Partners for Population and Development

A study on the manufacture of hormonal contraceptives in China, India and Thailand

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1. Introduction

Partners in Population and Development (Partners) is an inter-governmental alliance of 19 developing countries which are: Bangladesh, Benin, China, Egypt, The Gambia, India, Indonesia, Jordan, Kenya, Mali, Morocco, Nigeria, Pakistan, Senegal, Thailand, Tunisia, Uganda, Yemen and Zimbabwe.

Partners has endeavoured to support and encourage its member governments in achieving one of its goals to "Expand and improve South-South collaboration in the fields of Family Planning and Reproductive Health". As such, it has looked at how member governments could help each other in expanding the use of affordable products for reproductive health that are manufactured by industry in their countries. This was the theme of the Forum held in Kochi, India in 2001, which produced an Agenda for Action.

The following Partners Annual Board Meeting held in Jakarta, Indonesia in October 2003 declared that "We pledge commitment to work on the Kochi Agenda for Action by: Establishing mechanisms for sharing affordable commodities through South-South networks; ……"; and in the next meeting in Wuhan, China in September 2004, agreed to "Commit ourselves to use best practices and share resources including reproductive health commodities, among developing countries for effective reproductive health policies, programmes and services aimed at improving the quality of life of women, men and children."

Partners is also a member of the international Reproductive Health Supplies Coalition. The Coalition comprises representatives of organizations and constituencies that have a significant financial and/or programmatic stake in RH supply security. It provides a forum for sharing information and works to resolve supply problems and ensure long-term RH supply using new and existing resources and expertise.

The issue of adequate supply of contraceptives remains problematic and requires significant inputs by member governments. 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 a recent paper for WHO's Commission on Intellectual Property Rights, Innovation and Public Health, entitled "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?", I argued that for hormonal contraceptives, there is little need to establish new facilities to meet the demand for supplies but that attention should focus on developing a network of existing companies that can supply people in the developing world with products that are affordable and accessible (Hall, 2005).

A network of high quality manufacturers in the developing world could be the best safeguard the international community has to achieve a continuing supply of

affordable reproductive health commodities. This network should comprise a group of manufacturers which are willing to:

- ensure that their production facilities meet modern standards of GMP;
- access or produce the active pharmaceutical ingredients (APIs), manufactured to accepted standards of GMP with fully documented drug master files;
- allow regular manufacturing audits, as well as audits of manufacturing costs;
- participate in an international quality control programme;
- agree to preferential pricing for the public sector; and
- establish clear milestones for market access and quality manufacturing .

As a first step in the development of a network of qualified suppliers of hormonal contraceptives, and in order to respond to its declarations referred to above as well as to input into the work of the Reproductive Health Supplies Coalition, Partners decided to undertake a study on the generic manufacture of hormonal contraceptives in China, India and Thailand. Partners commissioned a consultant to identify and visit a group of pharmaceutical companies currently manufacturing hormonal contraceptives in China, India and Thailand to ascertain their potential role in addressing the need for affordable, quality contraceptives in low income countries and how they can help bridge the contraceptive commodity gap.

The plan for dissemination of the initial results of the study was to report the findings at two meetings organized by Partners, together with the Indian Ministry of Health and Family Welfare. The first was a small consultative meeting on “The role of generic products in meeting reproductive health commodity needs in lower and middle income countries” involving key stakeholders from lower and middle income countries and include a group of manufacturers of hormonal contraceptives from India and Thailand. This was held in New Delhi on 19 November. The second was an International Forum on Integration of ICPD Goals & Millennium Development Goals in Agra, 21-22 November.

2. Methodology

Visits were paid to six companies in Beijing, Chengdu, Shanghai and Zhejiang in China, three companies in Ahmedabad, Chennai and Mumbai in India, and seven companies in Bangkok, Thailand in October and November 2005.

The study involved open-ended interviews with senior staff of each of the companies, including production and marketing staff where possible. Visits were also paid to the manufacturing facilities and laboratories. The questions addressed to each of the companies were:

- What are the company’s business goals for oral contraceptives, injectable contraceptives and emergency contraception in the domestic market and or in the international market?
- What competence does the company have in export of products and selection of distributors in other countries? Has the company ever developed a registration dossier for another country, if so, was this to ICH requirements?
- Has the company ever competed in a national or international tender to supply hormonal contraceptives? If so, for which tendering body and what was the outcome?

- What is the manufacturing status of hormonal contraception?
  - has the company received national GMP certification, if so, when?
  - has the company been evaluated by any international assessor, if so, by which organization, when and by whom?
- Where are the APIs sourced from? Does the company have access to the Drug Master File and a CMC dossier that would allow registration in more stringent regulatory situations?
- Would the company be willing to agree to periodic quality audits and participate in an independent quality assurance programme?
- Has the company ever commissioned bioequivalence studies, if so, on what products and where?
- If the company is not currently exporting product, what would be required to achieve this, both in terms of manufacturing facility and documentation?
- Has the company been visited by other public sector or social marketing agencies? If so, does there appear to be competing agendas or a lack of clarity on the international agenda?

3. Visits to China, India and Thailand

3.1 China

With regard to the manufacture of pharmaceuticals, 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 still have to be imported. However, China's pharmaceutical market is growing at an annual rate of 15% with the pharmaceutical market valued at over $6 billion.

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 mixed and very, very few companies meet international GMP standards. 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.

This has resulted in significant changes in the organization of the pharmaceutical industry with several companies having been pulled together under the same general management, eg, the Shanghai Pharmaceutical Group (SPGC). SPGC, within its corporate structure, has several companies which are now being brought to international standards using a panel of consultants, however, there are still companies in the group which continue to have political constraints and still exist in a previous era.

In the field of contraception and reproductive health, there are a small number of small pharmaceutical companies that produce a range of oral contraceptives, once-a-month pills, once-a-month 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 then Chinese State Family Planning Commission (SFPC), now the National Population and Family Planning Commission (NPFPC).

Table 1. Companies in China and products being manufactured[1]

Company	Product	Name
Oral contraceptives		
Beijing Zizhu*	*LNG 150µg EE 30µg*	Compound LNG tablets
Nanjing Baijingyu*	*LNG 150µg EE 30µg*	Compound LNG tablets
Sichuan Huaxi*	*LNG 50/75/125µg EE 30/40/30µg*	Triphaser
Shanghai Sine Kang Jie*	*NET 600µg EE 35µg*	Compound NET tablets
Zhejiang Xianju*	*NET 600µg EE 35µg*	Compound NET tablets
Other tablets		
Shanghai Sine Kang Jie*	MEG-Ac 2mg EE	Pill no2
Shanghai Sine Kang Jie*	NET	
Emergency contraceptive pills		
Beijing Zizhu*	*LNG 1.5mg*	Yu Ting
Shanghai Sine Kang Jie*	*LNG 1.5mg*	
Injectables		
Shanghai General*	*MEG-Ac 25mg Estradiol 3.5mg*	
Shanghai General*	MPA 150mg (not for contraception)	
Zhejiang Xianju*	*NET-EN 50mg EV 5mg*	
Shanghai Xudong Haipu	17OH-prog cap EV	Injectable No1
Other companies		
Amersin/Hubei Pharmaceutical	?	
Hubei Pharmaceutical (other)	?	
Shanhai Dahua Pharm	Jadelle generic	
APIs		
Beijing Zizhu*	LNG, EE, MF	
Zhejiang Xianju*	MPA, NET, NET-Ac, MEG-Ac, desogestrel, drospirenone	
Amersin/Hubei Pharmaceutical	LNG (DMF with USFDA)	

[1] Companies visited are shown by * and products being purchased by CCSDC are shown in italics.

There are some eight or nine manufacturers of hormonal contraceptives in China. A group of six companies were identified by the China Contraceptive Supply and Development Centre (CCSDC) of NPFPC for visits, these are listed in Table 1. Five companies produced oral contraceptives, one injectables and one both orals and injectables. All were contractors to CCSDC.

Despite visiting CCSDC's 3rd China Reproductive Health/Family Planning New Technologies & Products Expo, which was held in Beijing, 16-19 November 2006, it was difficult to obtain information on other companies manufacturing hormonal contraceptives in China. There are at least, two companies manufacturing in Hubei province, one now part of an US joint venture. Further information still needs to be obtained. There are also two companies manufacturing six-rod and two-rod implants which should also be visited on a future occasion.

Each of the six principal companies manufacturing oral and hormonal contraceptives under tender to the government of China through CCSDC have enormous production overcapacity, most companies produce their annual quota of oral and injectable contraceptives in 4-6 weeks, once they receive their annual government order.

Although all factories visited comply with national GMP, it is unlikely that any would meet PICS[2] or any stringent regulatory authority requirements. While all factories had made significant efforts to upgrade their facilities in recent years, there is a wide variation between the factories in terms of their facilities and the way in which product flow and worker safety was handled. Although actual production was only observed in two of the six factories, in one of those we observed poor material handling procedures and inadequate worker protection during the process of tableting ethinyl estradiol.

None of the injectable manufacturers in China are producing sterile product by design, the normal practice being to use steam for post-manufacture sterilization. This was the practice at both Shanghai General Pharmaceutical and Zhejiang Xianju, and we were informed to be the practice at Shanghai Xudong Haipu, which still manufactures Injectable No 1.

There were also significant differences between the factories visited in terms of laboratory instrumentation, standard laboratory operating procedures and in the condition and environment of laboratories.

Few companies have the capability of developing registration dossiers required for the export of products to countries with strict regulatory requirements. This is both in terms of technical content as well as language ability. Several companies raised this issue and stated that they would like assistance in this area.

While it is unlikely that it would be necessary to undertake full bioequivalence studies on several products being produced, dissolution studies probably being adequate, there was a significant difference between companies in their understanding of bioequivalence. Several companies had undertaken some pharmacokinetic/ pharmacodynamic studies in local university clinical departments but it was difficult to ascertain what had been the comparator products used and to find out what the investigators knew about Good Clinical Practice (GCP) in terms of the conduct of the

[2] The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme are two international instruments between countries and pharmaceutical inspection authorities, which provide active co-operation in the field of GMP.

studies or Good Laboratory Practice (GLP) for the analysis of blood specimens collected.

Two of the companies visited, Beijing Zizuh and Zhejiang Xianju, manufacture steroid APIs and have been inspected and approved by the USFDA for certain products. Beijing Zizuh supplies some 55% of the steroid hormone APIs used in China and exports levonorgestrel and ethinyl estradiol to India and levonorgestrel to Europe. While this company provides 70% of the levonorgestrel ECPs and 30% of the monophasic LNG COCs ordered by CCSDC, it also is a major producer of the once-a-month pill (see below and section 4.3) and supplies more than 50% to the Chinese market as well as exporting to Viet Nam. The Beijing Zizuh production facility was subsequently visited by Humberto Zardo on behalf of the Concept Foundation, Bangkok and IPPF/ICON and his assessment will be available shortly.

The China Contraceptive Supplies Centre (CCSDC), which is part of NPFPC and is responsible for tendering for contraceptives for the national programme in China, make annual allocations for COCs, once-a-month injectables and emergency contraceptives. For 2005, the government tender was for COCs and ECPs, 46 million packs and 3.5 million doses for once-a-month injectables. This represents the bulk of hormonal contraception production by the major manufacturers, which provide 85-100% of their production for the government tender. The balance goes to the fledgling private pharmacy sector in urban areas. The major sales in the private sector are by the international companies, Schering and Organon.

Currently, CCSDC is purchasing the following products:
Combined oral contraceptives (COCs):
Monophasics. LNG 150ug + EE 30ug; and NET 600µg + EE 35µg
Triphasic, LNG 50/75/125µg + EE 30/40/30µg
Emergency contraceptive pills (ECPs):
LNG 1.5mg
Combined injectable contraceptives (CICs, once-a-month injectables):
Megestrol acetate 25mg + estradiol 3.5mg; and
NET-EN 50mg + estradiol valerate 5mg

As discussed In section 4.3, in response to the SIPPR review, the CCSDC no longer includes the once-a-month pill (levonorgestrel, 6mg + quinestrol, 3mg) on its procurement list. In addition, CCSDC has phased out Injectable No 1, however, there has not been a systematic review of the other once-a-month injectable contraceptives, although NET-EN 50mg + estradiol valerate 5mg was originally developed by WHO.

It is understood that CCSDC will eventually phase out the monophasic COCs in favour of the triphasic preparation. This was born out during my visit when purchases for 2006 were discussed with suppliers by CCSDC. The company manufacturing the triphasic LNG/EE pill had its order increased from 3.09 million packs in 2005 to 3.68 million for 2006. However, they are expecting to supply 12 million packs in 2007, as the monophasics, LNG/EE and NET/EE are decreased. This issue was also reviewed in the SIPPR systematic reviews and is discussed in section 4.3.

3.2 India

The Indian pharmaceutical industry has about an 8% share of global pharmaceutical production and is valued at some $10bn. The drug sector has some 300 large and moderate-sized firms, plus 10,000 small companies. Some 70% of production is by the top 100 firms and about a third is exports, which are rising by 25% a year. 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.

Despite there being such a huge drug manufacturing sector in India, very few companies produce hormonal contraceptives. There are two international companies, Wyeth and Organon which sell their companies range of products to the private sector. Organon has recently launched its Implanon in the private sector. Neither company competes for government tenders nor manufacturers low cost generics. In 2004, Organon moved from Kolkata to Mumbai and in the process sold its steroid manufacture plant to a private company which now undertakes contract manufacture of Organon's products. The same toll or contract manufacturer makes a small quantity of COCs (10,000 packs in 2005) for a device manufacturer, Contech, which markets them in the private sector under the brandname, Marilyn.

One of the biggest Indian companies, Zydus Cadila acquired the Schering subsidiary, German Remedies, in 2001, which it has absorbed into Cadila Healthcare Ltd. I visited Zydus in Ahmedabad but at the time of the visit, the company was in the process of completing final batch trials in a new separate steroid hormone production facility. The facility is likely to produce commercial products from the second quarter of 2006, following a final audit by staff of Schering AG. It will manufacture products under license for Schering AG, as well as producing generic contraceptives. It has launched Ecee2, a LNG ECP.

Table 2. Companies in India and products being manufactured[3]

Oral contraceptives	
Famy Care*	GoI supplier of Mala-D, also has a large range of branded COCs: LNG 150µg + EE 30µg, LNG 150µg + EE 50µg, LNG 125µg + EE 30µg, LNG 250µg + EE 50µg, LNG 250µg + EE 30µg, LNG 100µg + EE 20µg, NG 500µg + EE 50µg, NG 300µg + EE 30µg, desogestrel 150µg + EE 30µg, gestodene 75µg + EE 30µg, cyp-ac 2.0mg + EE 30µg, all are also available with Fe, LNG 50/75/125µg + EE 30/40/30µg, LNG 150/200µg + EE 30/40µg; POPs: LNG 30µg LNG, NG 75µg, NG 70µg, lynestrenol 500µg; and an ECP, LNG 750µg.
HLL*	Principal GoI supplier of Mala-D. Government-owned company. In private market sells an ECP, LNG 750µg and is starting desogestrel 150µg + EE 30µg and importing DMPA.
IDPL	GoI supplier of Mala-D. Government-owned company
Organon	Supplies Organon range of oral contraceptives to private sector, now produced by contract manufacturer.
Phaarmasia	GoI supplier of Mala-D. Own brand NG300µg + EE30µg + Fe
Wyeth India	Supplies Wyeth range of oral contraceptives to private sector
Zydus Cadila* (German Remedies)	Will manufacture Schering range of oral contraceptives to private sector as well as develop generic products and sells an ECP, LNG 750µg

[3] Companies visited are shown by *

Organon, Wyeth and Zydus Cadila primarily supply the private pharmacy sector in urban areas. The private sector supplies <5% of the COCs manufactured in India and an extremely small quantity of DMPA from Pfizer. However, it would appear that ECP use is increasing rapidly.

As shown in Table 2, there are two other private companies, Famy Care and Phaarmasia and two government-owned companies, Hindustan Latex Ltd (HLL) and IDPL. These four companies are the government contractors for COCs and ECPs. The volume of product provided through government tenders for COCs, 2002-2005 are shown in Table 3. I was informed that from the financial year 2005-6, HLL will automatically receive 55% of the government tender for COCs and that the balance will be divided between the other three companies. Famy Care, HLL and Phaarmasia also supply products to DKT, PSI, PSS and Janani for social marketing. This is a sector which has increases considerably in recent years.

Table 3. Indian government tenders for COCs, 2002-2005

Year	HLL		Phaarmasia		IDPL		Famy Care		Total
	million cycles	%	million cycles	%	million cycles	%	million cycles	%	million cycles
2002-3	50.0	44.80	25.7	23.07	10.0	7.80	25.7	23.70	111.4
2003-4	58.0	46.03	28.5	22.62	12.0	9.53	27.5	21.82	125.0
2004-5	55.0	44.00	27.5	22.00	15.0	12.00	27.5	22.00	125.0

The government tender for COCs represents 100% of the production of Phaarmasia and IDPL and as can be seen in Table 3, these are relatively small volumes. For Famy Care this represents about 40% of their production and for HLL, some 95%. Neither Phaarmasia nor IDPL were visited on this mission. IDPL in recent years has tottered on brink of closure and I was unable to make contact with them. However, at the time of my visit, GoI announced a substantial financial bale-out of IDPL, citing the need to make essential drugs available at a more affordable cost. I was also unable to visit Phaarmasia but understand that their facility, like that of IDPL, requires significant upgrading to comply with international GMP standards, despite them both having received WHO GMP certification.

While HLL is primarily a condom manufacturer, it is the principal supplier of COCs to government and is trying to expand its hormonal contraceptive market in India and to respond to international tenders. It also is the sole supplier of Centchroman, CDRI a non-steroidal anti-estrogen developed by the Central Drug Research Institute. This is a once-a-week pill marketed as Saheli, however, its efficacy is rather low. As well as manufacturing Mala-D for the public sector, it now produces a desogestrel COC and a LNG ECP for the private sector. It is trying to expand its hormonal contraceptive range by importing a generic DMPA from South Africa and has been involved in trying to get the Chinese once-a-month pill imported into India (see section 4.3).

HLL has a stand alone hormonal contraceptive facility near Belgaum and is intending to improve its GMP standards at this site. While it has participated in several international tenders, HLL as yet does not have the expertise to submit registration dossiers in other countries. This is something that it wishes to develop over the coming year.

Famy Care is the most active generic manufacturer in India. As well as suppling COCs to government and to social marketing organizations in India, it has registered, branded OCs in numerous countries in Asia, Africa and Latin America, as well as

Australia, and has applied for registration in a further 27 countries. It has a network of 45 distributors to support export to these countries. It exported >100 million cycles to 18 countries in 2005, including the private sector in 6 countries. It is in the process of finalizing registration dossiers for submission in Europe and the USA. The company has commissioned bioequivalence studies on three COCS, LNG 150µg + EE 30µg, NG 300µg + EE 30µg and the LNG triphasic product and the LNG POP. These studies were undertaken by a Mumbai based contract research organization.

Because it has become well known in recent years, the production facilities of Famy Care have been inspected by inspectors commissioned by Crown Agents for UNFPA and for PSI. It was subsequently visited by Humberto Zardo on behalf of the Concept Foundation, Bangkok and IPPF/ICON and his assessment will be available shortly. In terms of generic manufacturers, other than Zydus Cadila when it begins final production, Famy Care is the only company likely to pass international GMP. It is recommended that HLL get an international factory inspector to review its facility at Belgaum.

3.3 Thailand

Thailand has had a significant generic hormonal manufacturing base for almost 30 years. Generic formulations of the injectable contraceptive, depot medroxy-progesterone acetate (DMPA), were developed in the late 1970s when the government began tendering for contraceptives. Production by the major manufacturers continued for many years to be primarily in response to government tender. However, this was stopped in 2002 when responsibility for procurement was decentralized to regional hospitals purchase for regions, after which purchases have become less predictable. The volume of contraceptive products sold in the private market, especially in pharmacies, is now higher than that provided through the public sector.

Table 4. Companies in Thailand and products being manufactured[4]

Injectable contraceptives	
ANB Laboratories*	DMPA, 150mg/ml
General Drug Houses Co Ltd*	DMPA, 150mg/3ml
Olan-Kemmed Co Ltd*	DMPA, 150mg/3ml
Thai Nakorn Pattana Co Ltd*	DMPA, 150mg/3ml
Umeda Co Ltd*	DMPA, 150mg/3ml
Vesco Pharmaceutical Ltd Part*	DMPA, 150mg/3ml
Oral contraceptives and ECPs	
Asian Union	NG+EE; NET+mestranol+Fe
Biolab Co Ltd	LNG; LNG+EE; cyp-ac+EE
Brywood Pharmaceutical Ltd Part	LNG; NG+EE; LNG+EE; NET+EE; norgestimate+EE; NET+mestranol+Fe; ethynodiol diac+EE+Fe
Cox Laboratories*	NG+EE; LNG+EE; cyp-ac+EE
Lerd Singh	LNG+EE
Pond's Chemical (Thailand)*	LNG; NG+EE; LNG+EE; cyp-ac+EE; NET+mestranol+Fe
Thai Nakorn Pattana Co Ltd*	NG+EE; LNG+EE; lynestrenol+EE; NET+mestranol; lynestrenol

[4] Companies visited are shown by *

The surprising thing in Thailand is that there are some 18 companies which claim to be able to manufacture DMPA. Of these, 11 have been approved by Thai FDA (although one has requested suspension for renovation); nine of these companies are on the government-approved list for hospital purchase. Similarly there are nine manufacturers approved by Thai FDA to manufacture oral contraceptives (one has requested suspension for renovation and one is only making a lynestrenol POP); three companies are on the approved hospital purchase list.

A group of five companies were identified as being the major manufacturers of DMPA; four, the major producers of oral contraceptives; and one of both orals and injectables. These are listed, together with all the the companies approved by the Thai FDA and the products they manufacture, in Table 4. Because of the unavailability of senior staff during the time of my visit, it was only possible to visit five companies manufacturing DMPA, and two producing oral contraceptives. Thai Nakorn Pattana was visited by Khun Wanapa of the Concept Foundation on my behalf. The TNP production facility was also subsequently visited by Humberto Zardo on behalf of the Concept Foundation, Bangkok and IPPF/ICON and his assessment will be available shortly.

In 2004, companies in Thailand manufactured some 42 million cycles of oral contraceptives. These were: LNG 150µg + EE 30µg, 36.0 million (86.1%); norgestrel 300µg + EE 30µg, 4.0 million (9.5%); and other products, 1.8 million (4.4%). With regard to the three-monthly injectable DMPA, some 7 million vials were produced, of these, 6.15 million vials (87.7%) were of a dosage of 150mg/3ml and 0.86 million vials (12.3%) were 150mg/ml.

Two companies have supplied DMPA for tender by KfW, ANB to Nepal and Thai Nakorn Pattana (TNP) to Cambodia. Vesco has also exported to the private sector in Cambodia and TNP to other countries in south-east Asia. TNP has also exported contraceptive products to Viet Nam, Laos, Australia, and Ghana and its facilities have been inspected by representatives of the FDAs of these countries. TNP is the only Thai hormonal manufacture to export significant quantities of product, about one-third of their production of OCs and injectables are exported.

In Thailand several of the factories had been inspected by the Thai FDA in the past five years and had made significant upgrading of their facilities since that time. Several were scheduled for new inspections in the coming year. However, Thailand has applied for PICS membership and has informed its will apply PICS GMP in 2-3 years. The PICS GMP requires that hormonal steroid products should be produced in a physically separate facility, only TNP has separate buildings for its hormonal product lines.

Given the increasing cost of APIs, several companies are beginning to source APIs from China, rather than from Italy and Spain. One company has two branded DMPA products differentiated by name and price depending on whether the API was sourced from China or Europe and another is considering doing the same. TNP continue to import APIs from Europe and the USA. None of the Thai manufacturers have undertaken bioequivalence studies on any of their hormal contraceptive products

4. Discussion

4.1 Use of contraception in China, India and Thailand

Table 5 shows the prevalence rates for modern contraceptives in China, India and Thailand. These represent the latest figures available but it is acknowledged that these are old data, for example, the Indian data were collected in 1998, making it difficult to make valid conclusions on current use. The table shows that in both China and India, the use of hormonal contraception is extremely, while the use of both oral and injectable contraceptives is high in Thailand, contributing significantly to the high overall prevalence of contraceptive use.

Table 5. Prevalence rates for modern contraceptives in China, India and Thailand

	Year	Prevalence of modern methods	Sterilization	OCs	Injectables	Implants	IUDs
China	1997	83.3	41.2	1.7	0.4	<0.01	36.4
India	2000	42.8	36.1	2.1	0	0	1.6
Thailand	2000	79.2	23.8	26.8	22.0	1.5	3.1

Table 6 puts these prevalence rates into context with the rest of the world and also makes an attempt to quantify the numbers of women using these methods. Unfortunately, the UN Population Division compilations published in 2003, only refer to married women of reproductive age, making real comparison of overall use in different countries difficult.

Table 6. Estimated number of married women of reproduction age using oral and injectable hormonal contraceptives in different regions and the study countries

	Total no of married women of reprod age ('000s)	Prevalence of modern methods (%)	No of women ('000s)	OCs (%)	No of women ('000s)	Injectables (%)	No of women ('000s)
World	1,043,265	54.0	563,363	7.2	75,115	2.6	27,125
More dev'd regions	170,043	55.3	94,034	15.7	26,697	0.7	1,190
Less dev'd regions	873,223	53.7	468,920	5.7	49,774	3.0	26,197
China (1997)	263,325	83.3	219,350	1.7	4,477	0.4	1,053
India (2000)	195,818	42.8	83,810	2.1	4,112	0	0
Thailand (2000)	10,862	79.2	8,603	26.8	2,911	22.0	2,390

(UN Population Division, World Contraceptive Use, 2003)

I have attempted to reach an estimate of the anticipated number of packs of oral contraceptives and the number of doses of injectable contraceptives (allowing for the fact that once-a-month injectables are used in China and three-monthly injectables are used in Thailand) from these prevalence data. I have also allowed for women discontinuing treatment, say, by using a somewhat arbitary 12-month life table rate of 50%. Table 7 shows a comparison of these estimates with the actual number of cycles and doses manufactured in 2004-5. The figures indicate a small increase in oral contraceptive use in China and Thailand in the years since the surveys were undertaken but a three to four-fold increase in use in India. With regard to injectable use in Thailand there is little change but there is a significant decrease in China, which agrees with perceptions of use in those countries.

Table 7. Use of COCs and injectable contraceptives in China, India and Thailand

	Year	OCs	Anticipated no of cycles (millions)	Actual no of cycles, 2004-5 (millions)	Injectables	Anticipated no of doses (millions)	Actual no of doses, 2004-5 (millions)
China	1997	1.7	40-50	50-60	0.4	8-10	3.5
India	2000	2.1	35-40	135	0	0	>0
Thailand	2000	26.8	25-30	42	22.0	7-8	7.0

4.2 Production of hormonal contraceptives

The enormous production capacity for hormonal contraceptives in China is a consequence of the tendering process, in which companies that have not diversified into the fledgling private sector or have not tried to develop export markets, await their government order, which is announced in mid-late November each year, and then manufacture their requirements at the beginning of the following year. This is a hangover from a central command economy but is likely to change in coming years as China's pharmaceutical industry is forced to become both comply with modern GMP standards and become competitive.

I was able to discuss this with both Dr Zhao Baige, Deputy Minister, NPFPC and with UNFPA, Beijing. Dr Zhao is extremely keen to see very keen to see a group of Chinese companies being able to achieve international standards of GMP for the manufacture of hormonal as well as other contraceptives not only for supply within China but for export to other developing countries. In addition, as discussed in section 4.3, she would also like assistance to be provided to NPFPC to ensure that only products of adequate safety and efficacy are being used in China. As a consequence, it is anticipated that UNFPA will include a budget line in its new 2006-2010 country programme that would assist a group of Chinese manufacturers to achieve this.

In Thailand, except for one company, most companies also only manufacture DMPA over a period of 4-6 weeks each year. This again is a hangover from central government tendering which was terminated in 2002. However, it is becoming uneconomic for companies to maintain these facilities and as discussed above Thailand will apply PICS GMP in 2-3 years.

The PICS GMP requirements infer, although they are slightly ambiguous, that hormonal steroid products should be produced in a physically separate facility, This

is being applied in Europe and the USA and is now required by Brazil. As such, since only one of the Thai factories currently has a completely separate hormone facility this will require hard commercial decisions as to whether how many, if any, of the companies will make this significant financial investment. These considerations also apply to manufacturing facilities in China, where most are not located in separate buildings. In India, both Zydus Cadila and Famy Care have separate dedicated hormone facilities.

4.3 Product issues

There several issues about which hormonal contraceptive products are being produced and which should be considered for manufacture by producers of generic formulations.

Products with inadequate safety and efficacy data

In India and Thailand, most products being manufactured are generic versions of products developed by international pharmaceutical companies. This is also true in part in China, although in China there are also products which 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 which could not be registered in other countries because of lack of preclinical and clinical data. The CCSDC, however, has addressed this issue in regard to the majority of the products it purchases for the national programme.

The Shanghai Institute of Planned Parenthood Research (SIPPR), with the assistance of WHO, Geneva, undertook a systematic review of the widely-used once-a-month pill along with others on other methods. The results were reported at a national meeting in Shanghai in April 2004, where it was agreed that “There is sufficient evidence to state that the dose of the cyclopentyl ether of ethinyl estradiol, which is metabolized to ethinyl estradiol, of the once-a-month pills is far too high for it to be safe in longer term use. The rate of short-term side effects of the once-a-month pills is high and the discontinuation rate is high. The NPFPC should start preparations to phase out once-a-month pills.”

CCSDC immediately acted on this and discontinued the once-a-month pill from its procurement list. It was not included in the 2005 or the recently completed 2006 tender orders. 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). CCSC also no longer supply this product through the national programme.

There has recently been a memorandum of understanding signed between the governments of India and China on collaboration between Indian and Chinese companies in the area of family planning. Unfortunately, under this, one of the government-owned companies in India is considering importing the Chinese once-a-month pill into India. It is imperative that the Indian the task force on contraceptive research which includes representatives from government, the Indian Council for Medical Research, government-owned companies and UNFPA, consider the evidence from China and do not introduce this product into the Indian national family planning programme.

WHO's Model List of Essential Medicines

With regard to combined oral contraceptives (COCs), progestogen-only pills (POPs), emergency contraceptive pills (ECPs) and progestogen-only injectable contraceptives (POIs), clear guidance is given in the WHO 14th Model List of Essential Medicines (2005), see Box 1. While WHO's Expert Panel on Essential Medicines will consider expanding this list at its meeting in March 2007, it is unlikely that the COCs, POPs,POIs and ECPs will be changed, more likely additional contraceptive method types, such as combined (or once-a-month injectables and implants will be added.

Box 1. WHO Model List (revised March 2005)

18.3.1 Hormonal contraceptives

Oral contraceptives
ethinyl estradiol + levonorgestrel, tablet, 30µg+150µg
ethinyl estradiol + norethisterone, tablet, 35µg+1.0mg
levonorgestrel, tablet, 30µg

Emergency contraceptives
levonorgestrel, tablet, 750µg (pack of two), 1.5mg

Injectable contraceptives
norethisterone enantate, oily solution, 200mg/ml in 1ml ampoule
medroxyprogesterone acetate, aqueous microcrystalline suspension, 150 mg/ml in 1ml vial

Racemic mixtures

There are a couple of important issues that arise from the recommendations from WHO's Model List of Essential Medicines. The first is the question of the use of the progestogen, norgestrel (a racemic mixture) versus its active isomer, levonorgestrel.

In 1992, the Food and Drug Administration (FDA) issued new guidelines governing stereoisomerism in new-drug development. The guidelines strongly encourage the development of single isomers and discourage stereoisomeric mixtures. Nevertheless, this remains the major COC supplied by Wyeth for USAID, since it allows Wyeth to differentiate between products for the public and private sectors. Levonorgestrel is the preferred product and there is neither need nor justification for generic manufacturers to produce norgestrel containing COCs or POPs.

Multiphasic formulations

The other issue relates to monophasic v bi/triphasic preparations. 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. These allowed the companies to bridge the patent gap before a new progestogen could be made available. In fact, the SIPPR systematic reviews concluded that "The NPFPC may wish to give priority to provision of the monophasic levonorgestrel daily pill, since systematic reviews have shown that triphasic pills have no advantage over monophasic pills, in particular, they do not have higher continuation rates, and are

more expensive to manufacture. Moreover, practically all long-term safety data refer to monophasic pills." Nevertheless, as stated in section 3.1, it is understood that CCSDC is going to slowly phase out the monophasic COCs in favour of the triphasic preparation.

New progestogens

The final issue for generic manufacturers relates to which progestogen should be included in COCs and POPs. There are now many different progestogens available, often referred to in "generation" terms since they have appeared at the end of the patent life (or extended patent life, see multiphasic preparations above). We are now into the fourth generation of progestogens, with products such as drospirenone becoming available. Since this is still on patent such products tend not to be copied at once by generic manufacturers, although the Zhejiang Xianju company has begun manufacturing the API.

In reality, unless they are going to compete in the US or European markets there is little need for generic companies to manufacture the "latest" product that has come on to the market, at least not on the grounds of being able to sell a "better" product. Whenever 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. However, there are rarely any studies to back these claims up and there are never comparative trials to support them, moreover, 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. Essentially, the new product under patent protection is there for the company to protect its market share of the $2 billion US market and the $0.5 billion market of France, Germany and the UK.

WHO/HRP did a major comparative study on oral contraceptives and cardio-vascular effects and showed that women using the third generation progestogens, gestodene and desogestrel, had a statistically higher risk of venous thromboembolism (VTE) than the second generation levonorgestrel. It is accepted that the overall risk of death from VTE is extremely low, however, these products had been advertised as having a lower risk of cardio-vascular problems. Unfortunately, this remains a unique study and could only be done after long term use of products. There have never been comparative Phase III trials of new products, nor a comparison of a new product with those existing, although WHO/HRP is currently undertaking a Phase III study comparing the two implants, Jadelle and Implanon.

Dosage of DMPA

The dosage form of DMPA recommended in WHO's Model List of Essential Medicines (see Box 1) is 150mg/ml. All but one of the Thai manufacturers make this injectable as a 150mg/3ml formulation, which since it is given as a deep intramuscular injection means that it is a far more unpleasant injection for women. Although there is some dispute as to whether a smaller gauge needle can be used with the higher volume, the reason for the higher volume is purely historical. As stated in section 3.3, Thailand began manufacture of generic DMPA formulations in the late 1970s, at which time DepoProvera was available from Upjohn at this dose. This was accepted as the Thai standard, which, unlike the USA, has never been changed. Even though KfW has purchased generic DMPA from a company in Thailand for Cambodia, this is not the internationally accepted dose and should be changed.

5. Conclusions and recommendations

5.1 Production of oral and injectable hormonal contraceptives

The principal conclusions from the study are that:

- There is enormous production overcapacity, particularly in China and Thailand, where most companies produce their annual quota of oral and injectable contraceptives in a single period of 4-6 weeks in a year.
- Although all factories visited have received national GMP certification, there are still significant disparities between them and a very small number would meet PICS or any stringent regulatory authority requirements for GMP.
- Most companies are finding that APIs from European sources to be expensive but that they cannot easily obtain material made to acceptable GMP nor with the necessary drug master files to allow completion of registration dossiers.
- Few companies have the capability of developing registration dossiers required for the export of products to countries with strict regulatory requirements.

The overall question to be addressed by this study was “Can quality generic drugs help address the commodity supply and security needs of lower and middle income countries? The answer is a qualified yes, the qualifications being that:

a) the active pharmaceutical ingredients (APIs) are produced to internationally accepted GMP standards;
b) the production facilities for the hormonal contraceptives conform to internationally accepted GMP standards;
c) data are available to comply with regulatory requirements; and
d) the cost remains significantly lower than other available branded products.

Relatively few of the companies visited in China, India and Thailand would meet modern GMP standards, such as the PICS requirements, today. However, several could relatively easily achieve this in the medium term. It is ***recommended*** that they seek assistance by contracting factory inspectors from the European Union or other countries that are signatories to PICS to undertake a full review of processes, standard operating procedures and documentation and make recommendations of what the companies need to do meet international requirements. Once the company has undertaken these recommendations, and upgraded facilities where necessary, the inspectors should return and review what has been achieved. A similar technical assistance exercise could be undertaken with several manufacturers of APIs. It is ***recommended*** that such technical assistance is provided through bilateral or multilateral donors such as UNFPA. Companies will need to explore, however, whether it is feasible or commercially sound to raise the funding for investment in upgrading facilities.

Should the companies wish to continue to obtain EU, US or other stringent regulatory authority approval, or seek prequalification by WHO, and compete for international tenders, assistance could subsequently be provided on developing dossiers that meet regulatory requirements.

The development of prequalification activities on reproductive health commodities and particularly hormonal contraceptives is being planned by WHO. However, since this is such a critical component in assisting companies achieve the necessary

standards required for domestic use of products, as well their export, it is ***recommended*** that members of Partners should begin to pressure WHO to begin prequalification activities on RH commodities and particularly hormonal contraceptives now. This could be done by Ministers of Health tabling questions at the World Health Assembly in May 2006. A year lost is a year of fewer quality commodities/$, something that many countries can ill-afford.

It is also ***recommended*** that to assist both companies and procurers that UNFPA, together with WHO, establishes an independent quality assurance programme for the analysis of purity and content of generic hormonal contraceptives.

5.2 What else needs to be done?

It is ***strongly recommended*** that this inventory and review of companies manufacturing hormonal contraceptives in China, India and Thailand is extended to cover current manufacturers in other lower and middle income countries, as soon as possible. Both the Concept Foundation and UNFPA have expressed willingness to assist in this over coming months. It is further ***recommended*** that a joint publication is presented to members of the Reproductive Health Supplies Coalition at its meeting 27-28 April 2006.

While there is significant knowledge available from UNFPA and certain other procurement agencies on the generic production of IUDs and condoms, it is ***recommended*** that the exercise be extended to other RH commodities, particularly those products that are required, but are often unavailable, to implement safe motherhood programmes, such as oxytocin, magnesium sulphate and misoprostol.

It is ***recommended*** that in China systematic reviews are continued, particularly for the once-a-month injectable preparations. While I did not look into the current IUD situation as part of this study, given the advent of the Yuangong, MCu and the gamma IUDs, this exercise should also include continuation of systematic reviews of IUDs. It is anticipated that UNFPA will include a budget line in its new 2006-2010 country programme that would assist a group of Chinese manufacturers to produce products meeting international requirements both for use in China and for export; and to ensure that products produced have been adequately tested for safety and efficacy.

Many products are obtained through national or international procurement tenders. It is strongly ***recommended*** that such tenders, whether they be under World Bank or government specifications include quality criteria and not just price-related criteria. Stating that a factory must have obtained a certificate from national inspectors saying that it meets WHO GMP guidelines is inadequate, the factory must have obtained EU, US or other stringent regulatory authority approval and/or have been prequalified by WHO.

Even though generic pharmaceutical manufacturers are producing some 50% or more of the world's pharmaceutical products, there remains a considerable lack of knowledge about what generic products are. It is ***recommended*** that information is produced and disseminated to ensure that people understand that a prequalified quality product is a quality product whether it is manufactured in Berlin or Beijing, or Munster or Mumbai. Changing from a "Western" brand to a new "Southern" generic needs clear and accurate information to be provided at all levels - from the Minister to the client and, in particular, the health care providers. Health providers and consumers need to understand that properly produced generic products are as safe and effective as branded products.