

Quality of RH Medicines:

Update from WHO Prequalification of Medicines Programme and beyond.

4 October 2012, Paris

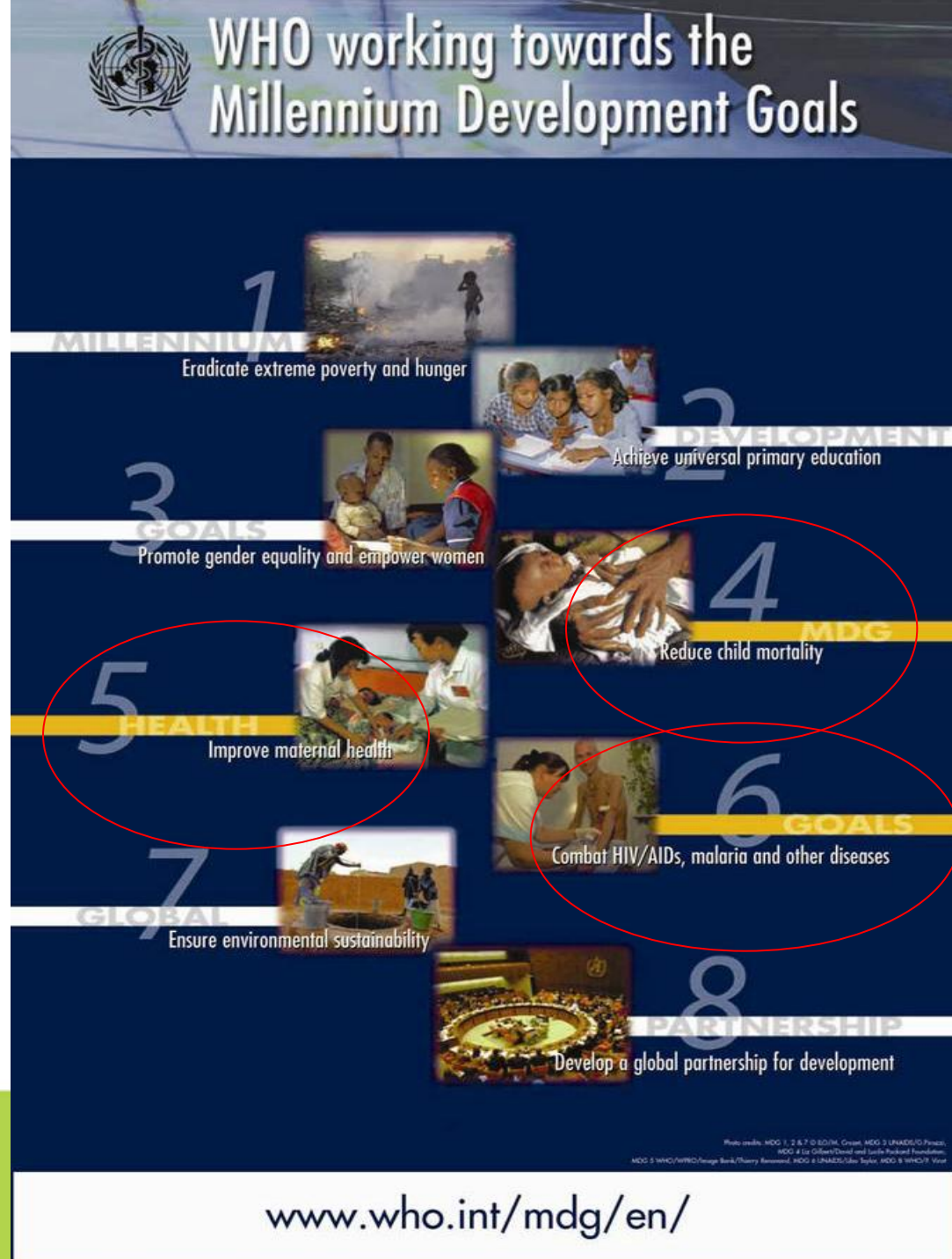
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PQP
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- The **Millennium Development Goals** (MDGs):
- Eight international **development goals** that 192 United Nations member states and at least 23 international organizations have agreed to achieve by the year 2015



WHO working towards the Millennium Development Goals

1 Eradicate extreme poverty and hunger

2 Achieve universal primary education

3 Promote gender equality and empower women

4 Reduce child mortality

5 Improve maternal health

6 Combat HIV/AIDS, malaria and other diseases

7 Ensure environmental sustainability

8 Develop a global partnership for development

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www.who.int/mdg/en/

Photo credits: MDG 1, 2 & 7 © SO/IM, Green; MDG 3 UNADEU/Pines; MDG 4 Lee Gifford/David and Lucie Probst Foundation; MDG 5 WHO/WHO/George Bank/Thierry Rousselle; MDG 6 UNAIDS/John Taylor; MDG 7 WHO/7 West



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Medicines work in WHO HQ

- **Department of Essential Medicines and Health Products (EMP)**
 - Three teams for medicines work
 - **Quality Assurance and Safety: Medicines (QSM)**
 - Medicines Access and Rational Use (MAR)
 - Medicine Programme Coordination (MPC)
- Collaboration with other clusters/departments/programmes/units in HQ
 - Vaccines and biologicals (IVB/QSS) – **Vaccines prequalification programme**
 - EMP – **Diagnostics prequalification programme**
 - Disease oriented programs (HIV/AIDS, malaria, TB, neglected diseases)
- Collaboration with WHO regional and country offices

QSM Technical Programmes

- International Nonproprietary Names (INNs)
- Quality Assurance
- Safety/Pharmacovigilance
- Regulatory support
- **Prequalification Programme for Medicines**
- Quality Assurance and Safety of Blood Products and Related Biologicals
- Anti SFFC (anticounterfeiting)



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Active collaboration with other international, regional and national organizations

- UN family, international organizations and donors:
 - UNICEF, UNFPA, UNIDO etc.
 - BMGF, Global Fund, UNITAID
 - Manufacturers associations
 - MSF
- Regional
 - **EMA/EU**
 - **Council of Europe/EDQM**
 - NEPAD
- Professional and scientific
 - FIP, CIOMS, IUPHAR, ISPE
- **National level**
 - **National Medicines Regulatory Authorities** (from all WHO Member States)



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Prequalification of Medicines Programme

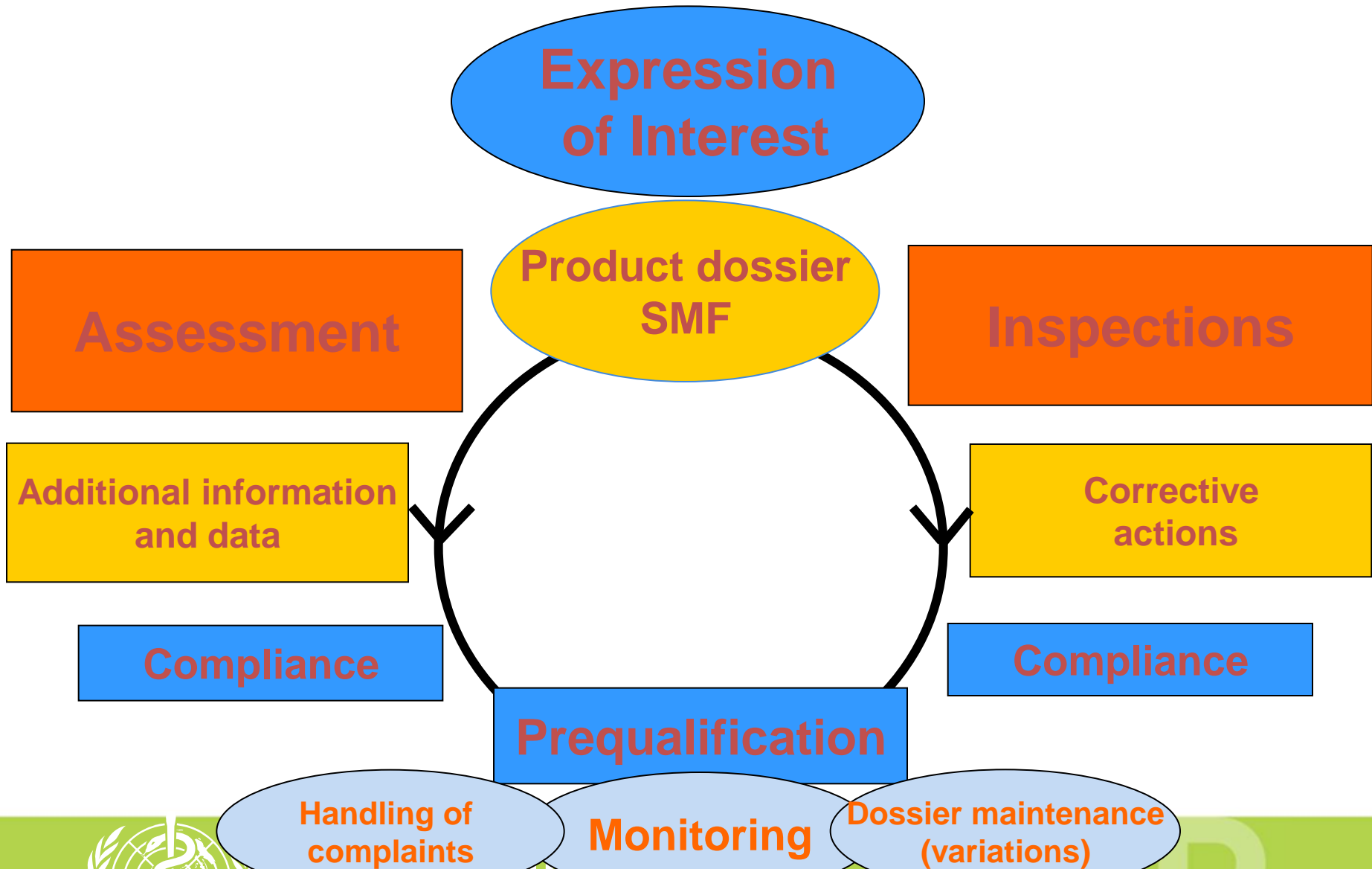
- ❑ The UN Prequalification Programme managed by WHO is ensuring that medicines procured with international funds are of assessed and inspected for *quality, efficacy and safety*, involves
 - Prequalification programme for medicines (finished dosage forms)
 - Prequalification of active pharmaceutical ingredients (APIs)
 - Prequalification of quality control (QC) laboratories
- ❑ The Prequalification Programme is *an action plan* for expanding access to priority essential medicines in the following four areas:
 - HIV/AIDS
 - Tuberculosis
 - Malaria
 - Reproductive Health
 - Selected individual products for other diseases (Flu, Zinc sulphate)

Extensive collaboration with regulators

- Not duplicating work done by stringent regulatory authorities
 - SRA approval of new and generic products – abridged procedure
 - US FDA tentative approvals – based on confidentiality agreement including in the PQ products list
 - European Medicines Agency (EMA) – Art 58 ... and beyond
 - Collaboration with EDQM, in particular in the area of APIs (confidentiality agreements with US FDA, EDQM, EMA ...)
- Active participation and involvement of
 - SRA experts
 - Regulatory authority experts from less resourced settings



Medicines Prequalification Process



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Transparency

- Very comprehensive web site
- Guidance for applicants
 - Technical guidelines
 - Guidance on specific issues (comparator products etc.)
- List of products prequalified and in pipeline
- WHO Public Assessment Reports (WHO-PARs)
- WHO Public Inspection Reports (WHO-PIRs)
- Notice of Concern (NOC) documents
- News, announcements for public meetings etc.



PREQUALIFICATION PROGRAMME

A United Nations Programme managed by WHO

Vision

Good quality medicines for everyone.

Mission

In close cooperation with national regulatory agencies and partner organizations, the Prequalification Programme aims to make quality priority medicines available for the benefit of those in need.

This is achieved through its evaluation and inspection activities, and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

Strategy

- Apply unified standards of acceptable quality, safety and efficacy.
- Comprehensively evaluate the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites.
- Prequalify quality control laboratories of pharmaceuticals.
- Build the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality.

Key output

LATEST NEWS

Micro Labs' levofloxacin
tabl prequalified

Paediatric lamivudine
tabl prequalified

First artesunate/
mefloquine prequalified

Experience of the
Expert Review Panel
(ERP)

Briefing note:
Prequalification of
Medicines for
Reproductive Health

15th International
Conference of Drug
Regulatory Authorities

All News

QUICK LINKS

Contact us


Prequalified Medicines

Prequalified APIs

Prequalified QC Labs

Dossier status

Transparency – WHO Public Assessment Reports (WHOPARs): a lot of information

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Search

WHO Medicines
Quality & Safety
Prequal home
About us
A-Z Listing of Documents
Information for applicants
Dossier assessments
Inspections
Quality Control Laboratories
Training material, workshops and meetings
Press and media

Home - Prequalification: World Health Organization Public Assessment Reports (WHOPARs): Overview of WHOPARs

Overview of WHOPARs of prequalified medicinal products

The below WHOPARs are listed by WHO reference number and therapeutic area. The International Nonproprietary Name (INN), dosage formulation and dosage strength, as well as supplier are included.

HIV/AIDS products

- **HA043:** Lamivudine - 150mg Film-coated tablets - Cipla Ltd - INDIA
- **HA060:** Lamivudine/Zidovudine - 150mg/300mg Film-coated tablets - Cipla Ltd - INDIA
- **HA097:** Lopinavir (+ Ritonavir) - 133.3mg (+33.3mg) Soft capsules - Abbott Laboratories Ltd - USA
- **HA098:** Lopinavir (+ Ritonavir) - 80mg (+20mg) Oral solution - Abbott Laboratories Ltd - USA
- **HA110:** Lamivudine/Zidovudine - 150mg/300mg Film-coated tablets - GlaxoSmithKline - UK
- **HA111:** Abacavir/Lamivudine/Zidovudine - 300mg/150mg/300mg Film-coated tablets - GlaxoSmithKline - UK
- **HA152:** Lamivudine/Zidovudine - 150mg/300mg Tablets - Hetero Drugs Limited - INDIA
- **HA153:** Lamivudine - 150mg Film-coated tablets - Hetero Drugs Limited - INDIA
- **HA210:** Nevirapine/Lamivudine/Stavudine - 200mg/150mg/40mg Bi-layer uncoated tablets - Cipla Ltd - INDIA
- **HA249:** Stavudine - 40mg Capsules - Aspen Pharmacare - SOUTH AFRICA

Transparency - WHOPIRs and NOCs

- These are published in response to the WHA Resolution WHA57.14 of 22 May 2004, which requested WHO, among other actions:
 - *"3. (4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available;"*
- **A WHO Public Inspection Report (WHOPIR)** provides a summary of the inspection (where found to be GMP complaint)
- **A Notice of Concern (NOC)** is a letter reflecting areas of concern where the non-compliances require urgent attention and corrective action by the manufacturer or contract research organization.



Why products do not get prequalified?

Original Paper

Journal of
**Generic
Medicines**

Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme

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Abstract

This study was undertaken to determine the type and extent of deficiencies in generic product dossiers in the therapeutic areas of HIV/AIDS, tuberculosis, malaria and reproductive health, as submitted to the WHO Prequalification of Medicines Programme. There were considerably more quality-related deficiencies in tuberculosis, malaria and reproductive health dossiers compared to HIV dossiers, especially in the category specification of active pharmaceutical ingredients, development pharmaceuticals, manufacturing method and finished pharmaceutical product specifications. The deficiencies related to the efficacy/safety portion of the dossiers displayed a trend similar to that observed in the quality portion in that the most critical deficiencies such as an incorrect study design, the use of an unacceptable comparator or the failure to include a study occurred considerably more frequently in the tuberculosis, malaria and reproductive health dossiers than in the HIV dossiers. The frequency of dossier-related deficiencies as determined on screening and assessment of the dossiers seemed to be inversely related to the number of product dossiers that had been prequalified by the end of 2010. The results of this study stress the need for continued capacity building of local generic manufacturers, further development of pharmacopoeial monographs by WHO (PhInt) and other pharmacopoeial commissions, not least to promote development of generic products, as well as development of new guidelines (WHO guidelines for development of generic and paediatric products and a technology transfer guidance document are currently being finalized). To our knowledge, this is the first comprehensive review of the quality and efficacy/safety portions of generic product dossiers, originating from pharmaceutical companies in emerging markets, and comparison of dossier deficiencies across four critically important therapeutic areas.



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Common deficiencies: quality

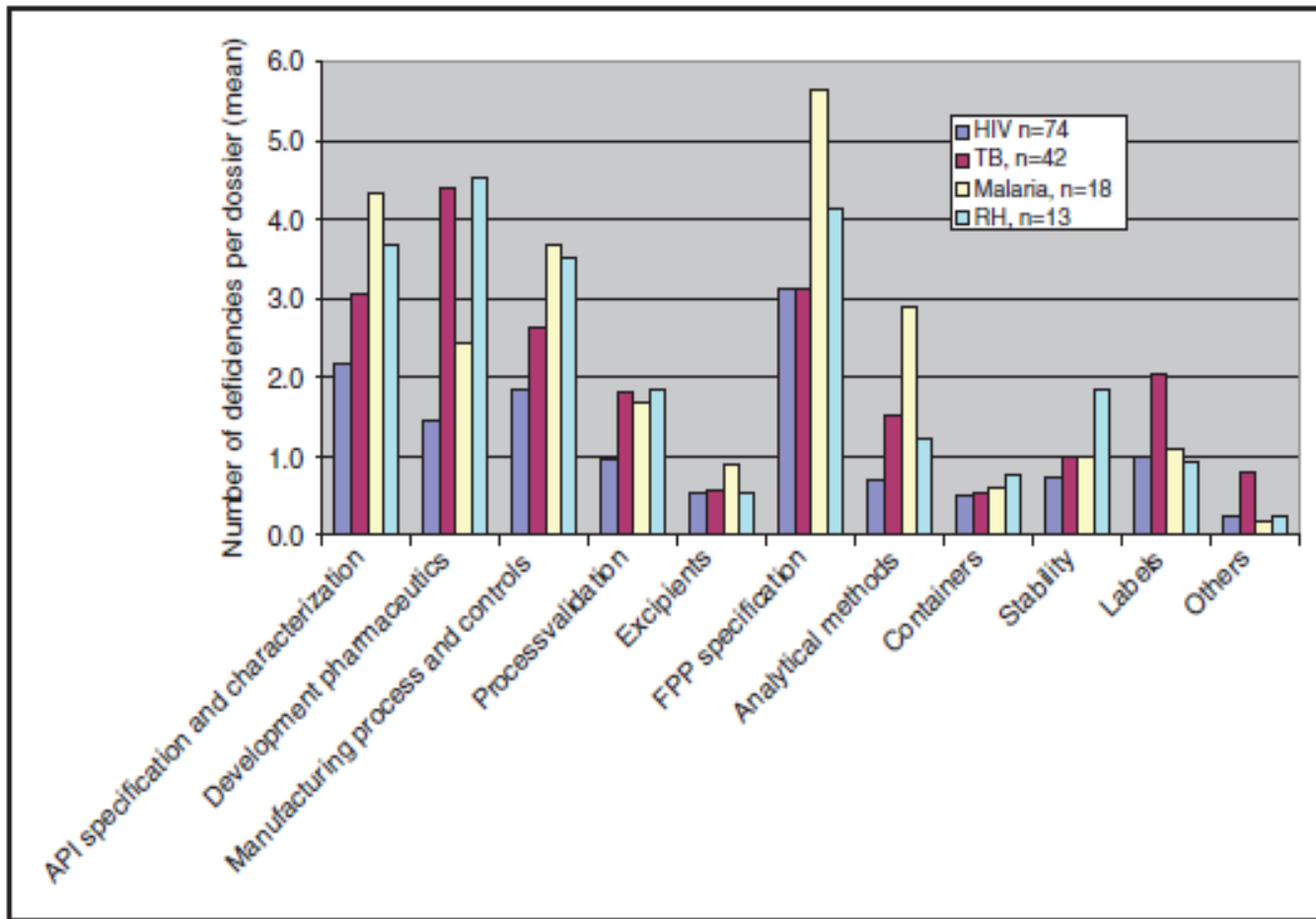


Figure 2. Deficiencies observed in generic product dossiers on the assessment of the quality (chemistry-pharmaceutical) part of the dossier, presented as the mean number of quality deficiencies per dossier and therapeutic area, by each of the 10 main categories.

Deficiencies are related to incomplete or incorrect information provided for the identified category.

Prequalification programme in 2011

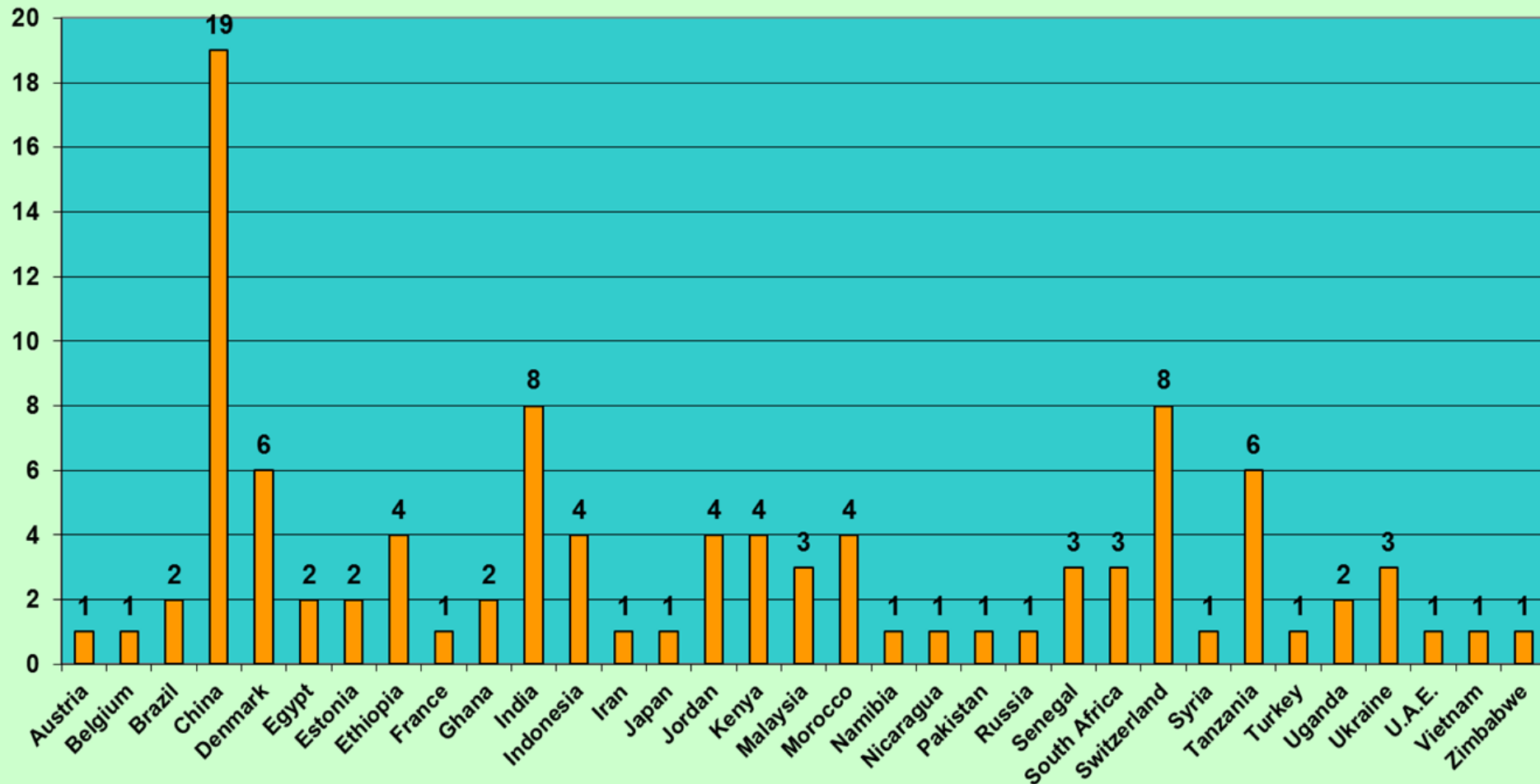
- During 2011 35 products (finished dosage forms) prequalified
- At the end of 2011, the WHO list of prequalified medicines - 269 products manufactured in 25 countries
- By the end of the year 8 active pharmaceutical ingredients (APIs) (6 for antimalarials and 2 for anti-TB medicines) prequalified
- 6 more medicines Quality Control Laboratories (QCL) prequalified (Belgium, Brazil, India, the Netherlands, Portugal and Tanzania). At the end of 2011, a total of 23 QCLs had been prequalified, covering all WHO 6 regions (further 32 were working towards becoming prequalified).



Training activities as a core

- PQP also organized, co-organized or supported 32 training courses, for nearly 1400 participants.
- Training on general or specific technical issues was given to manufacturers, and to NMRA and QCL staff.
- Courses generally also include an introduction or update on PQP requirements and services.
- PQP has a 3 months rotational post for developing country assessors – many regulators from China, Ghana, Tanzania, Kenya, Uganda, Botswana, Zambia, Zimbabwe, Ukraine etc. have been in this post – current fellow on post is from Kenya

Countries hosting workshops organized or co-organized by PQP in 2006-2011



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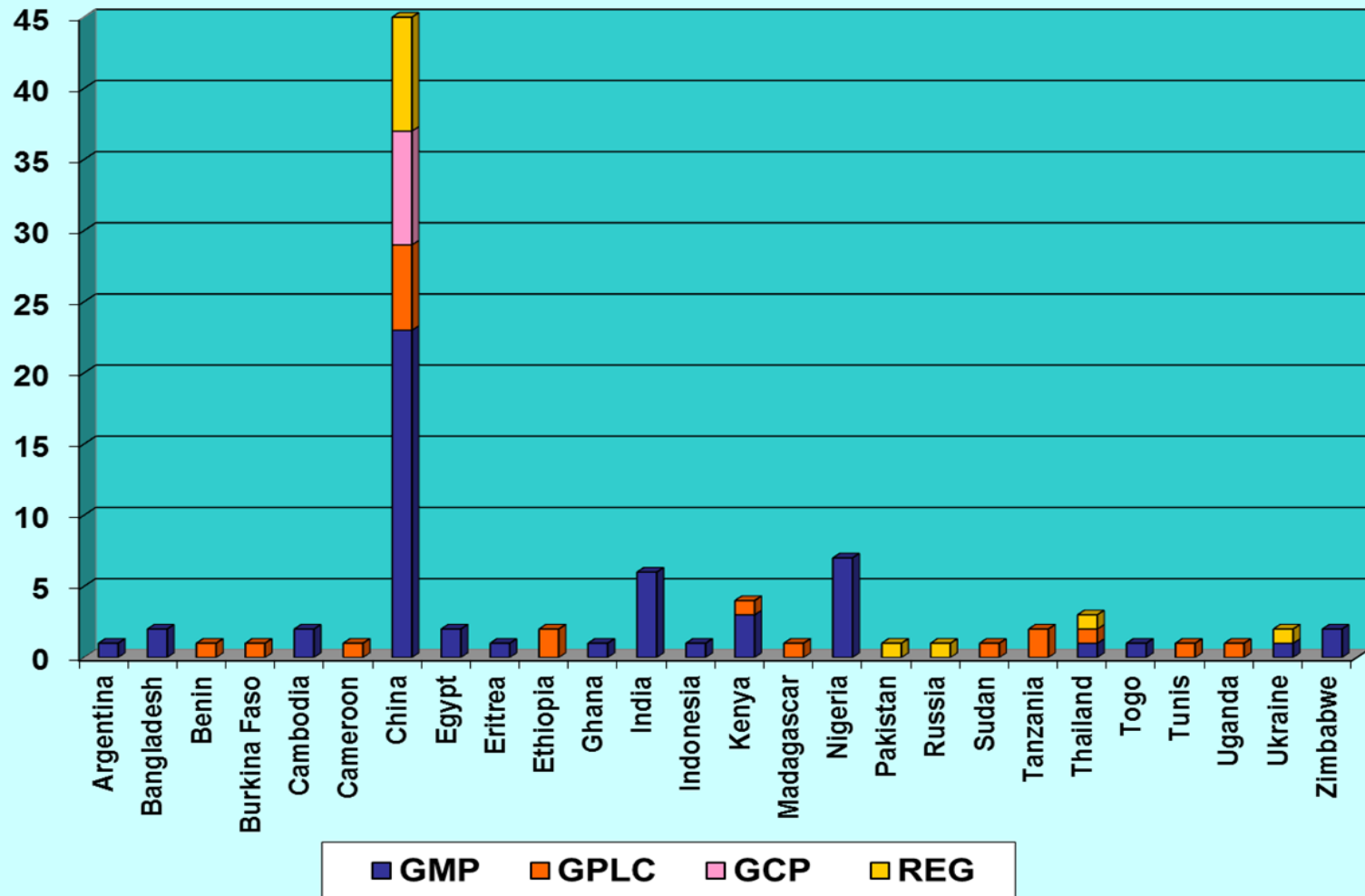
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Technical assistance

- In 2011, PQP organized 17 technical assistance missions to 13 pharmaceutical manufacturers in 5 countries (Bangladesh, China, Kenya, Nigeria and Pakistan),
- Technical assistance for 5 CROs in China,
- Technical assistance for 2 QCLs in China, and 1 QCL each in Benin, Cameroon, Madagascar and Thailand.
- Assistance took the form of an audit, followed by development of an improvement plan. Training in specific technical regulatory areas was made available where needed.



Technical assistances organized by PQP in individual countries



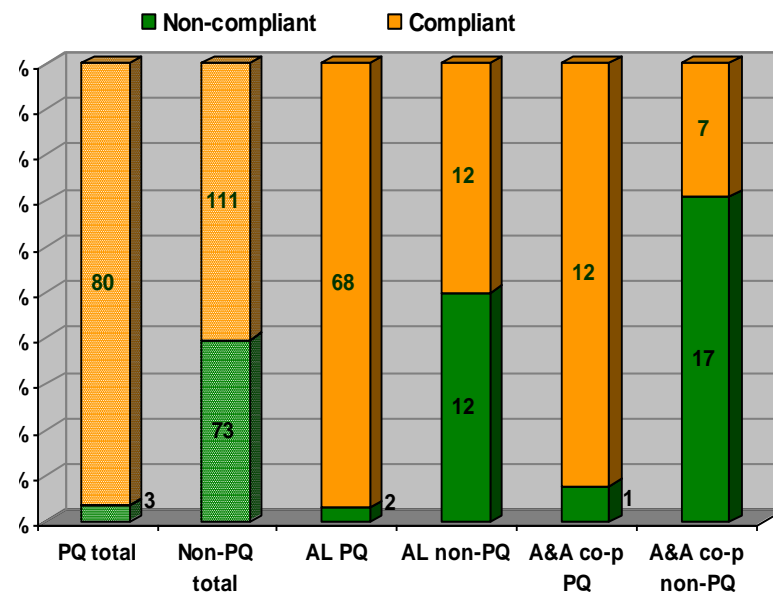
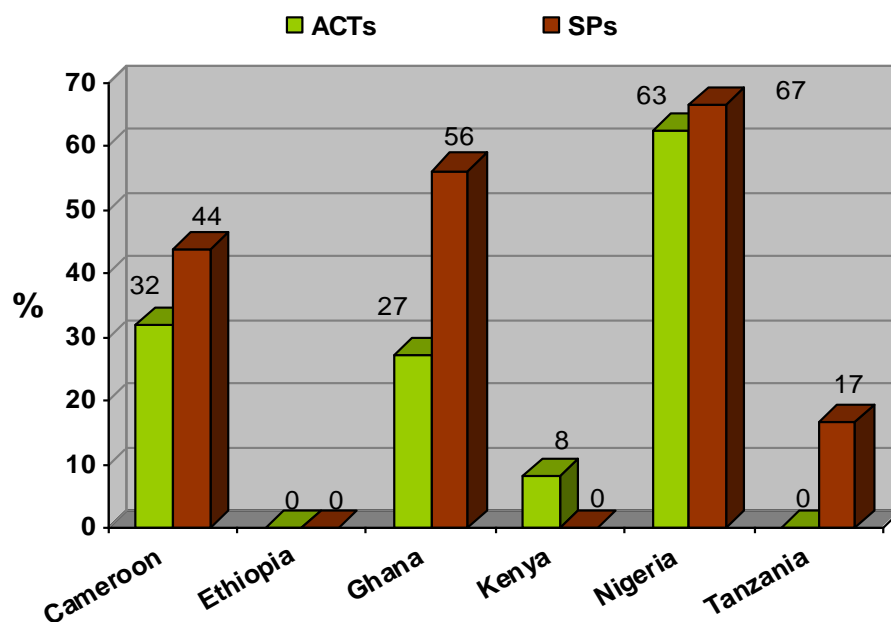
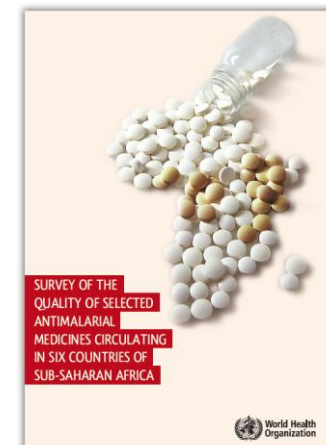
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Quality monitoring projects (1)

• Quality survey of antimalarials Africa

- Cooperation with NDRAs in Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania
- ACTs and sulfadoxine-pyrimethamine
- 935 samples collected and screened by Minilab, 306 tested in laboratory



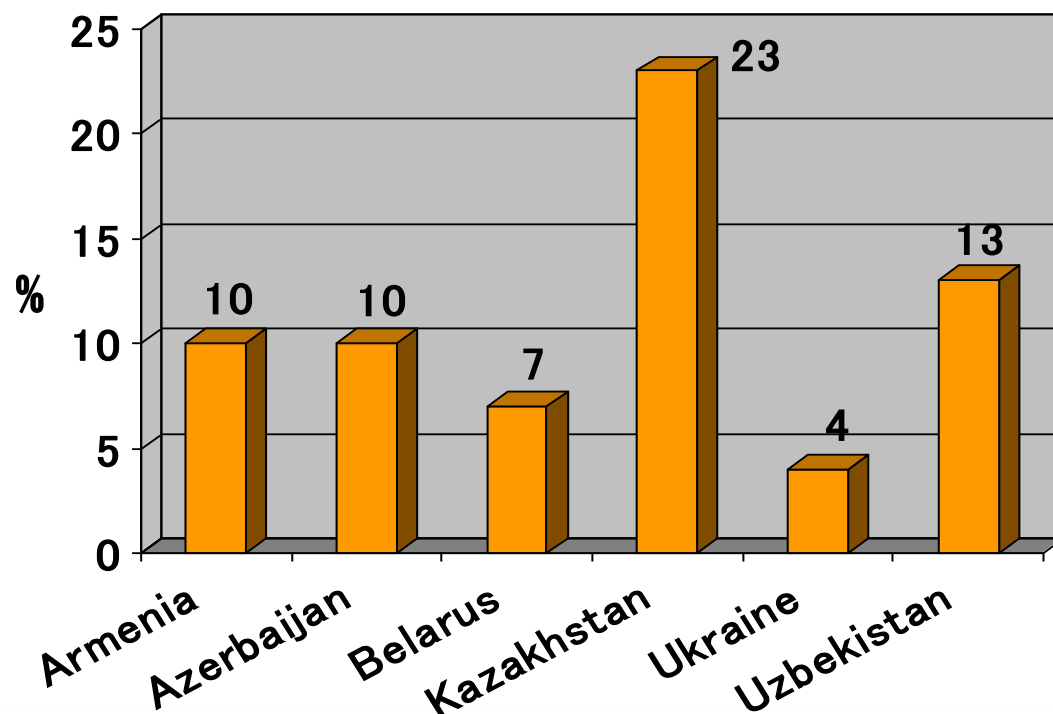
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Quality monitoring projects (2)

• Quality survey of anti-TB medicines in NIS

- Cooperation with NDRAs in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, Uzbekistan
- Rifampicin, Isoniazid, Rifampicin/Isoniazid, Ofloxacin, Kanamycin
- 291 samples collected and tested



- None of 38 samples of WHO-prequalified products failed



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What PQ can offer to the regulators and industries in the regions?

- Regulators
 - Capacity building/training – improved technical knowledge and skills
 - Practice and experience for collaboration and cooperation
 - Offers a lot of practical tools and guidelines
 - Helps to build more credible regulatory systems
 - Save resources
- Industries
 - Free of charge capacity building
 - Better quality production/products/regulatory knowledge – better access to markets
 - Access to international funds



RH medicines PQ: bad news and good news

- Only 10 PQ medicines
- NEW – from 2012 ERP in addition to PQ
 - ERP secretariat UNFPA
 - ERP technical work WHO
 - Concept – helping manufacturers to prepare for ERP
- 1st ever RH medicines ERP – 12 more products for procurement within couple on months!
- Would we need another ERP?

Status of RH: PQ and ERP

INN	WHO Prequalified	Supplier of Prequalified Product	Under PQ Assessment	Under PQ Screening	Number of products assigned ERP risk category 1 or 2*
Ethinylestradiol+Desogestrel	1	NV Organon, The Netherlands	0	0	3
Ethinylestradiol+Levonorgestrel	3	Famy Care (India), Cipla (India), Bayer Pharma (Germany)	3	0	3
Etonogestrel	1	NV Organon (The Netherlands)	0	0	0
Levonorgestrel	1	Bayer Pharma (Germany)	0	0	0
Levonorgestrel	1	Gedeon Richter (Hungary)	1	0	2
Levonorgestrel	0	n/a	1	0	2
Levonorgestrel	1	Bayer Oy (Finland)	1	0	0
Magnesium sulfate	0	n/a	0	0	0
Medroxyprogesterone acetate	1	Pfizer (Belgium)	0	0	0
Medroxyprogesterone acetate+Estradiol cyprionate	0	n/a	0	0	0
Mifepristone (for use with misoprostol)	0	n/a	0	0	0
Misoprostol	0	n/a	1	0	1
Norethisterone	0	n/a	0	0	1
Norethisterone enanthate	1	Bayer Schering Pharma (Germany)	0	0	0
Norethisterone enanthate+ Estradiol valerate	0	n/a	1	0	0
Norgestrel	0	n/a	0	0	0
Oxytocin	0	n/a	2	0	0
Total	10		10	0	12

Summary of results for all ERP reviewed products as of Oct 03, 2012

Product	Initial risk category	Risk category after additional data
Levonorgestrel/Ethinylestradiol 0.150 mg/0.03 mg Tablets + Placebo –Manufacturer 1	1	-
Levonorgestrel/Ethinylestradiol 0.150 mg/0.03 mg Tablets + Placebo –Manufacturer 2	2	-
Levonorgestrel/Ethinylestradiol 0.150 mg/0.03 mg Tablets- Manufacturer 1	4	-
Levonorgestrel/Ethinylestradiol 0.150 mg/0.03 mg Tablets- Manufacturer 2	4	2
Desogestrel/Ethinylestradiol 0.15mg/0.03mg tablets- Manufacturer 1	1	-
Desogestrel/Ethinylestradiol 0.15mg/0.03mg tablets- Manufacturer 2	2	-
Desogestrel/Ethinylestradiol 0.15mg/0.03mg tablets- Manufacturer 3	4	2
Norethindrone (Norethisterone) 0.35mg tabs-	2	-
Levonorgestrel 0.75mg tablets- Manufacturer 1	4	2
Levonorgestrel 0.75mg tablets- Manufacturer 2	4	2
Levonorgestrel 0.75mg tablets- Manufacturer 3	4	Additional data awaited
Levonorgestrel 0.75mg tablets- Manufacturer 4	4	-
Levonorgestrel 1.5mg tablets- Manufacturer 1	4	2
Levonorgestrel 1.5mg tablets- Manufacturer 2	4	2
Levonorgestrel 1.5mg tablets- Manufacturer 3	4	-
Misoprostol 200mcg tablets	4	2
Oxytocin 10 IU injection	4	3



Why RH manufacturers do not apply for PQ?

And when they apply why slow progress?

- Relatively small "market" for international standard quality products, enough market for products "as it is"
- The need to make human and financial investments
- A lack of technical and regulatory skills
- Not yet ready to participate internationally/globally – national/subregional markets unsaturated
- Differences between PQP and national regulatory requirements and their implementation
- Varying requirements and standards of procurers
- Risk of losing traditional markets once defined as sub-standard – PQ programme NOCs etc.



Way forward

- All partners to join efforts
- All have the same QA policies and promote Quality RH products
 - No poor quality products for poor people!
- Create and maintain "quality products" market
- PQ plus ERP can work to make quality assured products available!



Conclusions

- PQP is a powerful and effective mechanism to promote access to quality essential medicines (RH medicines is not an exemption!)
- PQP has saved lives
- PQP is not a replacement for national regulatory systems but a (time limited) mechanism to promote access to quality medicines
- PQP in conjunction with ERP more efficient
- Major proactive contributor to capacity building
- Promotes collaboration and cooperation among regulators, including relying on each others work and reducing duplications

