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A study of the capability of manufacturers of generic hormonal contraceptives in lower- and middle-income countries

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Abstract

Purpose: Studies were undertaken to assess the capability, competence and capacity of manufacturers of oral and injectable hormonal contraceptives in lower- and middle-income countries.
Methods: A qualitative study on 41 companies, which comprised in-depth interviews and facility observations, was undertaken. Also an in-depth quantitative study of 14 companies was undertaken, of which 3 have not been included in the first study. Following review of a questionnaire and other documentation, a visit was undertaken to each factory to assess staff competence, manufacturing facilities, manufacturing processes, quality management, worker safety and environmental protection.
Results: Of the 44 companies from 15 countries, less than 30% would meet the current Good Manufacturing Practice requirements of the World Health Organization (WHO), the Pharmaceutical Inspection Cooperation Scheme or any stringent regulatory authority; a further 20% could comply with investment and improvements in quality management. Few companies are able to develop adequate registration dossiers.
Conclusion: There is a limited number of companies that are capable of manufacturing high-quality generic products and which can provide a complete registration dossier for use outside their home markets. It is essential that, in the future, procurement agencies only use suppliers that are prequalified by WHO for the procurement of hormonal contraceptives.

Keywords: Manufacture; Generic; Hormonal contraceptives; cGMP; Prequalification

1. Introduction

Contraceptive supply security is an issue of the highest importance and relevance for the economical and social development of most developing countries. Despite the growing private sector, the public sector remains the principal supplier of contraception in many developing countries. As such, purchasers, whether they are government departments or donor agencies, must be able to procure products for the public sector or social marketing programs at the lowest possible price.

In many countries in the developing world, Western donor agencies have been significant players in the purchase of contraceptives for supply to the public sector, mainly purchasing products from large multinational pharmaceutical companies. However, this assistance has become more tenuous over recent years. Furthermore, the population of reproductive-age couples in developing countries is expected to increase by 23% between 2000 and 2015 [1]. As such, demand for contraceptives exceeds supplies in many developing countries and is increasing.

While contraceptive users in the developed world generally have a broad choice of types and brands of contraceptives, users in developing countries are often limited in what they can buy and afford. This gap in product access has attracted generic pharmaceutical manufacturers to supply their own versions of lower-priced hormonal contraceptives as off-patent copies of popular

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originator brands. Thus, users in middle-income countries have gained access to a broader range of hormonal contraceptives, while those in low-income countries still do not have similar access opportunities. Despite the presence of generic pharmaceutical manufacturers, the issue of an adequate supply of quality contraceptives remains problematic in many countries.

In response to this growing crisis, a group of organizations and constituencies that have a significant financial and/or programmatic stake in reproductive health (RH) supply security, including donor agencies, procurement agencies and several governments of lower- and middle-income countries, have established the Reproductive Health Supplies Coalition. The coalition is working to resolve problems and ensure the long-term supply of RH commodities using new and existing resources, expertise and approaches [2].

One approach to improve access to and provide an adequate supply of hormonal contraceptives would be to use existing market forces and expand supply from generic manufacturers. It has been argued that there is little need to establish new facilities to meet the demand for supplies of hormonal contraceptives. Instead, attention should focus on the feasibility of developing a network of existing generic pharmaceutical manufactures in lower- and middle-income countries that could supply their products to people in the developing world provided that those products are of appropriate quality and are affordable and accessible [3].

To assess the feasibility of this approach and ascertain the situation in the generic manufacture of hormonal contraceptives worldwide, two studies have been undertaken, which are reported in this article. They focused on the manufacture of the injectable contraceptive, depot medroxyprogesterone acetate (DMPA), and levonorgestrel-containing tablets, which take any of the following forms: the combined oral contraceptive (COC), levonorgestrel, 150 μg+ethinyl estradiol, 30 μg; the progestogen-only oral contraceptive, levonorgestrel, 30 μg; or the emergency contraceptive, levonorgestrel, 750 μg or 1.5 mg. These are all products that are listed in the World Health Organization's (WHO's) Model List of Essential Medicines [4,5] and represent the most common products procured for the public

Table 1
Questions addressed during the qualitative study

Item	Questions
General	What hormonal contraceptive products does the company manufacture?
	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 is the company's production capacity and actual manufacturing volumes?
	If the company currently exports or is planning to export its products, what competence does it have in export and selection of distributors in other countries?
	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?
	Does the company have a research and development facility?
Manufacturing facilities	Is the steroidal manufacturing facility in a separate building? If not, is it completely separated from other production lines, with separate air systems, and so forth?
	What is the physical status of the overall manufacturing environment, in terms of state and finish of ceiling, walls, floor, illumination, doors and windows?
	Is the facility adequately equipped and what is the state of the equipment?
Manufacturing capability	Does the production management team have the necessary training and experience?
	Does the production staff have adequate training in cGMP and the necessary SOPs?
	Does the facility have national GMP certification, other international GMP certification or has it been evaluated by any international assessor?
	Is there evidence of adequate qualification and validation of all equipment and processes?
	What measures are undertaken to ensure worker protection and safety?
QC/QA	Is there appropriate quality management?
	Is there appropriate QC of each step of the manufacturing process?
	Are SOPs posted for each operation?
	What is the physical status of the laboratory, in terms of state and finish of ceiling, walls, floor, illumination, doors and windows?
	Is the laboratory adequately equipped and what is the state of the equipment?
	What measures are undertaken to ensure laboratory worker protection and safety?
	Are there adequate stability studies?
Documentation	Is there adequate documentation of QC at each step of the manufacturing process? Is this information computerized? If so, is it generated electronically or entered later?
	Are all batch data stored appropriately and easily retrievable?
	Where does it source APIs from and does it have access to a drug master file?
	Has the company ever developed a registration dossier for another country? If so, was this to ICH requirements?
	Is there documented complaints procedure?
	Has the company ever commissioned bioequivalence studies? If so, on what products and where?

sector of many developing countries. In October 2006, WHO expanded its Prequalification Program to include essential medicines for RH, starting with these products [6].

In reporting these studies, it should be noted that the information generated is company specific. It was collected on a one-to-one basis, with acknowledgement of its confidentiality. As such, no identification of the companies visited is given in this article.

2. Methods

2.1. Study 1. Qualitative study

A review of manufacturers of generic hormonal contraceptives, specifically, the injectable contraceptive, DMPA, and levonorgestrel tablets, including COCs, progestogen-only pills (POPs) and emergency contraceptive pills (ECPs), was undertaken. Companies from 13 lower- and middle-income countries [Brazil, Chile, People's Republic of (PR) China, Costa Rica, India, Indonesia, Mexico, Oman, South Africa, Republic of China (Taiwan), Thailand, Uruguay and Vietnam] were visited. The review did not include the licensees of the major Western research and development companies or companies that are solely contract manufacturers.

The first part of the "qualitative" study was undertaken in late 2005 in China, India and Thailand by Partners for Population and Development, with funding from UNFPA. This was then expanded in 2006 by the Concept Foundation, with funding from UNFPA, to include companies from 13 low- or middle-income countries.

The study involved open-ended interviews with senior staff of each of the companies, including both production and marketing staff. Visits were also paid to the manufacturing facilities and laboratories. Questions addressed to manufacturers and issues observed are shown in Table 1. The findings from the four items [manufacturing facilities, manufacturing capability, quality control and quality assurance (QC/QA) and documentation] were ranked on a scale of 1 to 5, with 5 being the best.

2.2. Study 2. Quantitative study

In the "quantitative" exercise, an in-depth assessment of the manufacturing competence of 14 companies from Brazil, Chile, PR China, Colombia, India, Oman, Pakistan, South Africa and Thailand was undertaken by the Concept Foundation, which was funded by ICON/IPPF and UNFPA.

Each company was requested to complete a comprehensive GMP questionnaire and to return this to the Concept Foundation. Following review of the documentation, a visit to the factory was undertaken and a full assessment of staff competence, manufacturing facilities, manufacturing processes, quality management, worker safety and environmental protection was made. These issues were assessed and classified under 19 items. The items and the content of each item discussed are listed in Table 2. It must be

Table 2
Items evaluated in the quantitative study

Item	Content
Management	Training, experience and commitment to the project
Certification by health authorities	Certification by local and international authorities
Qualification and validation	Including vendors, equipment, calibrations, installations, process, cleaning and testing methods
Quality management	Including GMP training, stability studies, investigation of out of specifications and process improvement, internal audits and annual product review
Area dedicated to hormones	Considering the overall status of the premises, equipment, personnel and quality system
Appropriateness of the manufacturing environment	Ceiling, walls, floor, illumination, doors, windows, and so forth
Steroidal APIs and products handling techniques	Handling, weighing, mixing, filling, primary packaging, and so forth
Quality of the water system	Pretreatment, purified water, water for injection, storage, monitoring, alert limits and action limits
Air system	Pretreatment, intermediary and final filtration, monitoring, pressure differential, alert limits and action limits
Materials handling	Techniques for nonsteroidal items
Sanitary design of processing equipment	Wet surfaces, accessories, challenge for cleaning, sanitization and maintain cleanliness
Sizing of processing equipment	Suitable design of mixers, filling machine and other technical parts to manufacture lots lasting 8 or 16 h, depending on the maximum daily filling capacity
Readiness to start sourcing	Includes product registration and technical capability
Equipment cleaning	Procedures to clean and evaluate the level of residual contaminations (physical, chemical, microbiological)
Holding times for injectable forms processing equipment	Validation of the longest time equipment and utensils remains clean after sanitation
Holding times for bulk mixtures	Validation of the longest time bulk mixtures can remain before filling, primary packaging without developing unsafe bioburden or losing the suspension form specified characteristics
Level of exposure of products to manufacturing personnel	Protection to workers to avoid contact with product and protection to bulk, container and closure to avoid exposure to manufacturing personnel
Clean sampling methods	Method to collect samples of bulk, in process and finished product
Establishment and monitoring of critical operating parameters	Control for temperature, pressure, vacuum, particulate matter, bioburden, viable microorganisms, and so forth

Table 3
Qualitative study: ranking of major items by company

Company	Manufacturing facilities	Manufacturing capability	QC/QA	Document	Total
1	2.5[a]	3	3	3.5	11.5
2	(4)[a]	4	4	4	16
3	4[a]	4	4.5	4	16.5
4	4	3	3	3.5	13.5
5	4	3	3	3.5	13.5
6	3	3	3	3	12
7	3	3	3	3	12
8	3	2	2	3	10
9	1	2	2	2	7
10	2	2	1	2	7
11	3	2	2	2	9
12	2	2	2	2	8
13	1	1	1	2	5
14	2	1	2	2	7
15	2	1	3	3	8
16	(1.5)[a]	(2)	2.5	2	8
17	(4)	(4)	4	4	16
18	[b]				[b]
19	(3.5)[a]	(3.5)	3.5	3	13.5
20	4	4	4	4	16
21	3	3	3	3	12
22	4	3.5	3.5	4	15
23	2[a]	2	2.5	2.5	9
24	(3)[a]	(3)	3	3	12
25	3.5	3.5	3.5	3.5	14
26	3	3	3	3	12
27	2.5	3	3	2.5	11
28	4	4	4	3	15
29	4	4	3.5	4	15.5
30	(2)	(2)	4	3	11
31	1	1	2	2	6
32	3	2	3	3	11
33	(3)	(3)	2	3	11
34	(3)	(3)	3	2	11
35	3	2	3	3	11
36	(3)	(3)	3	2	11
37	(3)	(2)	3	3	11
38	3[a]	2	3	3	11
39	2	2	2	2	8
40	3	4	4	3	14
41	2	3	2	2	9

Those that are enclosed in parentheses denote the companies at which production was not running at the time of the visit.

[a] Companies at which the hormonal facility is in the process of renovation.

[b] Company about to renovate facility but currently not in position to manufacture.

noted that while an in-depth evaluation was undertaken, this visit was not equivalent to a full factory audit as would be undertaken by a stringent regulatory agency; therefore, the observations made were not intended to be an all-inclusive detection of nonconformity. Each of the items listed in Table 2 was then classified according to the following categories:

Category 1: Unsatisfactory
Category 2: Meets minimum requirements (WHO GMP main principles)
Category 3: Expected level (WHO GMP for steroidal pharmaceutical products)
Category 4: Consistently exceeds expected level

3. Results

3.1. Study 1. Qualitative study

Visits were paid to 41 companies in the following countries: Brazil, Chile, PR China, Costa Rica, India, Indonesia, Mexico, South Africa, ROC Taiwan, Thailand, Oman, Vietnam and Uruguay. Table 3 shows the ranking of the manufacturing facilities, manufacturing capability, QC/QA and documentation on a scale of 1 to 5, with 5 being the best.

Of the 41 hormonal contraceptive facilities visited, only 6 companies had a ranking of 4 or greater under both "manufacturing facilities" and "manufacturing capability." Six others had a total of 7.5 and 7, respectively, for these two categories. These 12 companies (29.3%) have the potential to be candidates for prequalification. A further eight companies (19.5%) have a ranking of 3 for both these categories and have the potential for eventual prequalification, if they are prepared to upgrade their facilities and take measures to improve their GMP practices. The remaining 21 factories (51.2%) need to take major steps for them to even be considered for the supply of hormonal contraceptives in national, let alone international, markets.

3.2. Study 2. Quantitative study

A total of 14 companies were visited. Table 4 lists the classification of the 19 items assessed at each company. On the basis of the quantitative assessment, only four of the companies evaluated in-depth could be considered for procurement of hormonal contraceptives. Of these, three are manufacturing oral contraceptives whereas one is manufacturing DMPA. One other company, which manufactures oral contraceptives, has the potential to be considered in the future, if it responds to the recommendations made during the assessment visit. A further seven companies, identified through the qualitative study, may also have the potential for future procurement but have not had a quantitative assessment.

4. Discussion

The studies show that relatively few manufacturers of generic hormonal contraceptives in lower- and middle-income countries are presently meeting acceptable quality criteria within their manufacturing. While many companies have 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 were handled. Despite that all of the 44 factories visited had received national GMP certification, there are still significant disparities between them. It is

Table 4
Quantitative study: ranking of major items by company

Company	Products	Total (maximum=76)	Category 1	Category 1.5	Category 2	Category 2.5	Category 3	Category 3.5	Category 4	N/A
	OCs									
20	COCs, POPs, ECPs	61					13		4	
3	COCs, POPs, ECPs	59					13		5	1
28	COCs, POPs	57					15		3	1
4	COCs, POPs, ECPs	55			2	3	12	1	1	
5	COCs, POPs, ECPs	53			3	8	6		2	
A[a]	COCs, POPs ECPs	45	2		9	1	6		1	
7	COCs, POPs, ECPs	44			13		6			
1	COCs, POPs, ECPs	40		2	11		5			1
35	COCs, POPs	34	8		7		4			
B[a]	COCs, POPs	33	4	4	7		3			1
	Injectables									
29	DMPA	54.5			1	3	15			
C[a]	OAM[b]	47		1	8	4	3	3		
32	DMPA	40.5		2	13	2	2			
36	DMPA	39.5		1	16	2				
B[a]	DMPA	16	12		2					5

[a] Companies not included in the qualitative study.
[b] Company is currently manufacturing a once-a-month injectable (OAM) and is establishing a DMPA production line.

unlikely that no more than 30% would meet WHO, Pharmaceutical Inspection Cooperation Scheme (PIC/S)[1] or any stringent regulatory authority GMP requirements. It is possible that a further 20% could comply with these requirements with some investment and improvements in quality management and practice. Some 50% of the facilities visited are manufacturing products under conditions that give cause for concern, and while some of them could upgrade their facilities and procedures to address these concerns, there are some factories that should reconsider the manufacture of products for human use.

In several countries, particularly Brazil, Chile, Indonesia and Thailand, there has been significant upgrading of regulatory requirements and application of current Good Manufacturing Practices (cGMP). For example, Brazil requires that hormonal steroid products should be produced in a physically separate building from other products and expects that companies will have full bioequivalence data on their generic products within the next 5 years. As part of the activities of the Association of Southeast Asian Nations Working Group on Technical Cooperation in Pharmaceuticals, there is considerable ongoing work to improve GMP of pharmaceutical companies in Southeast Asia, with several countries such as Indonesia, Malaysia, Singapore and Thailand implementing, or planning to implement, PIC/S GMP requirements.

Both WHO and PIC/S GMP requirements state clearly that "the production of certain hormones should not be conducted in the same facilities." There are, however, two ambiguities. The first is that they do not spell out the meaning of "certain hormones." The other is whether "... should not be conducted in the same facilities" means that production lines for hormonal contraceptives should be placed in a completely separate building or in a completely separate area with separate air handling and other services within a building in which other pharmaceutical products are being manufactured. The former is being applied in Brazil, Europe and the United States. If this is applied more broadly, it would infer that, for example, in Thailand, where none of the factories currently has a completely separate hormone facility and critical services, hard commercial decisions such as whether to make this significant financial investment will be required.

Only one of the injectable manufacturers is producing a product that is sterile by design — in most countries, the normal practice is to use steam for postmanufacture sterilization. The risk of contaminated product increases as manufacturers (a) do not follow compliant practices for the sterilization and depyrogenation of components, (b) use nonsterile active pharmaceutical ingredients (APIs) and (c) do not process the product in compliant clean rooms.

There is significant production overcapacity in several countries, particularly in China and Thailand and with some companies in India, where companies produce their annual quota of oral or injectable contraceptives in a single period of 4–8 weeks in a year. This is a direct consequence of the role, process and size of government tendering. In China, many companies just await their government order for the public sector. This is announced in November each year, and the companies then manufacture their requirements at the beginning of the following year, usually over a period of 4–6 weeks. In Thailand, except for one company, most companies only manufacture DMPA over a period of 4–6 weeks each year. This is a consequence of the termination of central government tendering for contraceptives in

[1] The Pharmaceutical Inspection Convention and its related PIC/S are two international instruments between countries and pharmaceutical inspection authorities that provide active cooperation in the field of GMP.

2002. In India, the government tender for COCs for the public sector, which is for relatively small volumes, represents 100% of the production of two companies and 80% of a third.

This overcapacity makes little economic sense and, more importantly, is likely to create major quality issues. Each time the production facility is reopened after having been closed down, it is necessary to revalidate all equipment and procedures, prior to reusing the facility. There was little evidence from several companies that this was actually done. Moreover, it is difficult to maintain staff competence and there was little evidence of retraining as part of the process of reopening the facility.

Most companies consider APIs from European sources to be expensive, and several companies are sourcing APIs from other countries. One company has two branded DMPA products differentiated by name and price depending on the country from where the API was sourced, and others are considering doing the same. Unfortunately, even if APIs from these alternative sources can be shown to be made under cGMP standards, an International Conference on Harmonization (ICH)-compliant drug master file, which is necessary for the completion of registration dossiers in those countries with stringent regulatory authorities, is rarely available.

While the majority of companies had adequate laboratory facilities and equipment to undertake necessary QC/QA testing, there were significant differences between the factories visited in terms of instrumentation, standard laboratory operating procedures and the condition and environment of the laboratories. Some laboratories did not conform to Good Laboratory Practices (GLP), and few paid adequate attention to laboratory worker safety and protection.

Only 25% of the companies have the capability of developing registration dossiers that are required for the export of products to countries with strict regulatory requirements. Several companies raised this issue and stated that they would like assistance in this area.

Bioequivalence studies are a requirement for stringent regulatory agencies and are starting to be required by more and more regulatory agencies in other countries. However, there was a significant difference between companies in their understanding of bioequivalence and most had not considered the need for such studies. Few companies have undertaken bioequivalence testing programs, with most supplying untested biosimilar products. Some companies had undertaken pharmacokinetic/pharmacodynamic studies in local university clinical departments, but it was difficult to ascertain what had been the comparator products used and how the investigators applied Good Clinical Practices in the conduct of the studies or GLP for the analysis of blood specimens collected. Most factories are undertaking adequate stability studies to ensure that the shelf life of the products is maintained as indicated on the package labels.

Following the approval of an Interagency List of Essential Medicines for Reproductive Health [5], which is complementary to WHO's Model List of Essential Medicines [4], WHO's Prequalification Program has been expanded to include the hormonal contraceptives considered in these studies [6]. This will go further than the presently reported studies and provide a list of companies from which governments and procurement agencies could purchase products with a guarantee of appropriate quality. This study provides important background information to WHO, and it is the opinion of the authors that only the companies with a ranking of 4 in the qualitative study, under both "manufacturing facilities" and "manufacturing capability," will be able to fulfill this prequalification process and that even some of them will not have bioequivalence data.

It is recommended that any company that does not meet the requirements of the WHO Prequalification Program seek technical assistance by contracting factory-qualified inspectors from countries that are signatories to PIC/S to undertake a full review of processes, standard operating procedures (SOPs) and documentation and make recommendations of what the companies need to do to meet international requirements. Obviously, companies will need to explore, however, whether it is feasible or commercially sound to raise the funding for investment required for upgrading facilities. Should the companies wish to continue to obtain EU, U.S. or other stringent regulatory authority approval, or seek prequalification by WHO, and compete for international tenders, assistance should also be sought on developing dossiers that meet regulatory requirements.

Many products are purchased through national or international procurement tenders. Companies invited to respond to such tenders must be able to assure product quality as expressed through fully GMP-compliant manufacturing practices. These practices can only be shown to be satisfactory if the product has been approved by a stringent regulatory authority and/or prequalified by the WHO program. The study shows that the practice in some countries of stating that a factory must have obtained a certificate from national inspectors that it meets WHO GMP guidelines is totally inadequate to arrive at a quality judgment of finished products.

Although there are many companies that aspire to supply international markets with their products, only a few are likely to be able to meet the quality performance required by WHO's Prequalification Program. Those that do are examples for their peers that it is possible to meet current GMP requirements while maintaining their low-cost position as generic suppliers to international procurement organizations, although investments may have been necessary. In order for them to be recognized as such, it is critical that donors and procurement agencies state unequivocally that they will only purchase generic products that have been prequalified by WHO or which are approved by a stringent

regulatory authority, defined as a National Drug Regulatory Authority participating in the ICH and the PIC/S.

Generic manufacturers that understand the need to comply with an internationally accepted set of manufacturing practices governed by the most current GMP regulations will help build the new layer of trusted suppliers into international markets, while others will stay confined to their territories of origin with noncompetitive products. As such, it is necessary that the regulatory agencies implement the most current GMP requirements to ensure that quality performance is achieved and, hence, build the trust of end users that there is no doubt that products are of necessary quality. Health providers and consumers need to understand that properly produced generic products manufactured under these regulations are as safe and effective as branded products from major multinationals.

In conclusion, in response to the question "Can quality generic drugs help address the supply of low-cost pharmaceutical products of assured quality and security needs of lower and middle income countries?", the answer is a qualified yes, the qualifications being that

1. APIs are produced to internationally accepted cGMP;
2. production facilities and manufacturing processes for hormonal contraceptives conform to internationally accepted cGMP;
3. data are available to compile ICH-compliant registration dossiers, including bioequivalence data; and
4. product costs remain significantly lower than other available branded products.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the views of UNFPA.

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