Medicines for Reproductive Health: Ensuring access to quality assured products 2011

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1. Introduction

At the turn of the millennium, world leaders gathered to ratify the Millennium Development Goals (MDGs). Despite the fact that it took a further six years to include the target of universal access to reproductive health, the acceptance of MDG 5[1] to improve maternal health and the world's population surging past seven billion have galvanized the international community and governments of many lower and middle-income countries into action, grappling to address the reproductive health needs of women in those countries.

A recent report by the United Nations Population Fund (UNFPA) and the Guttmacher Institute[2] showed that "maternal deaths in developing countries could be slashed by 70 per cent and newborn deaths cut nearly in half if the world doubled investment in family planning and pregnancy-related care. In addition, investments in family planning boost the overall effectiveness of every dollar spent on the provision of pregnancy-related and newborn health care. Simultaneously investing in both family planning and maternal and newborn services can achieve the same dramatic outcomes for US$1.5 billion less than investing in maternal and newborn health services alone."

It is absolutely clear that it will neither be possible to achieve these outcomes nor meet the indicators for MDG 5 without universal access to affordable reproductive health medicines of assured quality. It is a sad fact that after 50 years of modern contraception, we are still struggling to achieve this goal. This remains one of the greatest challenges to governments, donors and all those involved in improving access to reproductive health.

Just looking at family planning alone, in many countries in the developing world, 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 financial 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[3]. As such, demand for contraceptives exceeds supplies in many developing countries and is increasing.

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[1] Millennium Development Goal 5 "Improve maternal health" requires the reduction of the maternal mortality ratio (the number of maternal deaths per 100,000 live births) by three-quarters, between 1990 and 2015; and universal access to reproductive health by 2015.

[2] Adding It Up: The Costs and Benefits of Investing in Family Planning and Maternal and Newborn Health UNFPA & the Guttmacher Institute, New York. 2009 pp44

[3] United Nations Population Fund.(2002). Reproductive Health Essentials - Securing the Supply: Global Strategy for Reproductive Health Commodity Security. UNFPA, New York. See www.unfpa.org/publications/detail.cfm?ID=27&filterListType=

In response to the growing desire for novel approaches and funding to address these needs, a group of key stakeholders established the Reproductive Health Supplies Coalition (RHSC) in 2004. The Coalition now comprises some 140 organizations and constituencies that have a significant financial and/or programmatic stake in reproductive health supply security, including donor agencies, procurement agencies, several governments from lower and middle income countries, civil society and product manufacturers. The Coalition is working to resolve problems and ensure the long-term supply of RH supplies using new and existing resources, expertise and approaches[4]. It is continuing to provide the projections and funding estimates showing the challenge in meeting these needs which lie ahead[5].

The vision of RHSC is that all people in lower and middle-income countries can access and use affordable, high-quality supplies, including a broad choice of contraceptives, to ensure their better reproductive health. Its mission is to ensure that every person is able to obtain and use RH supplies. The Coalition has committed itself to achieving a sustained supply of affordable, quality reproductive health supplies in low- and middle-income countries.

The World Health Organization (WHO), UNFPA and other agencies developed an Interagency List of Essential Medicines for Reproductive Health[6]. The document represents "an international consensus" on the rational selection of essential reproductive health medicines. It is intended to support decisions regarding the production, quality assurance and national procurement and reimbursement schemes of these medicines. It was augmented by a guide "Essential Medicines for Reproductive Health: Guiding Principles for their Inclusion on National Medicines Lists"[7]. This document addresses the principal reproductive health medicines which are the focus of WHO's Prequalification Programme established in 2006 (see Table 3).

One of the fundamental problems in the provision of these essential medicines is cost. Despite the growing private sector, the public sector still remains the principal supplier of reproductive health medicines in many developing countries and purchasers, whether they are governments, donors or procurement agencies, are looking for a sustainable supply of the highest quality products at the lowest possible cost to meet the goal of achieving supply security of essential reproductive health medicines. This means that:

- manufacturers must have the incentives to produce the required essential medicines;
- procurement and regulatory agencies, together with national and international technical agencies, must ensure they are affordable and of assured quality;
- governments must create budget lines for these essential medicines; and
- donors must assist in ensuring these activities are supported.

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[4] Reproductive Health Supplies Coalition: http://www.rhsupplies.org/

[5] Contraceptive Projections and the Donor Gap: Meeting the Challenge, Reproductive Health Supplies Coalition, 2009 pp44. See http://www.rhsupplies.org/fileadmin/user_upload/RMA_WG_meetings/RHSC-FundingGap-Final.pdf

[6] World Health Organization (2006). The Interagency List of Essential Medicines for Reproductive Health, 2006, WHO, International Planned Parenthood Federation, John Snow Inc, Population Services International, United Nations Population Fund, World Bank. Geneva: World Health Organization. WHO/PSM/PAR/2006.1, WHO/RHR/2006.1. see http://whqlibdoc.who.int/hq/2006/WHO_PSM_PAR_2006.1_eng.pdf

[7] World Health Organization, UNFPA and PATH (2006). Essential Medicines for Reproductive Health: Guiding Principles for Their Inclusion on National Medicines Lists. PARTH, Seattle pp104

While contraceptive users in the developed world generally have a broad choice of types and brands, users in developing countries are often limited in what they can buy and afford. This gap in product access, as well as the potential of competing in developed markets, has attracted generic pharmaceutical manufacturers to supply their own versions of lower-priced hormonal contraceptives as off-patent copies of popular originator brands. As such, when a woman receives a cycle of contraceptive pills she is unlikely to have any idea of its origin and how the medicine came to be in her clinic. In the USA and other high-income countries it is more than likely to be a generic medicine.

Patents have expired on many of the hormonal contraceptive and other reproductive health medicines commonly used around the world and on practically all those used in less developed countries. In general health terms the emergence of generic competition is a positive development and provides policymakers with a powerful tool and access to lower drug prices. For less developed countries that depend upon international donor support for the procurement of their RH supplies, and indeed for the donor community themselves, lower price medicines means the opportunity of "more for less" a crucial advantage in today's economic environment.

At the same time a woman receiving her contraceptive services in Bangladesh, Burkina Faso, Cambodia, Peru, Zambia or any lower and middle-income country has an absolute right to know that the product she is using is of assured quality and that its safety and effectiveness have been evaluated and verified as being identical to the original drug. For this she relies upon her health professional who in turn relies upon the regulatory authorities of the country. While there is no doubt that generic RH medicines can offer a significant price advantage over their innovator competitors and have achieved a high degree of penetration in the global market-place, serious questions remain whether, in many lower and middle-income countries, certain products meet internationally accepted safety and efficacy and quality criteria.

This paper analyses the emergence and impact of generic reproductive health medicines and the challenge to international and national procurers of ensuring the quality, safety and efficacy of products. It focuses specifically on the role of WHO's Prequalification Programme in achieving this objective.

2. The role of the public and private sectors in providing medicines for reproductive health

Since the 1960s donor Governments and international agencies, such as UNFPA, the International Planned Parenthood Federation (IPPF) and many others have mobilized to educate, and provide quality family planning products and services to women around the globe, resulting in significant increases in contraceptive use and improved health and economic circumstances for individuals and their families. Despite the growing private sector, the public sector remains the principal supplier of contraception in many countries and purchasers, whether they are governments, donors or non-governmental organizations (NGOs), must be able to provide quality assured products for the public sector or social marketing programmes at the lowest possible prices.

Historically, in many countries of the developing world, Western donor agencies have been significant players in the funding and purchase of contraceptives for supply to the public sector, primarily purchasing products from large multinational pharmaceutical

companies based in OECD countries. Adopting an innovative and mutually beneficial strategy, donors and international agencies purchased and delivered specially adapted Blue Lady[8] presentations of patented contraceptives in support of country programmes, supplied by the innovator pharmaceutical manufacturers at a cost plus price, allowing clients in less developed countries access to high quality products at a fraction of their Western market price. This provided industry with an entry point for the introduction of their higher price versions and new preparations, with marketing costs significantly reduced. Over time as income levels increased in many countries, consumers traded up to the more expensive products. As well as proving an effective business model this approach also provided an appropriate vehicle for the companies' corporate social responsibility (CSR) activities.

This model has effectively remained in place for over 30 years as the main delivery mechanism, adapted over the years to include social marketing as country markets evolved, segmented and consumer preferences and approaches changed as a result of different educational promotional strategies, economic situations and newer products/formulations coming down the pipeline.

In 2011, donor agencies continue to play a critical role in ensuring availability of reproductive health medicines, using a wide range of approaches for procuring and channelling products to recipient countries, which include, funding and/or utilizing the services of international procurement organizations, supporting social marketing programmes and contracting out procurement to other entities in the private and public sectors. Increasingly, within the new aid architecture, donors are opting to provide funding directly to countries who undertake procurement themselves, without intermediaries.

The RHSC publication Contraceptive Projections and the Donor Gap: Meeting the Challenge (2009) shows that almost half the donor support to family planning products goes to hormonal contraception and is evenly split between oral and injectable methods. Despite the mainstreaming of generics in the US and other high-income countries, the current market place for quality assured public sector hormonal contraception can reasonably described as an oligopoly, with three Western research and development (R&D) orientated innovator (or their successors) companies[9] still supplying the majority of the market, despite the fact that nearly all of the relevant compositions have been off patent for many years.

From a cost perspective there is a powerful incentive for establishing a competitive roster of quality assured generic products, both for RH donors and procurers. In 2009, RHCS partners spent an estimated US$127 million on the purchase of hormonal contraception[10], with UNFPA (US$59 million/46%) the largest procurer in value terms (Table 1).

[8] The Blue Lady brand was developed as a non-proprietary mark by USAID to differentiate public sector products made available to programmes by USAID and IPPF from the commercial versions.

[9] Research and development innovator companies based in the USA, Europe and other OECD countries.

[10] Using published UNFPA value data from 2009, we have extrapolated the value of all donor related purchasing for the same year, cross referenced with the publication; UNFPA - Donor Support for Contraceptives and Condoms for STI/HIV Prevention 2009.

Table 1. Donor funded hormonal contraceptive purchasing by value

Donor	US$ million	% share
USAID	39.2	31%
UNFPA	58.6	46%
BMZ/KFW	14.0	11%
DFID	4.8	5%
PSI	1.5	1%
OTHERS	8.1	6%
Totals	126.2	100%

Through the uptake of generics there is an opportunity to make a significant medium-term financial impact on the cost of RH medicines, providing these medicines are of assured quality. Based upon the known cost structures and market pricing of generic hormonal contraception this could potentially reduce procurement costs for RHSC member organizations by US$60 million, or almost 50% annually.

It is interesting to note that a women in the US is more likely than not to receive generic medicines of assured quality when she next visits her provider, while donor support for RH medicines is still primarily utilized to purchase innovator versions. Paradoxically, in the private sectors of lower and middle-income countries there appears to be significant generic penetration of RH medicines, a number of governments have also made the switch to generic substitutes on an economic basis. The challenge is to ensure over time that these products meet appropriate quality assurance criteria. In the following sections we will consider some of the constraints.

3. The role of generic products in achieving MDG5

Firstly, what is a generic medicine? A generic product is a copy of the original innovator drug which can be produced and marketed in countries where the patent on the original product has expired; the drug has never been patented; or where a patent is not in force. It must contain the same active ingredients at the same strength as the innovator brand; and meet the same pharmacopoeial requirements for the preparation. Manufacturers of generic drugs are not required to duplicate the safety and efficacy studies that were undertaken on the original innovator product. However, they must show that they are of similar quality, being manufactured under CGMP and are pharmacokinetically bioequivalent. Hence, generics are identical in dose, strength, route of administration, safety, efficacy, and intended use to the original product, although they may have a different colour or shape from the original product and will be marketed under different brand names and presentation styles.

For more than fifty years, the Western R&D based pharmaceutical industry has made a truly significant contribution to the field of reproductive health by both the development of a range of products, particularly hormonal contraceptives[11] and in conjunction with major

[11] Hall PE. (2005). What has been achieved, what have been the constraints and what are the future priorities for pharmaceutical product-related R&D to the reproductive health needs of developing countries?

aid agencies, made them available at preferential prices for less developed countries. However, it is the R&D based pharmaceutical industry that has, in recent years, faced unprecedented revenue and profit declines as a result of generic competition in its first tier markets, such as the USA and Europe, and increasingly in middle-income and less developed countries. Overall estimates for yearly sales of generic drugs range as high as US$80 billion occurring at a time when the industry is bringing fewer drugs to market. A 2007 article in the New England Journal of Medicine[12] noted that, by 2010, patents on some 110 drugs will have expired, including some of the industry's most profitable sellers. In fact, by 2007, generic drugs accounted for 63% of all U.S. prescriptions for drugs[13].

In 2008, the hormonal contraceptive market was worth US$6.2 billion across the seven major first tier pharmaceutical countries alone, of which 50% is accounted for by oral contraceptives[14]. If we consider the latter figures, which relate to women who live in the USA and Europe and, in general, have unrivalled access to health care, they (or their national or private insurance schemes) spend US$3-4 billion on oral contraceptives. The developing world has 85% of the world's women of reproductive age and estimated sales of US$1.2 billion.

Because the oral contraceptive market was the most valuable hormonal contraceptive product in developed countries, for many years major pharmaceutical companies were reluctant to introduce new products, like implants, vaginal rings and patches, in case they cannibalized this market. However, by the mid-2000s, the contraceptive market in these countries, and particularly the USA, changed dramatically, partly because of the growth of generic oral contraceptive manufacturers. In the USA, two generic companies in particular aggressively introduced quality generic oral contraceptives and basically pushed most of the traditional big players out of the oral contraceptive business. At the same time, there was a significant reduction of the number of major pharmaceutical companies in the field, primarily because of mergers and acquisitions. Several changed their business strategies, with a number of companies that manufacture RH medicines withdrawing and/or discontinuing the provision of preferential priced medicines to less developed countries and in some cases stopping production of RH medicines altogether.

At the same time, more than 60 manufacturers producing generic hormonal contraceptives alone, and a smaller number manufacturing other RH medicines, such as misoprostol, oxytocin and mifepristone have emerged. The vast majority of these companies are located in and are serving lower and middle-income countries. Over the past decade, these companies have been rapidly expanding their reach and gaining market share in almost every country of the world, resulting in significant increase in competition, with the traditional manufacturers of hormonal contraception who are increasingly withdrawing their products from developing countries, creating additional space for the new generic entrants.

Commission on Intellectual Property Rights, Innovation and Public Health, World Health Organization, Geneva. See http://www.who.int/intellectualproperty/studies/reproductive_health/en/index.html

[12] The Ongoing Regulation of Generic Drugs Richard G. Frank, Ph.D.N Engl J Med 2007; 357:1993-1996

[13] Data from IMS Health, National Prescription Audit Plans, National Sales Perspective, for the 12 months ending June 2007.

[14] Commercial Insight: Hormonal Contraceptives - Look Beyond Oral Contraception for a Competitive Edge. Datamonitor, Oct 2009, pp243

However, while this market transition has resulted in the availability of cheaper products, it has not necessarily created a body of suppliers that can demonstrate to public and social marketing sector procurement agencies that their products can meet internationally accepted quality standards. The lack of a competitive and equitable supplier base represents a significant and growing problem for procurement organizations, many of which are, by necessity, purchasing to some degree from generic developing country manufacturers.

This problem was exemplified in a study undertaken by Concept Foundation[15] which showed that relatively few manufacturers of generic hormonal contraceptives in lower and middle income countries currently achieve acceptable levels of quality assurance. The study assessed 47 manufacturers in 15 lower and middle-income countries in late 2005 and early 2006. It found significant disparities between manufacturers in terms of their facilities and their ability to meet CGMP.

Despite the fact that every one of the 47 factories visited had received national GMP certification, it is unlikely that, at the time of the study, any one of them could have met WHO, PIC/S[16] or stringent drug regulatory authority (SRA)[17] requirements. It was considered that 30% of the factories could eventually meet these requirements by the end of 2009; it was also possible that a further 35% could comply with these requirements some time later if significant investment and improvements in quality management and practice could be made. The remaining 35% gave considerable cause for concern and many of these companies needed to reconsider their role in production of products for human use and close the facilities visited.

Unfortunately, the expectation that some 15 factories could meet internationally accepted quality standards by the end of 2009 proved to be over-optimistic. Even these "better" companies initially did not understand what was required to meet CGMP, and/or undertake appropriate bioequivalence studies and/or complete the required documentation. Hence many did not seek the necessary technical assistance. As a result, by April 2011, no generic reproductive health medicine has yet has been prequalified by WHO's Prequalification Programme (see Table 4), although one or two are very close. Nevertheless, in the past five years there have been significant changes and appropriate technical assistance is being made available which will lead to access to several high quality contraceptive products by the end of 2012.

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[15] Hall PE, Oehler J, Woo P, Zardo H, Chinery L, Singh JS, Jooseery SH and, Essah NM. (2007).A study of the capability of manufacturers of generic hormonal contraceptives in lower and middle income countries. Contraception. 75:311-317

[16] The Pharmaceutical Inspection Convention and its related Pharmaceutical Inspection Cooperation Scheme (PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide active cooperation in the field of GMP. Membership consists of 28 European states plus Argentina, Australia, Canada, Israel, Malaysia, Singapore, South Africa, Ukraine and the USA. Other countries such as Indonesia and Thailand are now transitioning to PIC/S GMP.

[17] Stringent Drug Regulatory Authority (SRA) means a regulatory authority (in case of the European Union both EMEA and national competent authorities are included) which is
a) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH (as specified on its website:); or
(b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or
(c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

As mentioned previously, patents have expired on most commonly used hormonal contraceptive and other reproductive medicines around the world. As a result, with the exception of contraceptive patches, vaginal rings and some of the newer oral contraceptive formulations, which are rarely used in less developed countries because they either have not been made available by the innovator or if they are available most women in the country could not afford them, hormonal contraceptive methods are available in generic form. Table 2 shows the situation of various types of contraceptives with regard to patents and the availability of generic products.

Table 2. Hormonal contraceptives, patents and the availability of generic products

Product type	Patent coverage	Generic products available?
Oral contraceptives		
- combined (COCs)	No (except for a few new products)	Yes
- progestogen-only (POPs)	No	Yes
Injectable contraceptives		
- progestogen-only, DMPA	No (except for subcutaneous delivery)	Yes
- combined injection, NET-EN	No	Yes
- combined injection, Cyclofem	No	Yes
- combined injection, Mesigyna	No	No
Intrauterine devices		
- copper T	No	Yes
- LNG-releasing	No	No
Vaginal rings		
- Monthly combined	Yes	Limited
Implants		
- Jadelle	No	Yes
- Implanon	Yes	No
Patches		
- Weekly combined	Yes	No
Emergency contraception		
- Levonorgestrel	No	Yes

4. How can we ensure the quality, safety and efficacy of generic medicines?

It is critical for both the procurers and the recipients of generic reproductive health medicines to know that the product that is being purchased is of assured quality and is safe and effective. However, it is the national drug regulators who are responsible for putting into place the criteria and processes, checks and balances to ensure the quality of the products that they approve for distribution in the country.

Most developed countries have well-resourced, stringent drug regulatory agencies[18] which can evaluate all aspects of the quality, safety and efficacy of medicines. However, there are many challenges facing National Drug Regulatory Agencies (NDRAs) worldwide, a report by Moran et al in 2010[19] which focussed on African agencies stated that only a minority have the resources to effectively evaluate new medicines de novo.

The report considered that the major factors behind the regulatory capacity shortfall to be: lack of a clear legislative framework; dispersion of regulatory responsibility; lack of financial resources; lack of experienced and qualified staff; lack of political support; and lack of appreciation of the importance of medicine regulation by stakeholders, including researchers, developers, government departments and the general public.

Given the constraints on regulators worldwide; the emergence of major markets for the manufacturers of reproductive health medicines; and the needs of international and national procurers to maximize the use of limited funds, how can we ensure the quality, safety and efficacy of generic medicines?

4.1 Quality assurance of reproductive health medicines

WHO defines quality assurance as "a wide ranging concept covering all matters that individually or collectively influence the quality of a product. With regard to pharmaceuticals, quality assurance can be divided into four major areas: quality control, production, distribution, and inspections. It is the totality of the decisions made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use." It goes on to define Good Manufacturing Practice (GMP) as "that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization."[20]

It is important for all players, whether they be manufacturers, regulatory agencies or procurement agencies, to understand that GMP is not static. Practices to maintain and improve quality are being continuously updated to meet the highest quality standards and address any issues that impact on quality that arise. This is why it is essential that manufacturers, regulatory agencies and procurement agencies understand what current GMP (CGMP) means. Manufacturers must make products to CGMP but they may not know what CGMP is because they either do not know or do not want to know how they may need to upgrade their facilities and processes. Furthermore, their national regulatory agencies may not have updated their GMP requirements and therefore are not inspecting manufacturing facilities for CGMP.

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[18] Stringent Drug Regulatory Authority (SRA) means a regulatory authority (in case of the European Union both EMEA and national competent authorities are included) which is
a) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH (as specified on its website:); or
(b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or
(c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

[19] Moran M, Guzman J, McDonald A, Wu L and Omune B. Registering New Drugs: The African context. New tools for new times. The George Institute for International Health, Sydney, Australia. 2010 pp38. See http://www.dndi.org/images/stories/advocacy/regulatory-report_george-institute-dndi_jan2010.pdf

[20] See http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/

So what requirements should a manufacturer be complying with? Obviously, in order to manufacture product in its own country, a company must meet national regulations enforced by the drug regulatory authority. But although it is the obligation of a national drug regulatory agency to ensure that national requirements meet current GMP requirements (CGMP), many have not done this. This not only means that national requirements are less stringent than those that manufacturers should be complying with to ensure that products are of assured quality, it also means that the products do not meet the needs of stringent regulatory authorities when a company tries to export its products to the lucrative high income export markets.

It remains of grave concern that many countries' regulations are, to a greater or lesser extent, found to be lacking. This can be found even in major drug producing countries that are exporting to countries with stringent drug regulatory agencies. For example, the authorities responsible for regulating products from several major exporters in one particular city still issue Certificates of Pharmaceutical Product that state "Do the facilities and operations conform to GMP as recommended by the World Health Organization? Yes/no, see footnote 15". Footnote 15 states "The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the report of the thirty-second Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report series, No 823, 1992, Annex 1"!! Hence, in theory, a company only has to manufacture under the GMP requirements of 20 years ago!

In order to assist companies meet these needs as well as providing guidance to meet best current practice, both WHO and PIC/S[21] provide key guidelines and recommendations for CGMP. References to WHO's documents can be found below[22] and in the attached document developed by Concept Foundation for WHO's Prequalification Programme entitled "Frequently asked questions on the prequalification of medicines for reproductive health".

Both the WHO and PIC/S GMP documents have common goals and objectives. They are similar in content and cover the basic principles of CGMP that influence the quality of a product. These include the following issues:

- Starting materials (APIs, excipients, primary containers)
- Premises
- Heating, ventilation and air conditioning (HVAC)
- Water for pharmaceutical use
- Equipment
- Methods, specifications and sampling
- Qualification and validation
- Documentation
- Personnel and training
- Complaints and product recalls

[21] PE 009-9 PIC/S GMP Guide, 2009, see http://www.picscheme.org/publication.php?id=4

[22] WHO, 2007 Quality Assurance of Pharmaceuticals - A Compendium of Guidelines and Related Materials - Volume 2, 2nd Updated Edition - Good Manufacturing Practices and Inspection. World Health Organization, Geneva, pp 416

WHO Expert Committee on Specifications for Pharmaceutical Preparations, 44th report. Technical Report Series 957, 2010. Annex 2. WHO good manufacturing practices for active pharmaceutical ingredients. Annex 3. WHO good manufacturing practices for pharmaceutical products containing hazardous substances. Annex 4. WHO good manufacturing practices for sterile pharmaceutical products.

- Sanitation and hygiene
- Self inspection

Despite the similarities of their GMP texts, WHO and PIC/S have different roles and responsibilities. WHO, is an intergovernmental organization, and can only make recommendations, and not implement requirements, to its 193 Member States. The WHO texts pertaining to good practices in production and good practices in quality control tend to be more detailed than other GMP texts.

PIC/S has, on the other hand, agreed requirements for its members. Only inspectorates meeting these specified requirements can become members of PIC/S. PIC/S has recently harmonized its GMP rules with the EU Guide to Good Manufacturing Practice for Medicinal Products.

It is essential that national drug regulatory agencies review and amend their GMP regulations at regular intervals to ensure that their national GMP is similar to WHO or PIC/S GMP and meet international expectations, norms and standards with a specific focus on quality assurance and related aspects. The response to manufacturers that wish to make products that meet the requirements of WHO's Prequalification Programme should be complying with WHO or PIC/S guidelines and recommendations, regardless of whatever requirements are demanded nationally.

Bioequivalence studies

As stated above, as well as demonstrating that products meet CGMP, a key requirement for manufacturers of generic drugs is that they demonstrate that the products are bioequivalent to the innovator product. This is the internationally accepted proxy for the in depth safety and efficacy studies that had to be undertaken by the innovator company before it could get the drug registered by a SRA and is one of the reasons that generic products are cheaper than innovators since the company has not had to bear the drug research and development costs.

Concept Foundation's 2007 study found that "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 programmes, 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 Practice (GCP) in the conduct of the studies or Good Laboratory Practice (GLP) for the analysis of blood specimens collected."

Virtually all companies in the study had met difficulties in addressing the design and conduct of bioequivalence studies. This has also become apparent as products have been submitted to WHO's Prequalification Programme and has been one of the key reasons contributing to the rejection or subsequent cancellation of submissions (see section 5).

Clear guidelines on the design and requirements for bioequivalence studies are to be found in WHO TRS 937[23] and in the European Medicines Agency's (EMA) "Guidance on the investigation of bioequivalence"[24]. Manufacturers need to seek advice from a professional statistician and also identify a qualified Clinical Research Organization that meets internationally accepted GCP and GLP. WHO's Prequalification Programme will provide advice to companies submitting products for prequalification. The key issues are addressed in Concept Foundation's document entitled "Frequently asked questions on the prequalification of medicines for reproductive health".

5. The United Nations Prequalification Programme and its role in assuring quality

The United Nations Prequalification Programme is managed by the World Health Organization (WHO). It was set up in 2001 to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. It is supporting the improvement in manufacturing capacity by prequalifying products which have been assessed, inspected and controlled to meet international norms and standards for quality, efficacy and safety; giving assurance that international norms and standards are applied at all the steps of the prequalification and within the process itself; and enabling access to good quality medicines.

Prequalification (as in prequalification to tender) was originally intended to give United Nations procurement agencies, such as UNICEF the choice of a range of quality medicines. With time, the growing list of products (i.e. medicines) that have been found to meet the set requirements has come to be seen as a useful tool for anyone bulk purchasing medicines, including countries themselves and other organizations. For instance, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) disburses money for medicines that have been prequalified by the WHO process.

In April 2011, there were 255 medicines prequalified (HIV/AIDS, 192; influenza, 7; malaria, 17; reproductive health, 8; tuberculosis, 31). The list changes regularly as products are added but also companies may withdraw products as, in the field of HIV/AIDS treatment, regimens change. The prequalification of products in certain treatment areas such as HIV/AIDS has transformed the availability and affordability of essential medicines and up to 90% of purchases by GFATM in this area are products prequalified by WHO.

Since 2006, WHO has worked on prequalifying medicines for reproductive health. In response to requests from an Inter-agency working group and the Reproductive Health Supplies Coalition, it put out an initial Expression of Interest in October 2006 for hormonal contraceptives. Most are listed on WHO's Model List of Essential Medicines and represent the main product of each type purchased by public sector procurement agencies. Since then it has expanded its scope and following its most recent Expression of Interest (May 2010) will accept requests for prequalification of all products listed in Table 3.

[23] WHO Expert Committee on Specifications for Pharmaceutical Preparations, 40th report, Technical Report Series 937, 2006. Annex 7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Annex 9. Additional guidance for organizations performing in vivo bioequivalence studies.

[24] European Medicines Agency, 2010. Guidance on the investigation of bioequivalence. Doc ref: CPMP/EWP/QWP/1401/98Rev1/Corr.

Table 3. Reproductive health medicines in WHO's Prequalification Programme

Hormonal contraceptives
Combined oral contraceptives, progestogen-only pills and emergency contraceptive pills
- ethinylestradiol + desogestrel, tablet 30 micrograms +150 micrograms - ethinylestradiol + levonorgestrel, tablet 30 micrograms + 150 micrograms - levonorgestrel, tablet 30 micrograms - levonorgestrel, tablet 750 micrograms (pack of two); 1.5 mg (pack of one) - norethisterone, tablet 350 micrograms - norgestrel, tablet 75 micrograms
Progestogen-only and combined injectable contraceptives
- medroxyprogesterone acetate, depot injection 150 mg/ml, in 1-ml vial - medroxyprogesterone acetate + estradiol cypionate, injection 25 mg + 5 mg - norethisterone enanthate, injection 200 mg - norethisterone enanthate + estradiol valerate, injection 50 mg + 5 mg
Implantable contraceptives
- two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg in total) - etonogestrel, implant, 68 mg of etonogestrel
Other medicines for maternal health
Oxytocics and anti-progestogens
- oxytocin, injection 10 IU, 1-ml - mifepristone 200 mg tablet (only to be used in combination with misoprostol) - misoprostol 200 microgram tablet
Prevention and treatment of eclampsia
- magnesium sulphate, injection 500 mg/ml, in 2-ml and 10 ml ampoule or Unject

It was approximately two years after the launch of the scheme in October 2006 before the programme was fully staffed and functional and in a position to effectively evaluate dossiers. As shown in Table 4, 42 reproductive health product applications have been submitted, of which, 25 (60%) have been rejected outright since they did not respond adequately to stated requirements or cancelled during the process of initial review. The majority of these were for generic products. The major reasons for rejection or cancellation have related to the product not meeting the required quality assurance standards, inadequate documentation or the conduct of an inadequate bioequivalence study.

A total of eight products[25] have been prequalified, although all are hormonal contraceptives produced by the innovator European or USA pharmaceutical company. These are shown in Table 5. As yet no generic product has been prequalified. Overall, generic submissions (31) represent 74% of those received since October 2006. Although none have been approved, there are 3 or 4 generic products currently under review which could be prequalified in the near future.

Table 4. Status of submissions of reproductive health medicines, April 2011

[25] http://apps.who.int/prequal/query/ProductRegistry.aspx?list=rh

Product	Submitted	Not accepted	Cancelled	Pending	Approved
Levonorgestrel/ ethinylestradiol, 150/30 µg tablets	16	5	5	5	1
Desogestrel/ ethinylestradiol, 150/30 µg tablets	1	—	—	—	1
Levonorgestrel, 750 µg tablets	5	2	2	0	1
Levonorgestrel, 30 µg tablets	4	1	2	0	1
Lynestrenol, 0.5 mg tablets	1	—	—	—	1
Levonorgestrel, 150 mg 2-rod implant	2	—	—	1	1
Etonogestrel, 68 mg implant	1	—	—	—	1
Medroxyprogesterone acetate, 150 mg injection	5	—	4	—	1
Norethisterone enantate, 200 mg injection	2	1	—	1	—
Norethisterone enantate/ estradiol valerate, 50/5 mg injection	2	2	—	—	—
Oxytocin, 10 IU/ml	3	—	1	2	—
Total	42	11	14	9	8

The process of prequalification is as follows:

- Product dossiers are submitted by the manufacturer.
- Dossiers are screened for completeness before being accepted.
- If accepted, the dossiers are assessed according to quality, safety and efficacy. There are two assessment tracks, the quality part and the safety and efficacy part. This is done in-house together with external international experts, mostly from SRAs
- Results are communicated to the applicant. If corrective actions are required, the decision on the acceptability of data and information is postponed.
- If the assessment is successful an inspection visit will be under taken, by WHO staff and external international inspectors.
- If the process is completed satisfactorily, the product and its site of manufacture will be listed on WHO's website.

The process would normally take 18-24 months.

Table 5. Reproductive health medicines prequalified, April 2011

INN	Formulation and strength	Applicant	Manufacturing site	Date of PQ
Ethinylestradiol+ Levonorgestrel	Coated tablets 30µg+150µg	Bayer Schering Pharma AG	Weimar, Germany	26 May 09
Ethinylestradiol+ Desogestrel	Tablets 30µg+150µg	NV Organon	Kloosterstraat, Oss, The Netherlands	29 Sep 10
Etonogestrel	Implant 68mg	NV Organon	Kloosterstraat, Oss, The Netherlands	02 Jun 10
Levonorgestrel	Coated tablets 30µg	Bayer Schering Pharma AG	Weimar, Germany	26 May 09
Levonorgestrel	Tablets 0.75mg	Gedeon Richter	Budapest, Hungary	20 Aug 10
Levonorgestrel	Implants 2 rods x 75mg	Bayer Schering Pharma	Turku, Finland	23 Sep 09
Lynestrenol	Tablets 500µg	NV Organon	Kloosterstraat, Oss, The Netherlands	02 Jun 10
Medroxyprogesterone acetate	Suspension for injection 150mg/ml	Pfizer	Rijksweg, Puurs, Belgium	20 Aug 10

There are certain incorrect perceptions about the Prequalification Programme on the part of certain procurers and manufacturers. One is that that the prequalification process is unnecessarily rigid, overly complex and therefore slow. Another is that it has favoured the Western R&D based pharmaceutical companies. Certainly, as stated above, the programme started slowly and for some time there was a lack of information such as that shown in Table 4. However, these perceptions have almost always resulted from the fact that existing suppliers did not have products prequalified and usually reflect their attitudes to prequalification, which are then relayed to their customers.

The Prequalification Programme applies internationally accepted criteria, as discussed in section 4, and uses the most qualified assessors and technical knowledge to assess the quality of products. It applies standards similar to those used in the European Union and the USA; it is no more or no less stringent. It certainly does not favour innovator companies and is keen to get generic reproductive health medicines prequalified. However, as discussed above, most generic companies have been unable to respond adequately to the requirements of the programme.

Product prequalification does provide several benefits to manufacturers, for example, it:

- allows participation in tender procedures organized by international and some national procurers;
- gives recognition as a WHO listed company;
- may facilitate registration in some recipient countries;
- can reduce inspections from some recipient countries:
- provides the possibility to be assisted by expert consultants; and
- provides a learning process to improve company's chances of succeeding with submissions to SRAs

However, WHO has been acutely aware of some of its limitations and commissioned a study of its service among manufacturers[26]. The conclusions of the study stated that "Overall, the findings from this survey indicate that pharmaceutical manufacturers consider PQP to be a well-designed, well-executed programme. PQP assessors and inspectors are meeting or exceeding manufacturer expectations for service delivery in the process. However, pharmaceutical manufacturer applicants place a premium on feedback, communications and problem resolution during the prequalification process – with particular emphasis on the assessment of product dossiers – and these are potential improvement areas in the service design of PQP."

Based on the survey results, WHO has implemented improvements to the Programme and, for example, has set specific time limits to inform and respond to manufacturers.

6. The procurement of quality assured generic medicines

The issue of validating medicines' quality is an increasingly important issue for procurement organizations, such as UNFPA, USAID and other procurers of reproductive health products, charged with the supply of donor financed or self-subsidized medicines to country programmes or third parties, and for an expanding group of national procurers, government departments/agencies and NGOs. Prior to the availability of generics, neither product quality nor ensuring adequate product liability cover was significant considerations in a procurer's job specification. This was because buyers were able to rely upon the traditional big pharmaceutical companies providing adequate quality and cover. As such, they could purchase with a degree of confidence, particularly as most of the products purchased were approved by an SRA.

Currently, if a national or international procurement agency wishes to purchase quality assured reproductive health medicines for use in developing countries they face a marked lack of choice. The quality products available are rarely available at the lowest unit prices, those attractive to cost-constrained procurers supplying developing country markets. As discussed above, the eight prequalified products are all hormonal contraceptives produced by European or USA R&D based pharmaceutical companies and were already SRA approved and available for purchase. Hence at present there is little downward pressure on prices. Moreover, the discontinuation of certain products (a phenomenon witnessed in recent years) is possible as the pharmaceutical industry continues to consolidate globally. More vigorous markets across these product groups is, therefore, likely to depend on the emergence of prequalified (or SRA approved) generic products.

The consequence, in this acutely resource-constrained environment, has been the proliferation of non-quality assured reproductive health medicines in many developing countries. Since, as of today, there is not a range of prequalified, and hence quality assured reproductive health medicine products that can exert downward pressure on prices, procurers (both international and national) are increasingly buying non-quality assured products in order to maximize the use of limited funds. In effect, this amounts to greater availability of products with lower quality guarantees compared with a smaller quantity of quality assured products.

[26] WHO, WHO Prequalification of Medicines Programme: survey of service quality provided to manufacturers. WHO Drug Information. 2010, 24:293-298

As a result, many procurers undertake their own risk management approaches to evaluate the safety and efficacy of the non-quality assured reproductive health medicines they procure. With a broad range of prequalified products, risk management will remain necessary but the quality component would have been evaluated under a coordinated scheme with much lower transaction costs and without the additional duplication of efforts and costs seen in the current fractured situation.

To achieve this, it is critical that appropriate procurement and other policies be in place within the international institutions mandated for product supply. Governments often require external financing of drug procurement for the public sector. Such financing might be provided directly by international agencies, bilateral donors or development banks; or the medicines themselves may be procured by the donor or another organization on behalf of the donor. These institutions can have conflicting policies and regulations regarding drug procurement, which in turn may conflict with existing local laws and regulations. In addition, major international NGOs may supply products for the public sector or for social marketing or other sectoral programmes.

There are currently a number of initiatives underway, examining the issue of ensuring medicines quality, including some, relating specifically to reproductive health which are being undertaken under the auspices of the Reproductive Health Supplies Coalition and its Working Groups. RHSC members are slowly moving towards adopting a common procurement policy, similar to that used by the Global Fund to Fight AIDS, Tuberculosis and Malaria. As a first step, UNFPA submitted its new procurement policy which was approved by its Executive Board. This policy states that Finished Pharmaceutical Products will only be procured if they have been prequalified by the WHO Prequalification of Medicines Programme or authorized for use by a Stringent Drug Regulatory Authority. This is an important step. As generic products start to be prequalified in coming months and years, it will put pressure on other manufacturers to get their products prequalified and on other procurements agencies to procure prequalified products.

In 2006, there was consensus among most procurers that the WHO scheme was “a good thing”, and an expectation that the programme would rapidly approve the emerging vendors they were engaging. Since then, with no discernible progress in relation to generic manufacturers, they have continued to develop supply relationships based primarily on price, opportunity and demand from the field, adopting various, and often in-complete approaches to quality assurance validation. It is fair to argue that the prevailing attitudes to prequalification are not entirely positive among procurers. Understandably, there is frustration at what is perceived as a lack of progress. More importantly, as time passes and supply relationships mature, the retrospective evaluation of their vendors becomes a more complicated and troublesome proposition, leading to a degree of resistance.

At a Procurer’s meeting, convened by UNFPA in Washington DC in May 2010, many of these issues were articulated and presented in detail for the first time, resulting in an increased awareness of the importance of quality assurance, the direct impact on the safety and efficacy of the products and the institutional risks and potential liabilities for the procuring organizations. It is planned to move towards continuing and consistent improvement in procurement practices until there is a sufficient number of prequalified products, and at the same time begin to reduce the risks through more informed purchasing decisions. The objective is to build consensus and acceptance of this more

harmonized approach and establish common approaches to limit risk exposure until prequalification is able to offer a range of products in each category, after which time prequalification products (or SRA approved) will prevail as the norm.

Conclusions

We believe that to achieve the Millennium Development Goals, reproductive health commodities do matter! We also believe, like WHO, UNFPA and many members of RHSC, that all reproductive health products made available to developing countries, should be of the same demonstrable quality as similar products provided to people in developed countries

To provide universal access to reproductive health commodities, they must be affordable and of assured quality, something that can only be addressed by accessing generic medicines. The recent adoption of UNFPA's procurement policy similar to that of GFATM underpins this view. As discussed, the primary reason for the lack of prequalified generic products is the ability of the manufacturers to meet this criterion. As such, assistance must be provided to those manufacturers which are willing to make the necessary technical and financial commitments and which we believe, with technical support and strategic investments, can bridge the gap to prequalification in the short to medium term.

The report of the 2007 study by Concept Foundation stated that "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 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."

Now manufacturers have the opportunity of getting their products prequalified by WHO and maximizing their markets through participation in tender procedures organized by international procurers. This also means that building confidence in the WHO Prequalification Programme is a prerequisite to acceptance of common quality assurance definitions and procedures the on the part of procurement agencies, based around prequalification of quality products.

There is still much to do. It is essential that within the next two to three years there is an adequate range of quality generic products prequalified by WHO and that procurement agencies begin to adopt common procurement policies that build on the availability of affordable products of assured quality. Manufacturers must have the incentives to produce the required essential medicines for reproductive health; governments must create budget lines for essential reproductive health commodities; and donors must assist in ensuring these activities are supported.