

The manufacture of generic hormonal contraceptives in lower and middle income countries: What is the current situation?

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Millennium Development Goals

A new target was recently adopted by the United Nations General Assembly, “to achieve universal access to reproductive health by 2015”, under Millennium Development Goal 5, to reduce by three quarters the maternal mortality ratio.

While the new target ensures the centrality of universal access to reproductive health in improving maternal and infant health and poverty reduction in the MDGs, it will require adequate funding and access to products for reproductive health not only of assured quality but at the lowest possible price.

What is expected from manufacturers of generic products?

Governments and international donors are looking for **sustainable supplies** of products of **assured quality** at the **lowest possible cost** to meet the goal of achieving supply security for reproductive health commodities.

Questions by the RHSC on the manufacture of generic hormonal contraceptives

- Can generic pharmaceutical manufacturers in lower and middle income countries make quality products available to donor agencies, governments, social marketing organizations at a more affordable price, while meeting the requirements of stringent regulatory agencies?
- Can any of these companies participate in the development of a total market approach which provides a “second tier” of products in the private sector that are affordable to some of those who are currently using free or subsidized public or social marketing sector products, and allow those programmes to focus on poorer users?

Generic hormonal contraceptives

Study 1. “Qualitative study”

- 41 Companies were visited in 13 lower and middle income countries: Brazil, Chile, PR China, Costa Rica, India, Indonesia, Mexico, Oman, South Africa, (Taiwan), Thailand, Uruguay and Viet Nam.
- Did not include the licensees of the major western R&D companies nor contract manufacturers.
- Study undertaken by Concept Foundation, Bangkok and Partners in Population and Development, Dhaka, funded by UNFPA.

Generic hormonal contraceptives

Study 2. “Quantitative study”

- Assessment of the manufacturing competence of 14 companies in Brazil, Chile, China, Colombia, India, Oman, Pakistan, South Africa and Thailand
- Study undertaken by Concept Foundation, Bangkok, funded by ICON/IPPF and UNFPA.
- Close link maintained between studies

Findings

- Although all 44 factories visited comply with national GMP, it is probable that less than 30% would meet cGMP requirements of WHO, PIC/S or any stringent regulatory authority.
- A further 20% could comply with some investment and improvements in quality management and practice.
- The other 50% of the facilities visited are manufacturing products under conditions that give cause for concern.

Findings

- There is enormous production overcapacity, particularly in China and Thailand, and to some extent 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 not only uneconomic but raises major quality issues, particularly in the revalidation (or lack of revalidation) of production and environmental procedures, as well as worker training.

Findings

- Most companies consider 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.
- Very few companies have undertaken bioequivalence testing.
- Most, but not all, factories are undertaking adequate stability studies.

Findings

- Few companies (<25%) have the capability of developing registration dossiers required for the export of products to countries with strict regulatory requirements.
- Many companies would like to access technical assistance to:
 - meet cGMP requirements; and
 - develop registration dossiers that meet stringent regulatory requirements

Conclusions

- Most companies manufacture products according to outdated requirements that do not conform to cGMP, or even outside GMP, but a few companies do manufacture products of assured quality according to cGMP requirements.
- Most are not in a position to supply products into international markets, not having considered regulatory approval for their products outside their home markets. Very few have positioned themselves adequately to get approvals to be able to deliver products outside of their home markets.

Can we access high quality products?

Yes, if the active pharmaceutical ingredients (APIs) and production facilities conform to internationally accepted GMP standards; and data are available to comply with regulatory requirements.

From the two studies reported, up to **ten** companies *could* comply in 2007 with minimal additional technical or procedural inputs (except for the completion of BE studies) and a further **three to four** could potentially do so in 2007 with investment and technical assistance.

<http://mednet3.who.int/prequal/>

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Follow the quick links below for general information on the prequalification of products and manufacturers, focusing on HIV/AIDS, Tuberculosis and Malaria.

PREQUALIFYING PRIORITY MEDICINES
Ensuring the quality, safety and efficacy of HIV/AIDS, Tuberculosis and Malaria medicines and diagnostics
A United Nations project managed by the World Health Organization

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Essential RH medicines for prequalification

The following essential medicines for RH agreed by an InterAgency Working Group and the RHSC for eventual inclusion in the prequalification programme:

Contraceptives

- levonorgestrel, 150µg + ethinylestradiol, 30µg, tablet
- levonorgestrel, tablet, 30µg, 750µg (pack of two), 1.5mg (pack of one)
- medroxyprogesterone acetate (DMPA), depot injection, 150mg/ml

Essential RH medicines for prequalification

Oxytocics

- oxytocin, injection
- misoprostol, vaginal tablet

Anticonvulsant

- magnesium sulfate, injection

Antifungal

- clotrimazole, vaginal tablet and cream

Essential RH medicines for prequalification

Essential medicines for reproductive health that are already in the WHO prequalification process:

Antibiotics, antifungals and antibiotics used in opportunistic infections

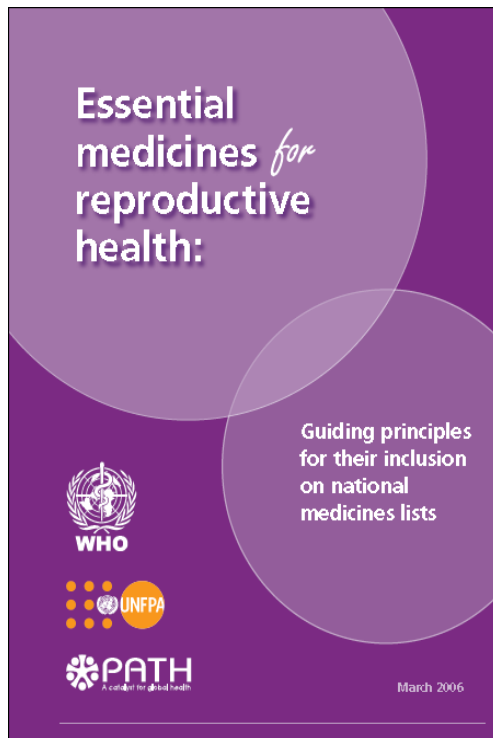
- azithromycin (EOI)
- cefixime (EOI)
- ceftriaxone, powder for injection (2 products prequalified)
- ciprofloxacin, tablet (10 products prequalified)
- clindamycin (EOI)
- fluconazole, capsule (7 products prequalified)
- sulfadiazine, tablet (1 product prequalified)
- co-trimoxazole (3 products prequalified)

Essential RH medicines for prequalification

Other reproductive health commodities that are being prequalified by UNFPA:

- Condoms
- Copper-bearing IUDs

Practical guideline for inclusion of essential RH medicines on national medicines lists



- Practical information for all stakeholders at national level to facilitate the integration of medicines for RH into national list
- Include 16 medicine briefs, as examples, that gather essential evidence
- Field testing of this version planned in 2 countries

What needs to be done?

Donor and procurement agencies wishing to access generic products will only purchase products that have been prequalified by WHO and adopt a procurement policy based on that used by the GFATM. This states:

“Accordingly a product may be procured if:
Option A: it is approved by the pre-qualification program.
Option B: it is approved by a stringent regulatory authority, defined as a National Drug Regulatory Authority (NDRA) participating in the International Conference of Harmonization (ICH) and the Pharmaceutical Inspection Cooperation Scheme (PIC/S)”

What needs to be done?

- Develop an advocacy strategy and informational materials for governments, national NGOs, international partners and other stakeholders, including healthcare providers and consumers on:
 - the WHO prequalification programme;
 - the need to use only suppliers prequalified by WHO for the procurement of injectable and oral contraceptives and eventually other RH commodities.
 - the broader issues around generic products.

What do we expect from the generic manufacturers?

Donors and procurement agencies are looking for **sustainable supply** of the **highest quality** products at the **lowest possible cost** to meet the goal of achieving contraceptive supply security.

This is what we are expecting manufacturers of generic contraceptives to deliver.

Can we access these quality products at the lowest cost and sustainably?

- Quality costs money – those companies that are prepared to invest in manufacturing quality products should benefit from that investment.
- Quality and economics require planned production – companies without regular and consistent orders incur major revalidation costs if they are to maintain quality and intermittent production is uneconomic.
- Lowest-costs at low profit margins for manufacturers need a low-risk environment for doing business – companies need accessible markets of known size and volumes.

What needs to be done?

As an incentive to manufacturers that would allow them to offer the inherent cost advantages to international purchasers and to exploit the full low-cost potential of generic supplies, manufacturers need a continuous purchase and supply mechanism as a platform to replace the current uncoordinated, *ad hoc* and discontinuous tender mechanism.

- Can individual donors support this platform?
- Can new joint financing and purchasing mechanisms be developed?