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A study of the capability of manufacturers of generic hormonal contraceptives in lower and middle income countries[1]

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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 and purchasers, whether they are governments or donors, must be able to purchase product for the public sector or social marketing programmes 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 (UNFPA, 2002). 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 originator brands. Thus, over the years, 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 non-OECD governments, have established the Reproductive Health Supplies Coalition. The Coalition provides an international forum for sharing information and works to resolve problems and ensure the long-term supply of RH commodities using new and existing resources and expertise (Reproductive Health Supplies Coalition, 2006).

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One promising approach to improve access to and provide an adequate supply of hormonal contraceptives would be to expand supply from generic manufacturers, utilizing existing market forces. It has been argued that because of existing capacity 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 (Hall, 2005).

If such an approach is feasible, the use of high quality manufacturers in the developing world could be the best safeguard in the field of reproductive health the international community has to achieve a continuing supply of low cost pharmaceutical products of assured quality. This would require, however, identifying a group of manufacturers which are willing to:

- ensure that their production facilities meet current GMP guidelines;
- access or produce the active pharmaceutical ingredients (APIs), manufactured to current GMP guidelines 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.

In order to assess feasibility of this approach and to ascertain what really is the situation in the generic manufacture of hormonal contraceptives worldwide, two studies have been undertaken which are reported in this paper. The first study was a mapping exercise and "qualitative" assessment in which visits were made to ascertain the capacity, capability and competence of manufacturers of generic hormonal contraceptives and allow a preliminary assessment of their potential role in addressing the need for affordable, quality contraceptives in low income countries.

The second was a "quantitative" study which required the submission and review of technical documentation based on a comprehensive GMP questionnaire, followed by an inspection of the manufacturing facilities of those companies that appeared to have the capability to comply, or which were close to complying, with current GMP guidelines and which could be candidates for supply to procurement agencies.

The two studies focussed on the manufacture of the injectable contraceptive, DMPA, and levonorgestrel containing tablets, either as the combined oral contraceptive, levonorgestrel, 150µg + ethinyl estradiol, 30µg; the progestogen-only oral contraceptive, levonorgestrel, 30µg; or the emergency contraceptive, levonorgestrel, 750µg or 1.5mg. These are all products which are listed on WHO’s Model List of Essential Medicines (WHO, 2005; WHO, 2006a) and represent the most common products procured for the public sector of many developing countries. Towards the end of 2006, WHO will begin to expand its Prequalification Programme for the prequalification of essential medicines for reproductive health, starting with these products (WHO, 2006b).

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 paper.

Methodology

Study 1. "Qualitative study"

A review was undertaken of manufacturers of generic hormonal contraceptives, specifically, the injectable contraceptive, DMPA, and levonorgestrel tablets, including combined oral contraceptives (COCs), progestogen-only pills (POPs) and emergency contraceptive pills (ECPs). Companies were visited in 14 lower and middle income countries: Brazil, Chile, PR China, Costa Rica, India, Indonesia, Malaysia, Mexico, Oman, South Africa, RoC (Taiwan), Thailand, Uruguay and Viet Nam. The review did not include the licensees of the major western R&D companies nor 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, Dhaka, Bangladesh with funding from UNFPA. This was then expanded in 2006 by the Concept Foundation, Bangkok, with funding from UNFPA, to include companies in a total of 14 countries, all non-OECD countries, except for Mexico.

The study involved open-ended interviews with senior staff of each of the companies, including both production and marketing staff where possible. 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; and documentation were ranked on a scale of 1 to 5, with 5 being the best.

Table 1 Questions addressed during mapping exercise

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, etc. 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 GMP 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? Is 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 a documented complaints procedure? Has the company ever commissioned bioequivalence studies, if so, on what products and where?

Study 2. "Quantitative study"

In the "quantitative" exercise, an in-depth assessment of the manufacturing competence was undertaken of 10 companies in: PR China, Colombia, India, Oman, Pakistan, South Africa and Thailand by the Concept Foundation, Bangkok, funded by ICON/IPPF and UNFPA.

Each company was requested to complete a comprehensive GMP questionnaire and return this to the Concept Foundation. Following review of the documentation, a visit was undertaken to the factory and a full assessment was made of staff competence, manufacturing facilities, manufacturing processes, quality management, worker safety and environmental protection. These issues were assessed and classified under 19 items. The items and the content of each item discussed are listed in Table 1 below. It must be 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 non-conformity.

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

Table 2 Items evaluated during in-depth assessments

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, etc.
Steroidal API and products handling techniques	Handling, weighing, mixing, filling, primary packaging, etc.
Quality of the water system	Pre-treatment, purified water, WFI, storage, monitoring, alert limits & action limits
Air system	Pre-treatment, intermediary and final filtration, monitoring, pressure differential, alert limits & action limits
Materials handling	Techniques for non-steroidal 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 8h or 16h, 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 & 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, etc.

Findings

Study 1. "Qualitative study"

Visits were paid to 39 companies (a further five are about to be undertaken) in the following countries: Brazil, Chile, PR China, Costa Rica, India, Indonesia, Malaysia, Mexico, South Africa, ROC Taiwan, Thailand, Oman, Viet Nam 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.

Table 3 Ranking of major items by company

Company	Manufacturing facilities	Manufacturing capability	QC/QA	Document	Total
1	3.5*	4	3	3.5	14
2	4*	4	4	4.5	16.5
3	5*	5	5	4	19
4	5	5	5	3.5	18.5
5	4	3	3	3.5	13.5
6	3	3	3	3	12
7	3	3	4	3	13
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)*	(2)	2.5	2	8
17	(4)	(4)	4	4	16
18	To be visited				
19	To be visited				
20	4	4	4	4	16
21	3	3	3	3	12
22	4	4	3	4	15
23	3*	2	3	3	11
24	(3)*	(3)	3	3	12
25	4	4	4	4	16
26	3	3	3	3	12
27	To be visited				
28	2.5	3	3	2.5	11
29	4	4	4	3	15
30	4	4	3	4	15
31	(2)	(2)	4	3	11
32	1	1	2	2	6
33	3	2	3	3	11
34	(3)	(3)	2	3	11
35	(3)	(3)	3	2	11
36	3	2	3	3	11
37	(3)	(3)	3	2	11
38	(3)	(2)	3	3	11
39	3*	2	3	3	11

40	2	2	2	2	8
41	To be visited				
42	To be visited				
43	3.5	4	4	3.5	15
44	2	3	2	2	9

* Companies at which the hormonal facility is in the process of renovation.
() Companies at which production was not running at the time of the visit.

Study 2. "Quantitative study"

A total of 10 companies were visited. These are listed below together with the categories obtained for each of the 19 items assessed.

Company	Products	Total (max 76)	Cat 1	Cat 1.5	Cat 2	Cat 2.5	Cat 3	Cat 3.5	Cat 4	N/A
	OCs									
20	COCs,POPs, ECPs	61					13		4	
29	COCs, POPs	57					15		3	1
A*	COCs, POPs	45	2		9	1	6		1	
7	COCs, POPs, ECPs	44			13		6			
36	COCs, POPs	34	8		7		4			
B*	COCs, POPs	33	4	4	7		3			1
	Injectables									
30	DMPA	54.5			1	3	15			
C*	OAM**	47		1	8	4	3	3		
33	DMPA	40.5		2	13	2	2			
37	DMPA	39.5		1	16	2				
B*	DMPA	16	12		2					5

* Companies not included in the qualitative study.
** Company is currently manufacturing an once-a-month injectable and is establishing a DMPA production line.

Conclusions and discussion

From the qualitative study, in which (39) hormonal contraceptive facilities have been visited, only 9 companies had a ranking of 4 under both "Manufacturing facilities" and "Manufacturing capability". Three of these have had an in-depth evaluation and the remaining six companies are about to have an in-depth evaluation undertaken (see below), together with three others which had a total of 7.5 and 7 respectively, for these two categories. These 12 companies (30.8%) have the potential to be candidates for prequalification.

A further 8 companies (20.5%) have a ranking of 3 for both these categories and could be considered for an in-depth evaluation, if the companies were willing to provide evidence that they had upgraded their facilities and were willing to take measures to improve their GMP practices.

The remaining 19 factories (48.7%) would have to take major steps to even be considered for the supply of hormonal contraceptives in national, let alone international, markets.

On the basis of the quantitative assessment, only three out of the 10 companies evaluated in depth to date could be considered for procurement of hormonal contraceptives: two for oral contraceptives and the other for DMPA. Of these two are manufacturing oral contraceptives and one DMPA. Three other companies (two manufacturing oral contraceptives and one DMPA) have potential to be considered in the future, if they respond to the recommendations made during the assessment visit.

A further nine companies, identified through the qualitative study, may also have the potential for future procurement and will be visited in coming months as part of the quantitative assessment.

The principal conclusions from the two studies are that:

- Although all factories visited have received national GMP certification, there are still significant disparities between them and less than one out of three are likely to meet PIC/S or similarly stringent regulatory GMP requirements. Some 50% of the facilities visited are manufacturing products under conditions that give cause for concern and while certain of them could upgrade their facilities and procedures to address these concerns, there are some factories that should not be certified for the production of products for human use and be closed.
- There is enormous production overcapacity, particularly in China and Thailand, and with a few companies in India, where companies produce their annual quota of oral or injectable contraceptives in a single period of 4-6 weeks in a year. This raises major quality issues, particularly in the revalidation (or lack of revalidation) of production and environmental procedures, as well as worker training.
- Most companies are finding APIs from European sources to be expensive but cannot easily obtain material from other countries that are made to acceptable GMP criteria nor having the necessary drug master files to allow completion of registration dossiers.
- Few companies (<25%) have the capability of developing registration dossiers required for the export of products to countries with strict regulatory requirements.
- Very few of the companies have undertaken bioequivalence testing programmes and, as such, supply untested biosimilar products.
- Most, but not all, factories are undertaking adequate stability studies.

Good Manufacturing Practice

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 was handled. Although all factories visited comply with national GMP, it is unlikely that no more than 30% would meet PIC/S[6] or any stringent regulatory authority requirements. A further 20% could comply with these requirements with some investment and improvements in quality management and practice.

[6] The Pharmaceutical Inspection Convention (PIC) and its related Pharmaceutical Inspection Co-operation Scheme (PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide active co-operation in the field of GMP.

While the majority of companies did have adequate laboratory facilities and equipment to do the necessary quality control and quality assurance testing, there were significant differences between the factories visited in terms of laboratory instrumentation, standard laboratory operating procedures and in the condition and environment of laboratories. Certain laboratories did not conform with Good Laboratory Practice (GLP) and few gave adequate consideration to laboratory worker safety and protection.

In several countries, particularly, Brazil, Chile, Indonesia and Thailand, there has been significant upgrading of regulatory requirements and application of stringent GMP. For example, ANVISA in 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 five years. As part of ASEAN activities, there is considerable work ongoing to improve GMP of pharmaceutical companies in south-east 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 USA. 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 will be required as to whether to undertake this significant financial investment.

Only one of the injectable manufacturers is producing product that is sterile by design - in most countries, the normal practice is to use steam for post-manufacture sterilization. The risk of contaminated product increases as manufacturers do not follow compliant practices for the sterilization and depyrogenation of components, use non-sterile MPA API, and do not process the product in compliant clean rooms.

In two countries, China and Thailand, as well as with several companies in India, there is considerable over-capacity for the production of hormonal contraceptives. This is a direct consequence of the role, process and size of government tendering.

In China, many companies that have not diversified into the fledgling private sector or have not tried to develop export markets and just await their government order for the public sector. This is announced in mid-late November each year, and then the companies manufacture their requirements at the beginning of the following year, usually over a period of four to six weeks. In recent years, the number of products, the absolute volumes and the number of companies contracted by the national programme have all decreased and only a few companies have additional market needs to continue their production lines. Moreover, additional investment and improved technical competence will be necessary in coming years as China’s pharmaceutical industry is forced to comply with current GMP standards and become more competitive.

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 2002. In India, the government tender for COCs for the public sector, represents 100% of the production of two companies and 90% of a third, moreover, these are relatively small volumes.

This over capacity not only makes little economic sense but, more importantly, is likely to create major quality issues. Each time the production facility is 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 as required by current GMP regulations! Moreover, it is difficult to maintain staff competence and there was little evidence of retraining as part of the process of reopening the facility.

Information required for registration in other countries

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.

The requirement for bioequivalence studies is now becoming more prevalent on the part of regulatory agencies. However, there was a significant difference between companies in their understanding of bioequivalence. Most had not considered the need for such studies. 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 to find out what the investigators knew about Good Clinical Practice (GCP) in terms of the conduct of the studies or Good Laboratory Practice (GLP) for the analysis of blood specimens collected.

Given the increasing cost of APIs, several companies are beginning to source APIs from China, rather than from European sources, e.g. 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 others are considering doing the same. Unfortunately, even if this material can be shown to be made under acceptable GMP standards, a cGMP compliant drug master file, necessary for the completion of registration dossiers in those countries with stringent regulatory authorities, is rarely available.

WHO Prequalification Programme

The Prequalification Programme was set up in 2001 by the World Health Organization (WHO) to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. Prequalification was originally intended to give United Nations procurement agencies, such as UNICEF and UNFPA, the choice of a range of quality medicines (see mednet3.who.int/prequal).

Following the approval of an Interagency List of Essential Medicines for Reproductive Health, 2006 (WHO, 2006a), which is complementary to WHO's Model List of Essential Medicines (WHO, 2005), it has been agreed that WHO's Prequalification Programme would be expanded to include a limited range of reproductive health products.

The following hormonal contraceptives have been considered as priorities by both an InterAgency Working Group and members of the Reproductive Health Supplies Coalition for eventual inclusion in the prequalification programme:

COC - levonorgestrel, 150µg + ethinylestradiol, 30µg +
POP - levonorgestrel, tablet, 30µg,
ECP - levonorgestrel, 750µg (pack of two), 1.5 mg (pack of one)
PIC - medroxyprogesterone acetate (DMPA), 150mg/ml

WHO's Prequalification Programme will begin to include these products by the end of 2006. 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 will provide 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 fulfil this prequalification process and, even some of them will not have bioequivalence data.

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 to this question is a qualified yes, the qualifications being that:

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

Recommendations

Only 30% of the 42 companies in the 16 countries visited to date in the two studies are likely to meet current GMP standards, such as the PIC/S requirements, today. This will be seen once WHO's Prequalification Programme begins in the near future. However, any of these companies that do not get prequalified, as well as a further 20% of the companies visited, could, with appropriate investment and technical assistance, 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 PIC/S 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, if necessary using the services of engineering and service providing organizations cognizant with current GMP requirements, the inspectors should return and review what has been achieved. A similar technical assistance exercise should be undertaken with several manufacturers of APIs.

It is ***recommended*** that such technical assistance is provided through bilateral or multilateral donors. 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, US 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. How these generic manufacturers are bound into any subsequent, comprehensive international supply mechanism and how donors would make sure that their investments are adequately honoured on a quid-pro-quo basis with the manufacturers is a separate issue that will require further analysis.

It is also ***recommended*** that technical assistance to generic manufacturers is complemented by an independent quality control and assurance programme for the analysis of purity, potency and manufacturing content uniformity of generic hormonal contraceptives to assist both companies and procurers with adequate quality information. This independent quality assurance program could be initiated by WHO and should be mandatory for any supplier prequalified by WHO and optional for other companies.

Many products are obtained through national or international procurement tenders. It is strongly ***recommended*** that companies invited to respond to such tenders, be able to show product quality indicators as expressed through fully GMP compliant manufacturing practices. These practices can only be shown to be satisfactory if the product has been approved by EU, US or other stringent regulatory authorities and/or prequalified by the WHO programme. The common 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, as this study shows. It is also critical that prequalification is used to move donors or governments away from criteria that are weighted towards price. Quality must be a given before competition on price determines to which company a tender contract is awarded to.

This study shows that relatively few manufacturers of generic hormonal contraceptives in lower and middle-income countries are presently meeting acceptable quality criteria within their manufacturing. Although there is a larger number of companies aspiring to supply international markets with their products, only these few are likely to be able to meet the quality performance required by WHO's Prequalification Programme. These companies are examples for their peers that it is possible to meet most actual current GMP requirements while maintaining their low cost position as generic suppliers to international procurement organizations, even though investments may have been necessary. In order for them to be recognized as such, it is ***recommended*** that those donor and procurement agencies that are members of the Reproductive Health Supplies Coalition start this ball rolling by stating unequivocally that they will only purchase generic products that have been prequalified by WHO.

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 supra-national markets, while others will stay confined to their territories of origin with non-competitive 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.

Even though generic pharmaceutical manufacturers are producing some 50% or more of the world's pharmaceutical products, there remains a considerable lack of knowledge and awareness about what generic products are. It is ***recommended*** that

information is produced and disseminated to ensure the understanding that only products from prequalified manufacturers adhering to current GMP practices for their entire manufacturing operations are quality products. These products need to be able to be registered appropriately wherever they are being supplied with adequate bioequivalence data as proof of identical performance to the originator product. Then we can speak of a quality generic product regardless of whether it is manufactured in Berlin or Beijing, or Manchester or Mumbai.

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