RH and UNCoLSC products status in PQP

Deus K. Mubangizi

Group Leader, Inspection Services (Medicines, Diagnostics & Vaccines)

E-mail: mubangizid@who.int

WHO Prequalification Team (PQT)

Regulation of Medicines and other Health Technologies (RHT)

Department of Essential Medicines and Health Products (EMP)

World Health Organization

20, Avenue Appia

CH-1211 Geneva 27, Switzerland

In this presentation:

- Progress in prequalification of RH products.
  - Common dossier deficiencies
- Inspection status of sites
  - Major GMP deficiencies
- TA for RH and UNCoLSC products
  - ERP for UNFPA and UNICEF (Amoxicillin)
- UNCoLSC – Preliminary results from surveys:
  - Regulatory status in selected countries
  - Quality of LSC
- Facilitating national registration
- Concluding remarks

RH Applications accepted for assessment

2007 – 2014 (as at 14th March 2014)

Year	2007	2008	2009	2010	2011	2012	2013	2014
Accepted for Assessment	10	4	7	7	3	3	14	1
Cum. total	10	14	21	28	31	34	48	49
In total **66** applications were submitted to PQP								
Prequalified	-	-	**3**	**5**	**3**	-	**10**	**1**
Cum. total	-	-	**3**	**8**	**11**	**11**	**21**	**22**
In total **22** products were prequalified by WHO-PQT								

1. Oral hormonal contraceptives	No of FPPs prequalified	FPPs under assessment
Ethinylestradiol + desogestrel, tablet 30 micrograms +150 micrograms	3	1
Ethinylestradiol + levonorgestrel, tablet 30 micrograms + 150 micrograms	7	
Levonorgestrel, tablet 30 micrograms	1	
Levonorgestrel, tablet 750 micrograms (pack of two)	2	1
Levonorgestrel, tablet 1.5 mg (pack of one)	1	1
Norethisterone, tablet 350 micrograms	2	
Norgestrel, tablet 75 micrograms		

Category and Products	No of FPPs prequalified	FPPs under assessment
2. Injectable hormonal contraceptives		
Medroxyprogesterone acetate, depot injection 150 mg/ml, in 1-ml vial	1	
Medroxyprogesterone acetate + estradiol cypronate, injection 25 mg + 5 mg		
Norethisterone enanthate, injection 200 mg	1	
Norethisterone enanthate + estradiol valerate, injection 50 mg + 5 mg		
3. Implantable contraceptives		
Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg in total)	1	1
Etonogestrel, implant, 68 mg of etonogestrel	2	

Category and Products	No of FPPs Prequalified	FPPs under assessment
4. Oxytocics		
Oxytocin, injection 10 IU, 1-ml		1
Mifepristone, 200 mg tablet (only to be used in combination with misoprostol)		
Misoprostol, 200 microgram tablet	1(Art.58)	2
5. Prevention and treatment of eclampsia		
Magnesium sulphate, injection 500 mg/ml, in 2-ml and 10 ml ampoule		

ZINC-SULFATE MEDICINES FOR TREATING DIARRHOEA IN EARLY CHILDHOOD	Number of individual FPPs prequalified	Number of individual FPPs under assessment
Zinc sulfate, dispersible tablet 10 mg		
Zinc sulfate, dispersible tablet 20 mg	2	3
Zinc sulfate, oral liquid 10 mg per unit of dosage forms		
Zinc sulfate, tablet 10 mg		
Zinc sulfate, tablet 20 mg		

APIs for Reproductive Health	No of APIs prequalified	APIs under assessment
Desogestrel		
Estradiol cypionate		
Estradiol valerate		
Ethinylestradiol	1	
Etonogestrel		
Levonorgestrel	1	1
Medroxyprogesterone acetate		1
Mifepristone	2	
Misoprostol		2
Norethisterone enanthate		
Norgestrel		
Oxytocin		
API FOR PRODUCTS USED IN THE TREATMENT OF DIARRHOEA		
Zinc sulfate		1

Statistics in General

- Of 18 applications received in 2013 : 1 rejected (Not in EoI), 2 withdrawn, 8 prequalified and 7 still in assessment.
- To date 23 RH products on our PQ list – 10 innovators and 13 generic (1 generic via EMA Article 58).
- 10 RH products prequalified in 2013 (9 generics, 1 innovator)
- 1 generic product prequalified so far in 2014.
- 8 generic RH products currently under assessment

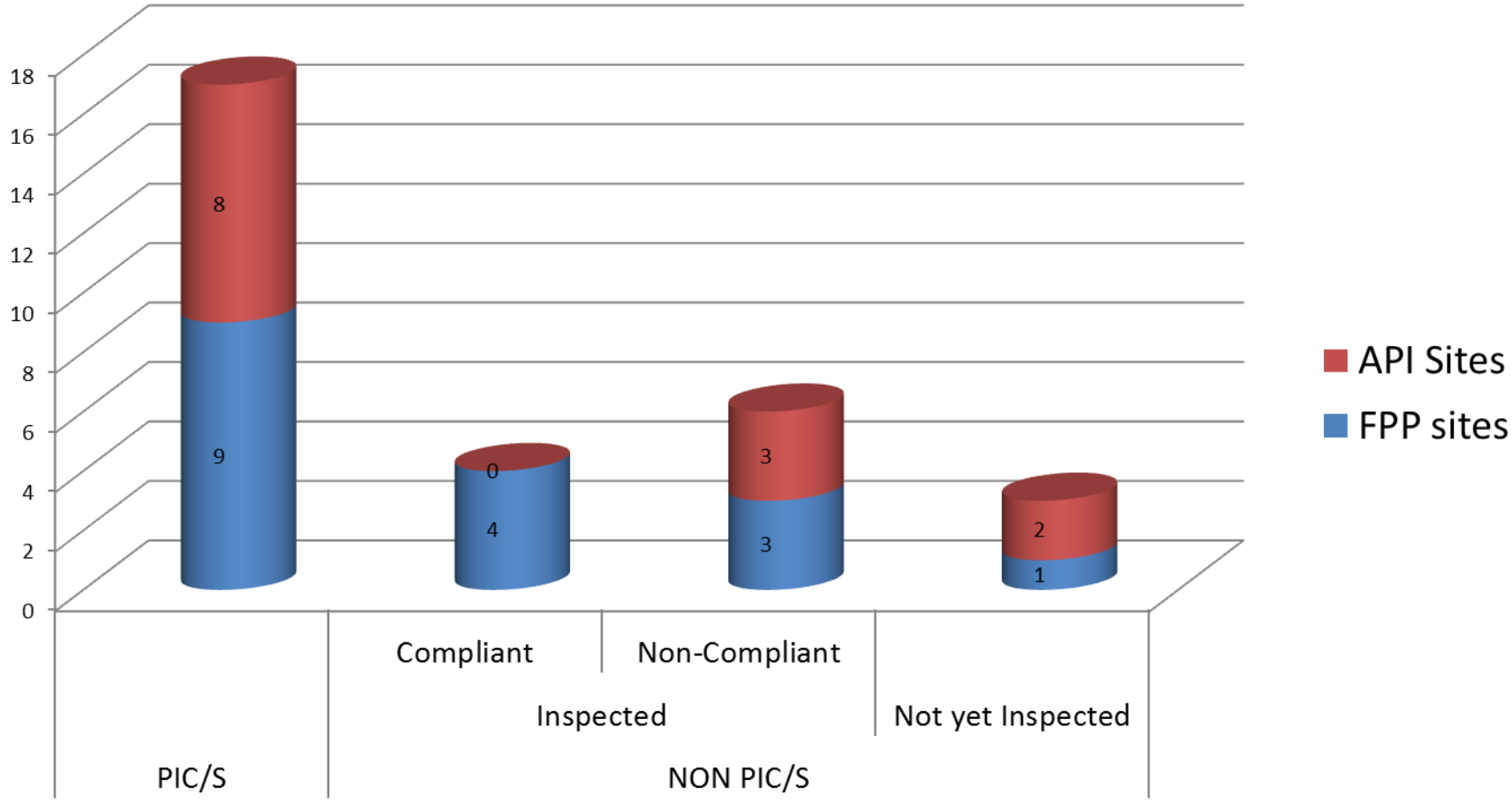
Common critical/major dossier deficiencies: Generic product dossiers

- No BE study or Comparative dissolution data (where applicable)
- Wrong comparator used in BE, Comparative Dissolution and Pharmaceutical Development studies
- Critical information on the stability, validation, bioequivalence batches not available
- Evidence of Validation of API manufacturing process (sterile API) not submitted
- Inadequate stability data for FPP, inadequate number of batches, some tests not included or results show visible trends
- No or poor validation of in house analytical methods
- Data on presence or absence of pharmacopoeial related substances/impurities missing
- RoS (Route of Synthesis) involves one step and no details of starting materials provided
- No pharmaceutical development data to support formulation and manufacturing process
- Inadequate FPP specifications (incl. failure to include or perform all pharmacopoeial tests and specifications)
- Poor validation of BE analytical method
- BE study not compliant with GCP or not monitored

RH Sites: Inspection status

	PIC/S	NON PIC/S			Total
		Inspected		Not yet Inspected	
		Compliant	Non-Compliant		
FPP sites	9	4	3	1	17
API Sites	8	0	3	2	13
Total	17	4	6	3	30

RH Sites: Inspection status



Major GMP deficiencies

- Inadequate premises:
  - Inadequate dedication and self-containment.
  - Inadequate HVAC system – challenge of negative pressure.
  - Inadequate dust containment and control – no scrubbers.
  - Inadequately controlled storage facilities and conditions.
- Inadequate production procedures:
  - Challenges of dispensing small quantities.
  - Challenges of mixing and blending – trituration.
  - Challenges of uniformity of content.
  - Challenge of uniform coating.
  - Challenges of pattern co-blistering with a placebo.

Major GMP deficiencies

- Inadequate facilities for personnel protection:
  - Inadequate breathing suits
  - Inadequately filtered compressed air.
  - No or inadequate air showers or equivalent on exit.
  - Personnel not adequately monitored for hormone exposure.
- Challenges of quality control:
  - Validation of analytical procedures – small values - µg – LOQ.
  - Challenges of actual analysis – data integrity
- Challenges of sourcing raw materials:
  - Few API manufacturers and low GMP status.

TA for RH and UNCoLSC Products

- 3 GMP expert consultants and 1 quality assessor from SRA engaged on as need basis for TA activities.
- TA organized for manufacturers in:
  - 1 Zimbabwe (ZnSO4, ORS), ZnSO4 dossier submitted to PQ.
  - 1 Kenya (ZnSO4, ORS).
  - 1 Pakistan (ORS).
  - 2 Indonesia:
    - Oxytocin Injection, dossier recently submitted to PQ;
    - Amoxicillin DT submitted to ERP.
  - Nigeria (ZnSO4, ORS, Amoxicillin DT, MA, HA):
    - 3 pre-audits conducted, 3 companies close to GMP compliance.
    - Several being assisted with dossier compilation.
    - ZnSO4 dossier submitted to PQ

ERP for Reproductive Health (RH) products

RH - Difficult area;

- Few dossier submissions to PQP
- Limited progress in the PQP pipeline
- Few prequalifications
- Limited business incentive to improve quality?
- Many RH manufacturers outside of ICH region are currently non-GMP compliant (or no evidence of GMP as inspected by PQP/SRA)
- Many have limited experience of regulatory submissions to PQP/SRA

ERP was done for UNFPA to evaluate RH products using modified ERP eligibility criteria

Revised ERP eligibility criteria for RH products

- GMP status
  - Evidence of GMP compliance as inspected by but not limited to WHO PQP, SRA, PIC/S member inspectorate
    - As part of the submission applicants were also requested to submit any available inspection report even if negative and/or CAPAs
- Dossier submission status
  - Dossier has been submitted to PQP/SRA and accepted for assessment, or
  - Commitment to submit dossier to PQP/SRA within three months from the date of 1st ERP review

RH dossiers to ERP- 2013

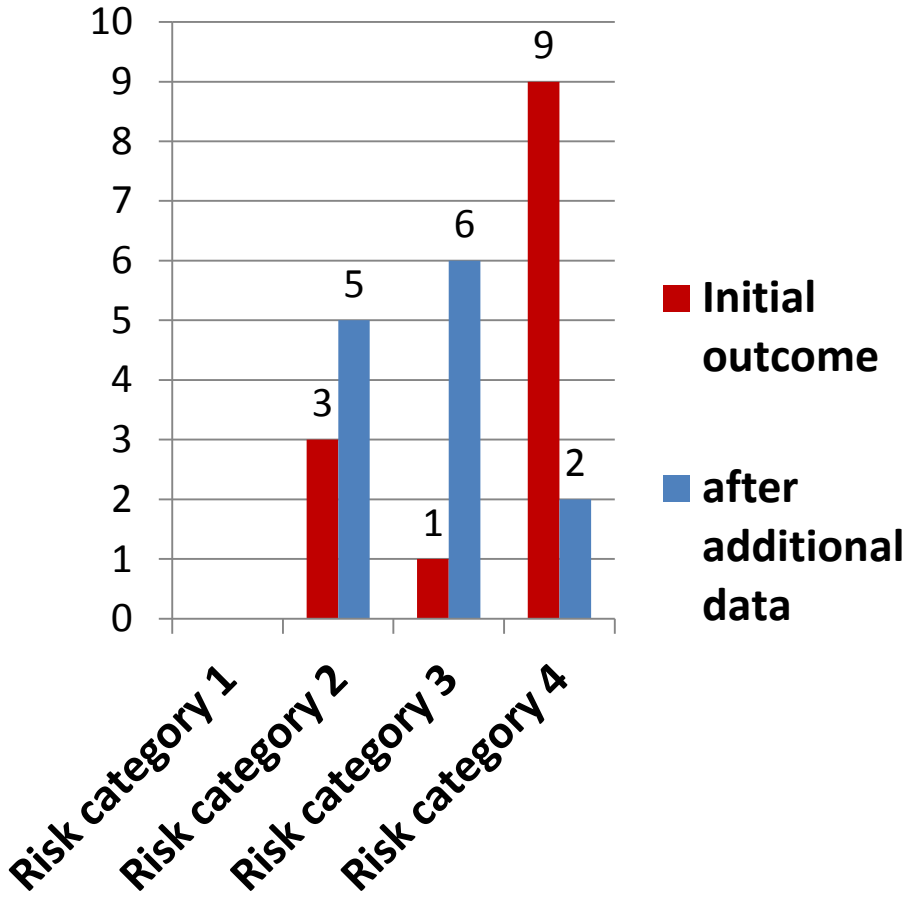
	ERP III, June 2013	ERP IV, November 2013
Dossiers submitted to UNFPA	13 + 4 requests for extension	3
Dossiers passed UNFPA screening and received by ERP	10 + 4 requests for extension	3
Dossiers that went to full ERP review (after GMP risk assessment)	10 + 3 Extension (1 was prequalified in the meantime)	3

Outcome of GMP risk assessment

GMP risk rating level	No of manufacturers (ERP III and ERP IV)
0	-
1	2
2	4
3	3
4	1 (not considered eligible for dossier review)

- Products manufactured at the sites of GMP risk level of 0, 1, 2 and 3 were taken for dossier review.
- Note:
  - The best possible ERP risk category for a product falling in risk category 3 on dossier review is 3 (irrespective of the GMP risk level - 0, 1, 2 or 3).
  - Likewise, the best possible ERP risk category for a product manufactured at a GMP risk level 3 site is 3

ERP III and IV outcome (2013)



- 7 additional data submissions (out of 7 invited) were received and reviewed
  - 2 products improved from risk category 4 to 2
  - 5 product improved from risk category 4 to 3

ERP for Amoxicillin

- ERP for Amoxicillin was undertaken mainly with an objective of identifying deficiencies (areas for improvement) for possible technical assistance to manufacturers under the UN Commission on Life Saving Commodities for women and children.
- For this, the ERP eligibility criteria (GMP status) was modified to attract several applicants.
  - allowed submission of evidence of inspection as performed by UNICEF

ERP for Amoxicillin

	Number of dossiers submitted and reviewed	Initial outcome (June 2013)	Result after additional data (November 2013)
Amoxicillin 250mg dispersible tablets	9 (only 7 met modified eligibility criteria but all 9 were reviewed)	7 products- risk category 4; 2 products were not categorized but deficiencies communicated	Add data received for 4 products; 2 improved from risk category 4 to risk category 3
Amoxicillin 500mg dispersible tablets	1	Risk category 4	remained risk category 4

ERP-GMP risk assessment

- The following aspects were considered
  - Site location and related NMRA status (SRA/PIC/S or not)
  - Available FPP site GMP certification, Inspection reports and/or CAPAs
  - Information on API GMP status
  - Other possible discriminating factors (simple/complex site & process; company known to WHO PQP/SRA, recalls? complaints? etc)

GMP Risk assessment – Risk categories

Risk rating	Input from current Inspection Findings
0	Product manufactured within a SRA territory.
I	Site GMP compliant + assured supervision by SRA/PICS or WHO-PQT **OR** A Category II site + strong discriminating factors + robust controls
II	Site GMP compliant but with **a lower assurance level of continuing compliance than category I** **OR** A Category III site + strong discriminating evidence factors + robust controls
III	Site outside SRA/PIC/S territory + not yet inspected by SRA/WHO/PIC/s **OR** A site within an SRA/PIC/s territory **but no or minimal robust evidence of compliance with GMP** BUT with a positive agreed action plan awaiting confirmation by re-inspections by an SRA/WHO
IV	Site is either inside or outside an SRA/PIC/S territory and has been found to be **NON-COMPLIANT/Subject to on-going regulatory action** e.g. NOC/Consent decree/warning letter/NCC by SRA/WHO/PIC/s **OR** where follow up inspection has shown inadequate progress to previous regulatory action

UNCoLSC

Recommendation 4: Quality strengthening

"By 2015, at least 3 manufacturers per commodity are manufacturing and marketing quality-certified and affordable products"

Recommendation 5: Regulatory efficiency

"By 2015, all EWEC countries have standardized and streamlined their registration requirements and assessment processes for the 13 life saving commodities with support from Stringent Regulatory Authorities, the WHO and regional collaboration"

Survey on the Regulatory Status of LSC

Objectives & Methods

Overall Objectives

- Establish the regulatory status of LSC in EWEC Countries

Specific focus of this presentation

- Establish the registered manufactures for the life saving commodities by country
- Determine the proportion of life saving commodities with at least 3 registered manufactures in each country

Methodology

- Online Survey
  - (Structured questionnaire: using excel format and WHO Data col)
  - Field tested in Senegal in March 2013
  - Distributed to 49 EWEC countries – self administered.
- Review of the national medicine registers

Preliminary Results: *Manufacturers per LSC*

No. of Registered Manufacturers for Reproductive Health Commodities by Country

	Contraceptive implants for Family Planning		Emergency Contraception	
	Levonorgestrel 75mg Implant	Etonogestrel 68mg implant	Levonorgestrel 1.5mg tablet	Levonorgestrel 0.75mg tablet
Burkina Faso	2	1	2	0
DRC	1	1	0	1
Ethiopia	2	1	0	3
Ghana	1	0	2	3
Guinea	0	0	0	0
Kenya	3	1	0	8
Kyrgyzstan	2	0	1	0
Madagascar	2	1	2	2
Malawi	1	1	1	1
Nepal	3	0	6	5
Nigeria	3	1	0	3

No. of Registered Manufacturers for Reproductive Health Commodities by Country

	Contraceptive implants for Family Planning		Emergency Contraception	
	Levonorgestrel 75mg Implant	Etonogestrel 68mg implant	Levonorgestrel 1.5mg tablet	Levonorgestrel 0.75mg tablet
Senegal	0	0	1	3
Sierra Leone	1	0	1	1
Somalia	0	0	1	0
Tajikistan	0	1	0	0
Tanzania	1	1	0	2
Uganda	2	1	2	1
Uzbekistan	1	1	1	1
Viet Nam	0	1	1	5
Zambia	1	1	0	0
Zimbabwe	1	1	3	2

No. of Registered Manufacturers for Maternal Health Commodities by Countries

	Post Partum Heamorrhage		Pre eclampsia /severe eclampsia	
	Oxytocin Inj. 10IU in 1 ml	Misoprostol 200µg Tablets	Magnesium sulfate Inj. 500mg/ml, 2ml, 5ml, 10ml vials	Calcium gluconate Inj. 100mg/ml, 10ml amp
Burkina Faso	0	0	2	1
DRC	1	0	0	1
Ethiopia	1	1	1	1
Ghana	3	0	0	0
Guinea	1	0	1	1
Kenya	2	3	4	1
Kyrgyzstan	2	2	0	3
Madagascar	2	2	0	3
Malawi	1	1	1	0
Nepal	2	0	1	0
Nigeria	9	6	4	1

No. of Registered Manufacturing Companies for Maternal Health Commodities by Country

	Post Partum Heamorrhage		Pre eclampsia /severe eclampsia	
	Oxytocin Inj. 10IU in 1 ml	Misoprostol 200µg Tablets	Magnesium sulfate Inj. 500mg/ml, 2ml, 5ml, 10ml vials	Calcium gluconate Inj. 100mg/ml, 10ml amp
Senegal	2	2	0	1
Sierra Leone	0	2	1	0
Somalia	2	1	1	1
Tajikistan	0	2	0	1
Tanzania	2	3	1	0
Uganda	5	4	3	3
Uzbekistan	1	1	0	10
Viet Nam	2	2	0	0
Zambia	1	1	1	1
Zimbabwe	6	2	1	0

Regulatory status survey: *Next Steps*

- Complete the analysis of the collected data
- Discuss with respective countries and conveners (*Tentatively June 2014: In Africa? In Geneva?)*
- Correlate with results of quality survey to identify prospective manufacturers of LSC.
- Publication of results.
- Develop strategies to:
  - Support prospective manufacturers to improve quality.
  - Ensure that each country has at least 3 suppliers of quality assured product for each LSC.

Preliminary Results: *Quality survey for LSC*

Objectives of the medicines quality survey

- Primary
  - To identify products which are of good quality (or the quality of which can be improved in short period of time)
- Secondary
  - To evaluate the quality of products currently available in selected countries at the first level of distribution chain (e.g. central medical stores, NGO central stores, warehouses of importers or major distributors)
    - To avoid any influence of inappropriate storage conditions
  - Results should also assist responsible authorities in the countries in meeting the Commission targets

Selection of medicines for sampling & testing

- To optimize use of resources the assessment of benefits brought by testing and risks posed by individual medicines was performed
  - Medicines the quality of which is assured not included
    - Contraceptive implants, Ulipristal tablets – only innovator products
    - Misoprostol tablets, Chlorhexidine digluconate gel/solution already in focus of partners (Concept, Path)
  - Low-risk ORS not included

Medicines included in the survey

- Oxytocin injection 10IU in 1ml (if not available, 5UI/ml)
- Magnesium sulfate injection 500mg/ml in 2ml, 5ml or 10ml ampoule (if not available, lower strength)
- Gentamycin injection
  - 40mg/ml in 1ml or 2ml ampoule (80mg/2ml) or
  - 20mg/ml in 1ml ampoule or
  - 10mg/ml in 2ml ampoule
- Procaine benzylpenicillin injection 1g (= 1 000 000 IU) in a vial *(synonyms: Procaine penicillin, Procaine penicillin G)*
- Ampicillin injection 250mg, 500mg or 1g in a vial
- Ceftriaxone injection 250mg, 500mg or 1g in a vial
- Betamethasone injection
  - Suspension 5.7mg/ml (3mg/ml as betamethasone sodium phosphate + 2.7mg/ml as betamethasone acetate) in 1ml ampoule (aqueous injection) or
  - Solution 4mg/ml in 1ml ampoule or 8mg in 2ml ampoule (as betamethasone phosphate disodium salt)
- Dexamethasone injection 4mg/ml in 1ml ampoules (as dexamethasone phosphate disodium salt)
- Amoxicillin 250mg or 500mg dispersible tablet
- Zinc sulfate 10mg or 20mg dispersible tablet or 10mg/5ml syrup
- Levonorgestrel 1.5 mg or 0.75mg tablet
- Mifepristone 10mg, 25mg tablet

10 countries selected for sampling

- Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Vietnam, Zimbabwe
- Criteria
  - Majority of selected medicines in country registers
  - Several products from various manufacturers per medicine
  - Longer experience in medicines regulation
  - Representation of countries from various geographic regions
  - Willingness of NMRAs to cooperate
- Advice requested from regional and country offices


Arctic Ocean
Arctic Ocean
Arctic Ocean
Greenland (Den.)
Iceland
Norway
Finland
Sweden
Russia
Canada
United States of America
North Atlantic Ocean
Kazakhstan
Mongolia
Tajikistan
Nepal
China
India
Turkey
Iran
Morocco
Algeria
Libya
Egypt
Saudi Arabia
Oman
Yemen
Mauritania
Mali
Niger
Chad
Sudan
Burkina Faso
Nigeria
Ethiopia
Somalia
Uganda
Kenya
Tanzania
Rwanda
Burundi
Zaire
Congo
Gabon
Angola
Zambia
Malawi
Mozambique
Zimbabwe
Madagascar
Namibia
Botswana
Swaziland
South Africa
Lesotho
Seychelles
Mauritius
Vietnam
Philippines
Malaysia
Indonesia
Australia
Indian Ocean
Brazil
Peru
Bolivia
Paraguay
Uruguay
Chile
Argentina
Colombia
Venezuela
Ecuador
Mexico
Cuba
South Atlantic Ocean
Antarctica

Quality Survey: *Activities by March 1214*

- Protocol for the survey prepared and finalized after discussion with focal persons from 10 countries
  - Meeting with focal persons 12-13 Aug 2014 in Tanzania
- 205 samples collected and sent to testing laboratories in the period Sep – Nov 2013
  - Samples of innovators products were not collected
- Testing in 3 laboratories almost finalized
  - NQCL Kenya, InphA Germany, SGS Belgium
  - Non-compliant result investigated

Preliminary outcomes: *Quality Survey*

- Oxytocin injection
  - 22 samples from 15 manufacturers from 6 countries
    - India, China, Germany, Hungary, Italy, Russia
  - Samples collected in all 10 countries
    - In Burkina Faso, Nepal, Tajikistan, Tanzania, Vietnam only 5IU (10IU not available)
  - Manufacturer's storage conditions
    - 3x 2-8°C;
    - 7x below 20/25/30°C;
    - 1x 2-15°C;
    - 1x above 0°C;
    - 3x not available
  - Some problems with the content, impurities and visible particles

Preliminary outcomes: *Quality Survey*

- Magnesium sulfate injection
  - 19 samples from 14 manufacturers from 9 countries
    - India, France, Russia, China, Germany, Saudi Arabia, UK, Ukraine, Vietnam
  - Samples collected in 9 countries
    - No sample collected in Madagascar
    - In Tajikistan collected only 250mg/ml and in Vietnam only 150mg/ml (500mg/ml not available)
  - All samples complied with specifications

Preliminary outcomes: *Quality Survey*

- Levonorgestrel tablets
  - 14 samples from 9 manufacturers from 4 countries
    - India, Vietnam, Bangladesh, Hungary
  - Samples collected in 8 countries
    - No sample collected in Burkina Faso and Nigeria
    - 13 samples 0.75 mg, 1 sample 1.5mg
  - All samples complied with specifications

- Mifepristone tablets
  - 8 samples (all 10mg) from 5 Vietnamese manufacturers
  - Samples collected in Vietnam only
  - All samples complied with specifications

Planned activities: *Quality Survey*

- Testing results will be provided to all participating NMRAs
- Outcomes will be discussed with NMRAs in the closing meeting (June 2014)
  - Corrective measures, if necessary, will be recommended
  - Responsibility to take any relevant measures in the countries lies with the respective NMRAs
- Outcomes and report from the survey will be published by WHO
- Survey outcomes serve as a source for selection of manufacturers for discussion and potential technical assistance

Facilitating National Registration

- WHO-PQ outputs in public domain for use by NMRAs:
  - List of prequalified products, WHOPARs, WHOPIRS.
- Joint assessments:
  - WHO-PQ/EAC: currently 5 products (2 RH and 3 MA)
  - ZaZiBoNa facilitated by WHO-PQ: 1 RH
- Joint inspections:
  - EAC – 6 in 2012, 2 in 2013, panning for 2014 ongoing
  - WHO-PQ/UNFPA: 1RH site in China.
- Accelerated National Registration:
  - 13 products completed: 9HA, 2MA, 1RH, 1 TB
  - 13 products ongoing: 4HA, 1MA, 3RH, 5TB

Concluding Remarks

- The RH pipeline is complex but it is slowly responding to multiple efforts:
  - WHO-PQ engagements with manufacturers.
  - TA assistance from multiple players: WHO-PQ, Concept Foundation, USP, FHI, etc.
  - Engaging funders and procurers by WHO through IPC and IAPG; Concept Foundation, etc.
  - Momentum created by the UNCoLSC
  - Multiple approaches to national registration of quality assured medicines
- The momentum created by these efforts need to be sustained