to the end consumer, but rather to the people who are authorized to prescribe them, typically licensed physicians. As a result, pharmaceutical companies have traditionally focused their marketing efforts on this target group. Marketing to physicians involves hiring medically trained staff that regularly visits doctors' offices and other SDOs. These visits rarely last more than a few minutes and focus on discussing new launches and addressing product-related issues. This activity is referred to as *detailing* and it is the main marketing tool companies use to sell products in the commercial sector. It is also a costly activity that involves hiring and training qualified staff and investing in sophisticated provider databases and monitoring systems.

In addition to detailing, pharmaceutical companies invest in extensive public-relations programs and continuing education for providers. The main objective of these activities is to establish trust in a company's products and ensure the loyalty of prescribing physicians. The companies that choose commercial channels to distribute their brands therefore tend to be well established, have wide product portfolios, and command high prices. Many of them are R&D or large locally-owned pharmaceutical companies.

FIGURE 1: COMMERCIAL SUPPLY AND MARKETING CHANNELS FOR PHARMACEUTICALS



4.2 THE PUBLIC SECTOR

A large proportion of hormonal-product users in developing countries obtain their supplies from the public sector, where they can be obtained for free or for a nominal price. Public clinics and other government SDOs are considered part of the commercial network as long as they purchase products from commercial channels. Pharmaceutical companies and distributors that supply the public sector service them the same way they do private clients: by delivering products to SDOs and including public providers in their detailing and promotional programs. As a result, the cost of supplying the public sector through commercial channels is the same as for private retailers and SDOs.

In many countries, however, commodities available in the public sector are donated by development agencies or procured by local governments through competitive tenders. Because these products can be obtained at lower costs from company headquarters, procurement agencies buy products offshore and take on the responsibility of distributing the products in their country. Commodities procured through this system therefore are only available in public-sector SDOs.

Little marketing is involved in the procurement business. Competitive advantage is achieved by offering the lowest possible price, abiding by contract terms, and providing products of consistent quality. Brand image and product differentiation play a small role in the procurement business so that no investment in research, advertising, or promotion is required. The prices extended to procurement organizations are low because they do not include R&D or marketing margins that are systematically applied to all products sold through commercial channels.

Both R&D companies and manufacturers of biosimilar products compete for public-sector tenders in any given country, but international tenders issued by donor organizations have generally favored Western-based companies that can satisfy stringent prequalification requirements such as FDA approval. Manufacturers of bioequivalent generic contraceptives have been notoriously absent from international bidding. A likely explanation is that more lucrative opportunities exist for these companies in the fast-growing European and North American generic markets.

4.3 SOCIAL MARKETING

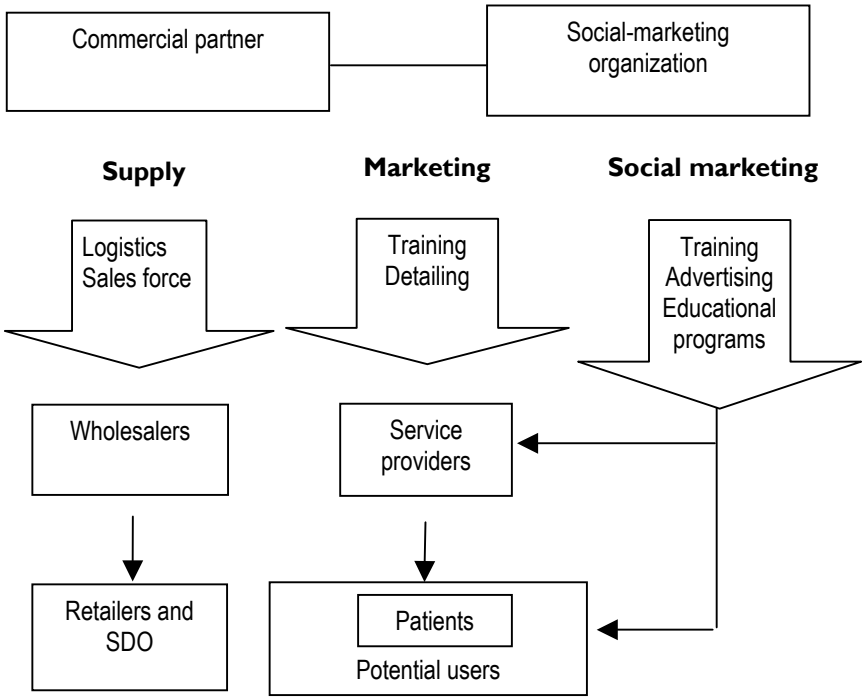
In many developing countries, social-marketing programs are a major supplier of hormonal products. Approximately 90 million pills and 8 million injectables were distributed through social-marketing programs in 2000, mostly at subsidized prices (DKT 2005).

Social-marketing organizations that market hormonal contraceptives often adopt the same approaches and techniques as pharmaceutical manufacturers (such as partnering with a distributor), but their pricing and investment strategies differ. Social-marketing programs must complement commercial approaches, which are effective in achieving wide product availability, but are designed to maximize cost efficiency and profits. Common social-marketing strategies include educational campaigns designed to increase the number of contraceptive users and improved distribution in areas commercial suppliers may under serve. In some countries, social-marketing brands of OCs can be sold without prescription and are promoted through the mass media.

Social-marketing programs do not manufacture products but use the same supply mechanisms as governments and donors (usually a competitive bidding process). Some programs receive donated commodities from USAID or use donor funds to purchase products on the world market. Hormonal contraceptives, however, are more difficult to procure than condoms, which are manufactured at low cost in several Asian countries. Social-marketing organizations are increasingly purchasing products from local manufacturers, prompted by dwindling donations, increasing commodity prices, or new donor policies. DKT International, for example, has been procuring OCs from Thailand for the Philippines market and ICs from Indonesia for its India program. Population Services International (PSI) is now sourcing products from an Indian manufacturer for its KfW-funded Guinea program.

Not all social-marketing organizations have to purchase contraceptives. Programs based on a partnership with a commercial manufacturer use existing commercial brands and market them through combined commercial and social-marketing approaches (see figure 2). Most of these partnerships, however, have traditionally involved R&D companies with a history of supplying donor-funded programs.

FIGURE 2: SUPPLY AND MARKETING CHANNELS FOR SOCIAL-MARKETING PROGRAMS BASED ON COMMERCIAL PARTNERSHIPS



5. INCREASING THE SUPPLIER POOL

5.1 KEY CHALLENGES

Product Quality and safety

All pharmaceutical manufacturers are expected to adhere to World Health Organization (WHO) Good Manufacturing Practices (GMP) and technical standards developed by the International Organization for Standardization (ISO). These guidelines ensure that products are produced according to high quality and safety standards. GMPs are moving targets that require continuing investments in buildings, equipment, and technology upgrades. The high cost of adherence to these standards, which is mandatory in industrialized countries, is a substantial barrier to entry in the pharmaceutical-manufacturing business. This fact explains why large multinational companies with considerable investment capacity dominate the pharmaceutical market.

Although the same GMP apply to the manufacture of all pharmaceutical products, hormonal contraceptive production poses additional challenges due to the small amount of active ingredients in those products. Content uniformity requires sophisticated facilities that monitor the flow of air, water, raw materials, waste, personnel, and products. In addition, workers must be protected from the health risk of exposure to potent steroids through strict sanitation, hygiene, and protective measures in the design of manufacturing facilities. Sustained quality-assurance systems and adequate worker protection, however, are vulnerable to a manufacturer's attempt to cut corners. For this reason, regulatory controls are necessary to ensure the quality and safety of a country's product supply.

Monitoring of manufacturing Facilities

A well-functioning national drug regulatory authority (NRDA) and a competent national quality-control laboratory are two requirements for the production of high-quality hormonal contraceptives (WHO 1994). The NRDA is responsible for ensuring that all manufacturing processes and procedures are conducted in compliance with GMP. To be effective, the NRDA must be able to conduct independent product evaluations, including inspecting and monitoring manufacturing facilities, as well as testing and inspecting finished products. It also should have the authority to recommend and enforce corrective actions (WHO 1995).

The most stringent regulatory systems and enforcement agencies are in the United States, Canada, Australia, Japan, and Western Europe. Other countries also have regulatory systems that quality experts considered stringent: Brazil, Mexico, Colombia, Argentina, Guatemala, Costa Rica, South Africa, and others have comprehensive regulations and well-trained inspectors (Zardo 2005). Outside of these countries, however, it is difficult to obtain reliable assurances as to the quality and safety of locally manufactured drugs. The quality and safety of Chinese products, for example, may vary drastically from one company to another. Some experts even question the standards used in the production of raw materials (steroids), which China exports to other countries (Zardo 2005).

In the absence of regulatory enforcement, even government-controlled manufacturing facilities may have trouble maintaining adequate quality controls. The Egyptian government supported local contraceptive manufacturing in the 1980s for domestic use and export to neighboring countries, but quality issues developed that made exporting Egyptian products impossible. According to a recent assessment, the factory still was unable to comply with GMP in 2000.

Although WHO and the Program for Appropriate Technology in Health developed comprehensive technical guidelines to ensure the quality and safety of worldwide hormonal-contraceptive production (WHO 1994, 1995),

there is no centralized, uniform system to assess and monitor manufacturers in developing countries. A company may be approved by one procurement agency only to be turned down by another. For example, the United Nations Population Fund (UNFPA) disqualified an Asian manufacturer of ICs because its products failed a clinical test—even though it had been supplying another country's national family-planning program for some time. WHO plans to develop a list of pre-qualified hormonal-contraceptive suppliers similar to the lists of condom and ARV manufacturers, but its completion may be years away (Smith 2005). Prequalification lists, to be reliable, must be backed by regular product testing, plant inspections, and quality assurance auditing.

Market Conditions and Business Strategies

Manufacturers of generic and biosimilar products only will produce contraceptives if there is sufficient market potential for them. Aché, one of the largest Brazilian pharmaceutical companies, markets several OC brands in the commercial sector because there is high demand for affordable products and subsidized contraceptives are not ubiquitous. In contrast, the Indian market offers limited opportunities for local manufacturers outside of government programs because free and subsidized brands occupy the middle-to-low-price market segment. Thus, the presence of well-intentioned government programs discourages the manufacturers most likely to supply affordable commercial products from doing so.

Business practices also have a major role in the availability and price of commercial contraceptives (Bulatao 2002). The decision to market a brand in a developing country, as with anywhere else in the world, is subject to a favorable assessment of market potential based on the projected return on investment. A manufacturer seeking to maximize short-term profits may "skim" the market by targeting the most-profitable and motivated user segment. Consequently, many users may remain underserved by this type of supplier. In contrast, a manufacturer that seeks to build a high-volume market, albeit with lower profit margins, likely will be serving a larger segment of the population. The presence of a range of products at different prices is subject to business decisions, but it is likely to be optimized if a variety of manufacturers compete in any given market.

Market conditions and a company's sense of its competitive standing influence business strategies. Asian manufacturers, in particular, see themselves as making low-cost products for others to market and distribute. The bulk of their business still comes from institutional tenders, which do not require developing and marketing proprietary brands. An increasing number of Indian suppliers, however, are developing the capacity to market products commercially both in and outside India. One company has registered its OC brand in over 20 developing countries, with the dual goal of bidding on government and donor procurement tenders, as well as establishing a long-term commercial presence.

Procurement Policies

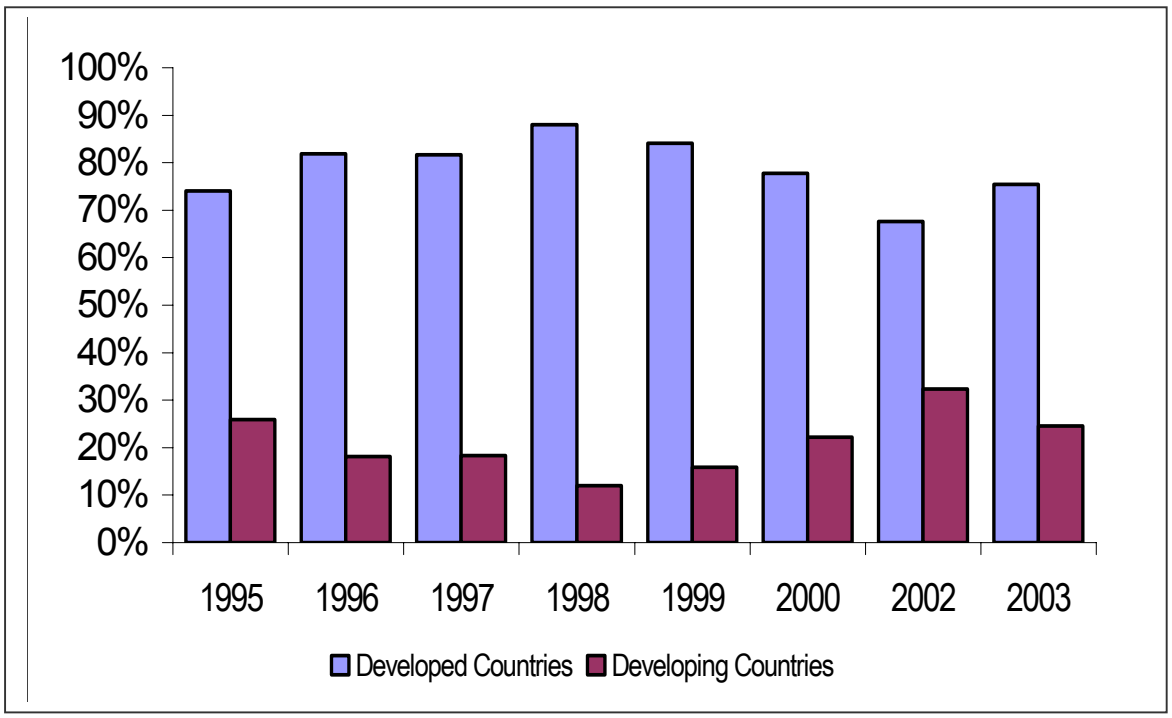
Procurement for public-sector and social-marketing programs is typically done through national or international institutions that issue tenders with specific prequalification guidelines. Donor and government procurement policies can influence the type of suppliers that gain access to developing markets. IPPF, UNFPA, and USAID account for nearly 60 percent of the world's donated contraceptive supplies (Supply Initiative 2005). As a result, the few manufacturers that supply these organizations are the most-widely represented in developing countries.

Public and social-marketing programs in the poorest developing countries also have created an oligopoly that benefits Western-based large contraceptive manufacturers (Stanback 1997). Wyeth and Pfizer (United States), Schering (Germany), and, more recently, Organon (Netherlands), have registered brands in most developing countries, partly in anticipation of winning large international tenders. In addition to providing significant economies of scale, donor and government programs allow manufacturing companies to develop brand recognition and establish long-term loyalty among health providers.

Both IPPF and UNFPA increasingly are seeking new manufacturers to obtain lower prices for their affiliates or clients (see figure 3). The proportion of contraceptives companies in developing countries supply to these institutions, however, still is limited to mostly condoms and intrauterine devices. USAID must give priority to U.S.-

based manufacturers and only can buy products from offshore companies that have obtained FDA approval or undergone an equally stringent certification process.

FIGURE 3. UNFPA CONTRACEPTIVE SOURCES



Product Registration

Hormonal contraceptives are under the control of the NDRA, which registers each drug formulation, whether imported or manufactured domestically. The registration or approval process typically involves a detailed review of data contained in a scientific dossier the manufacturer submits in support of the safety and efficacy of the formulation. Registering a new drug in a developing country may cost several thousand dollars and the approval process may take a year or longer to be completed.

Product-registration rules can be serious obstacles in a developing-country context. Some countries that lack the qualified staff to oversee the registration process request certificates demonstrating that the product already has been approved by regulatory agencies in the European Union, United States, Canada, or Japan. In other countries, rules may be less stringent, but bureaucratic delays can be considerable. In most cases, however, the presence of locally manufactured products and the importation of generic and biosimilar products from other developing countries is facilitated by the absence of legislation requiring bioequivalence testing.

5.2 ACCESS TO PROCUREMENT PROGRAMS

For many manufacturers located in developing countries, bidding on domestic and international tenders is a bread-and-butter business. Most are looking to secure and expand their contract business, both domestic and international. Some manufacturers in India and other countries have begun to supply government programs through UNFPA, which can substantially increase the cost-efficiency of public-sector programs. Foreign governments are the most-promising channels for contract manufacturers based in developing countries. There are signs that these manufacturers have begun to match and even outperform R&D suppliers in their bids for

public-sector contracts. Industry experts feel that some Indian companies, in particular, have the capacity to supply large international tenders (Chambers 2005).

A Thai manufacturer recently priced a DMPA formulation at around $0.65 a vial, or $0.20 lower than Pfizer's lowest-recorded bidding price. Similarly, a well-known Indian supplier has been offering family-planning programs a generic equivalent of *Duofem* for less than the price quoted by the R&D firm. Following India, China, and Indonesia, some other Asian governments now are looking at regional manufacturers as low-cost alternatives to R&D suppliers. The Ministry of Health of Bangladesh for example, recently achieved substantial savings by switching from an R&D supplier to an Indian generic supplier. As one industry insider put it, "Eventually, it will all be a South-to-South business."

Tackling the Quality Issue

The fragility of the local regulatory environment in developing countries does not necessarily imply that products manufactured in those countries fail to meet international quality standards. According to international experts, product quality and plant conformity are subject to the owner of the business's policies. China, Indonesia, and Thailand are known to have reliable suppliers, even though regulatory enforcement in these countries may be weak or inconsistent (Carter 2005). Some countries where problems frequently were reported in the past have come a long way. A respected quality-control expert recalled traveling to India in the mid-1980s and finding poor-quality products and substandard or unsafe manufacturing facilities. The same expert recognizes, however, that much progress has been made since then (Zardo 2005).

It is possible to improve the quality of products manufactured in developing countries through collaboration and capacity building. PATH invested a lot of time and resources in China in the 1990s, working on product quality and sharing expertise in product testing and quality assurance (PATH 1990, 1991). The FDA, for its part, has been providing technical assistance to Chinese national authorities to improve their capacity to test products and conduct site inspections.

More commonly, government agencies and client organizations send inspectors overseas to verify the quality and safety of foreign manufacturing plants. The Australian equivalent of the FDA, the Therapeutic Goods Administration, conducted site visits and product quality testing to assess the export potential of a contraceptive-manufacturing plant in Thailand in 1993. The Colombian and Brazilian regulatory agencies conducted site visits in China, Mexico, and India before granting registration approval to manufacturers in those countries (Zardo 2005). Social-marketing organizations, such as Population Services International, DKT International, and PROFAMILIA/Colombia also conduct their own technical assessments of potential suppliers.

Monitoring the quality of products originating in countries with less-stringent regulatory frameworks, therefore, is not insurmountable and can be achieved with collaboration between regulatory authorities and local manufacturers. The question of which standards should apply in the developing world, however, is far from being resolved (Smith 2005).

Revising Procurement Practices

Donors and other procurement organizations traditionally have favored Western-based manufacturers that can supply large quantities of products and demonstrate high-quality standards, generally through FDA or European Union product certification. Even when USAID is able to procure contraceptives outside the United States, its rules tend to favor multinational companies that can invest in the FDA-approval process. Manufacturers based in developing countries will go through such stringent and lengthy processes only if they are considering marketing their products in the United States. Contraceptives are made mostly by small contract manufacturers that are not well positioned to compete internationally against U.S.-based R&D and generic companies. These companies, therefore, have little incentive to apply for FDA registration. It also may take up to three years to obtain FDA approval, a process that involves in-depth clinical testing and plant inspections.

In contrast, UNFPA does not require registration by the FDA or another stringent regulatory institution. As long as it purchased contraceptives from R&D pharmaceutical companies (some of which also supplied USAID) UNFPA relied on a manufacturer's reputation, documentation of quality and safety standards, and pre-shipment product testing. Because the agency makes it a point to increase the sourcing of products and services from developing countries, however, it recently began to apply a more thorough and systematic assessment of products and plant facilities. UNFPA typically verifies compliance with ISO 9000 standards and GMPs, conducts site visits to assess plant conditions, and examines all aspects of the financial and commercial structure of a manufacturer. Consultants, such as Crown Agents, conduct inspections of factories and sample products on site, while other institutions such as SGS and Family Health International (FHI) test product quality for UNFPA.

KfW, which traditionally procured contraceptives through U.S.- or European-based suppliers, also is trying to encourage competition from a wider pool of suppliers. Contraceptive tenders KfW funds require advertising in Germany and the country for which the products are being procured. Because many Southern-based generic manufacturers cannot obtain FDA or European Union certification, KfW conducts its own quality and safety assessments.

Besides international procurement organizations, an increasing number of NRDA, such as Brazil's Agência Nacional de Vigilância Sanitária (ANVISA) and Colombia's Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), have developed their own systems to screen international suppliers. These systems are based on compliance with GMP and guidelines issued by WHO, the International Organization for Standardization, and the Pharmaceutical Inspection Convention (PIC). As a result, it may be possible to assess a manufacturer's compliance with international standards through its ability to pass inspections by NRDAs in countries outside the OCDE.

Improved collaboration between procurement outfits (including donor, government, and non-profit organizations) could go a long way towards sharing costs, harmonizing requirements, and avoiding duplicate assessments. Such collaboration appears to be underway through the activities of the Supply Initiative, a partnership of leading reproductive-health organizations that is exploring opportunities to engage generic manufacturers (Supply Initiative 2005). One expert suggested the creation of a "composite evaluation score" that would assess multiple criteria linked to quality product supply (Zardo 2005). Such criteria might include:

- Compliance with WHO and ISO guidelines for validations, qualifications, documentation and training
- Procurement and delivery processes and past compliance with contract specifications
- Product quality assessment (including physical-chemical and microbiological aspects)
- Handling of complaints, and history of corrective and preventive actions

5.3 COMMERCIAL MARKETS

R&D firms tend to see markets in developing country as divided between the private brands, targeting high and upper-middle income customers, and public-sector or social-marketing brands, targeting lower-income groups. Multinational companies have little interest in changing this paradigm, as they tend to have monopolies in both ends of the market. Institutional contracts help develop economies of scale and maintain brand loyalty, while private markets contribute to profits. Some companies are challenging this vision but no group of suppliers stands to benefit more from a different approach than Southern-based ones.

Table 8 provides an illustrative example of the costs R&D and generic manufacturers that market OCs in commercial markets incur. Manufacturer's prices of $3.00 and $1.50 are typical of a mid-price combined OC formulation and translate into retail prices of roughly $6 and $3 in a middle-income country, such as Brazil. Marketing and R&D costs may be spent on other product lines or different therapeutic categories. In effect, OCs often subsidize other businesses within the company, which is why R&D manufacturers only will compress these margins if substantial economies of scale or market-share increases can be achieved. When negotiating with a

potential commercial partner, one should not simply look at whether a company is still making money after a hypothetical price cut, but whether it is still generating the margins needed to sustain its overall business.

TABLE 8. PROFIT AND LOSS STATEMENT FOR OC MANUFACTURERS[7]

Major P&L line items	R&D manufacturer		Generic manufacturer	
	$/unit	Ratio to revenue	$/unit	Ratio to revenue
Net sales	3.00	100%	1.50	100%
Less: Manufacturing costs	0.30	10%	0.20	13%
Equals: gross profit	2.70	90%	1.31	87%
R&D expense	0.39	13%	0.02	1%
Sales and marketing costs	0.90	30%	0.60	40%
General and administrative	0.30	10%	0.08	5%
Taxes, interest and other	0.39	13%	0.24	16%
Equals: Net Profit	0.72	24%	0.37	25%

Southern-based generic manufacturers typically are leaner operations that compete on the basis of price, rather than innovation or image-based marketing. Not only are their costs lower, but their desired market positioning is more compatible with a middle-to low-income consumer target. Thus, these manufacturers may help improve the affordability of contraceptives sold in commercial markets, provided they see profitable opportunities in these markets.

Creating Market Opportunities

Large-scale donation programs, however, have created a situation in many countries where commercial suppliers are relegated to a high-price segment because they cannot compete with widely accessible subsidized brands. This condition may be convenient for R&D companies seeking to maximize profits in export markets while supplying large-scale government programs through procurement channels. It does not, however, favor the development of a mid-price market, nor does it encourage low-cost manufacturers to market their products commercially.

PSP-*One* has found that Indian contract manufacturers are not interested in launching a dedicated affordable brand for the commercial sector (Beer 2005). Large generics manufacturers, with the technical capacity to produce and market OCs, and smaller contract manufacturers alike argue that there is no market potential for a local, mid-priced brand in India. As in many other countries, there are only two ways to market a contraceptive in India: to medical providers, who have been courted by R&D firms, and over the counter, where cheap social-marketing and government brands abound. These companies assume that the situation is similar in other developing countries and are even less inclined to export a commercial contraceptive brand.

This market distortion perpetuates a situation where free and subsidized products are perceived as necessary because no affordable brand exists on the commercial market. The only way to attract new commercial entrants to market lower-priced products is to open up market opportunities for them. Planned phase-outs of donated commodities in some countries may provide such an opening: in the Philippines, the PRISM[8] project hopes to convince local and international manufacturers to launch a mid-price pill. The incentive for investing in such a product is the increase in demand for commercial products that is expected to result from a planned phase-out of USAID-donated commodities.

Emergency contraception and monthly injectables, which are rarely included in government or donor procurement programs, provide some insight into the ability of local manufacturers to fill a void when market opportunities

[7] Pritchard 2005.

[8] Private Sector Mobilization for Family Planning

exist. In Latin America and Asia, several manufacturers produce ECPs or injectables but not regular OCs, reflecting market distortions caused by government procurement and subsidies.

Fostering Partnerships

Southern-based manufacturers are potential partners in initiatives to increase the sustainability of product supply, as long as they are willing to develop and support their own brands. Helping manufacturers identify potential distributors in developing countries can facilitate access to new markets. Such partnerships are based on a model the USAID-funded Social Marketing for Change (SOMARC) project developed, which encouraged R&D companies to introduce affordable contraceptives in developing markets. This approach is the most sustainable in the long run, although it may require significant initial investments. The Key Social Marketing program managed by the Futures Group in Pakistan is a rare example of a partnership with a local manufacturer based on this model (see inbox).

Key Social Marketing (KSM) program in Pakistan is a rare example of a partnership between a social-marketing organization (SMO) and a local manufacturer. Until 2000, KSM had been marketing *Key Nordette*, produced by Wyeth, at a subsidized price. When Wyeth decided to discontinue production of the pill and import a more-expensive product, KSM turned to a local pharmaceutical company: Zafa Pharmaceutical Laboratories. Zafa agreed to invest in plant equipment, personnel, and extensive quality-control systems. KSM and its local partner launched *Key Familia 28* at a non-subsidized price that was lower than the subsidized *Key Nordette* price. By the end of February 2001, *Key Familia* was already the leading brand of OCs in Pakistan (Khan 2001).

Not all contraceptive manufacturers, however, have the capacity to compete in commercial markets. Contract manufacturers in particular are lukewarm about marketing their own brands because their margins do not accommodate marketing or promotion costs. Exporting branded products beyond international tenders presents an additional challenge: Southern-based manufacturers have marketing offices, sales forces, or distribution systems of their own in other countries, because it would be prohibitively expensive for them. Registration costs are an additional barrier for some companies, although a major Indian manufacturer reportedly registered its products in several African countries.

These companies may need to be matched with other organizations that are able to market and distribute products in commercial markets. Social-marketing organizations (SMOs) and Family Planning Associations are good potential partners for contract manufacturers; some already purchase products from local suppliers in several countries, although the goods they market are often subsidized. Low-cost manufacturers are logical suppliers for SMOs looking to segment a market with commercially sustainable brands. This approach also may be a good progressive sustainability strategy for SMOs in low-income countries and those facing a commodity donation phase-out.

There are limitations in partnerships involving Southern-based generic manufacturers, however: their capacity and willingness to develop extensive marketing and demand-creation activities are unlikely to match those of R&D companies. Working with low-cost manufacturers helps increase the financial sustainability of product supply but does not eliminate the need for marketing, education, and behavior-change interventions that are indispensable in building a contraceptive market.

Furthermore, Indian, Thai or Chinese brands do not have the same image and reputation among providers and users as R&D brands. Decades of marketing efforts by large multinationals have built perceived value for their products that translates into low price sensitivity among their target consumers. It remains to be seen whether generic and biosimilar products made in Southern countries can command the prices that would position them in the much touted but still hypothetical middle market. Social marketing organizations and other potential distributors of Southern-made products need to be aware that special marketing efforts may be necessary to build acceptance for these products in each new market.

6. CONCLUSION

Achieving a Sustainable Product Supply is a Public-Health Priority

As demand for reproductive-health products and services grows, ensuring a sustained commodity supply in the most donor-dependent countries becomes increasingly difficult. Many country programs that receive donor assistance are expected to finance, procure, and deliver contraceptives on their own in the future. Accessing a wide range of low-cost suppliers and relaxing legal barriers while ensuring sustained product quality and safety is already a major challenge for these programs. According to a thirteen-country survey conducted in 2000, major challenges to sustainable family-planning programs include "high contraceptive prices on the international markets" and "fiscal constraints on governments to purchase contraceptives" (Interim Working Group on Reproductive Health Commodity Security 2000).

Low-Cost Manufacturers Can Make a Difference

Because of their streamlined cost structure, manufacturers of generic and biosimilar drugs, especially those based in middle-income and developing countries, can play a key role in supplying government programs. These companies tend to specialize in high-volume, low-margin production and have a natural interest in developing products for a lower-income audience (Prahalad 2004). Thus, they may be able to market mid-price commercial products that wean some users away from free and subsidized products.

Immediate Opportunities

Contract manufacturers of off-patent hormonal-contraceptive products appear ready to compete in the international procurement business, provided they adopt quality-assurance and safety-monitoring systems that meet international standards. Some forward-thinking entrepreneurs, such as Famy Care in India and A.N.B. Laboratories in Thailand, already have made significant inroads in this business area.

Manufacturers of branded biosimilar products also may be appropriate partners in public/private initiatives targeting the so-called commercial *middle market*, between high-priced R&D brands and subsidized products. Market distortions caused by untargeted subsidized programs, however, will need to be addressed in order to create incentives for these manufacturers.

A Look to the Future

Many countries have adopted policies on generic medicines and bioequivalence regulations that improve the affordability and safety of the drug supply. Bioequivalence-testing programs, however, remain too costly for developing countries and can be a threat to the local pharmaceutical industry. As a result, emerging markets are likely to remain dominated by R&D companies, suppliers of untested biosimilar brands, and contract manufacturers serving the public sector. However, a growing number of entrepreneurs with ambitions to conquer foreign markets understand that bioequivalence testing is the cost of doing business in an increasingly regulated pharmaceutical environment. At least one expert suggested that donors fund such testing for products made by low-cost manufacturers that commit to a quality assurance program (Zardo 2005). The combination of generic substitution programs, market-building policies, and competitive forces can profoundly change the dynamics of the contraceptive market, bringing users in the developing world a choice of sustainable, high-quality products at prices they can afford.

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