USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program

Improved Access. Improved Services. Better Health Outcomes.

Improving Access to Maternal, Newborn, and Child Health Products in LMICs: Considerations for Effective Registration Systems

April 27, 2021

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USAID MEDICINES, TECHNOLOGIES, AND PHARMACEUTICAL SERVICES (MTaPS) PROGRAM

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Speakers

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Denylson Namburete, MTaPS Country lead, Mozambique

Birna Trap, MTaPS Country Portfolio Director, Nepal

Q&A Moderator

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Introduction

- A **strong regulatory system** is a critical public health priority – it ensures the safety, efficacy, and quality of medical products and improves outcomes for maternal, newborn, and child health, or MNCH.
- **Registration or "marketing authorization"** – often the most recognized regulatory function – evaluates the safety, efficacy, and quality of a product and the appropriateness of the product information before entering a market
- In many LMICs, challenges in the **registration process limit the availability** of lifesaving, quality-assured MNCH medical products

MTaPS conducted a nine-country study to assess the challenges in LMICs of registering MNCH and other essential medical products

Methodology

- Nine countries:
  - Bangladesh
  - DRC
  - Mali
  - Mozambique
  - Nepal
  - Rwanda
  - Senegal
  - Tanzania
  - Uganda
- Document review
- Interviews with regulators and pharmaceutical manufacturers
- Thematic analysis to identify major challenges
- Options for consideration to strengthen the system

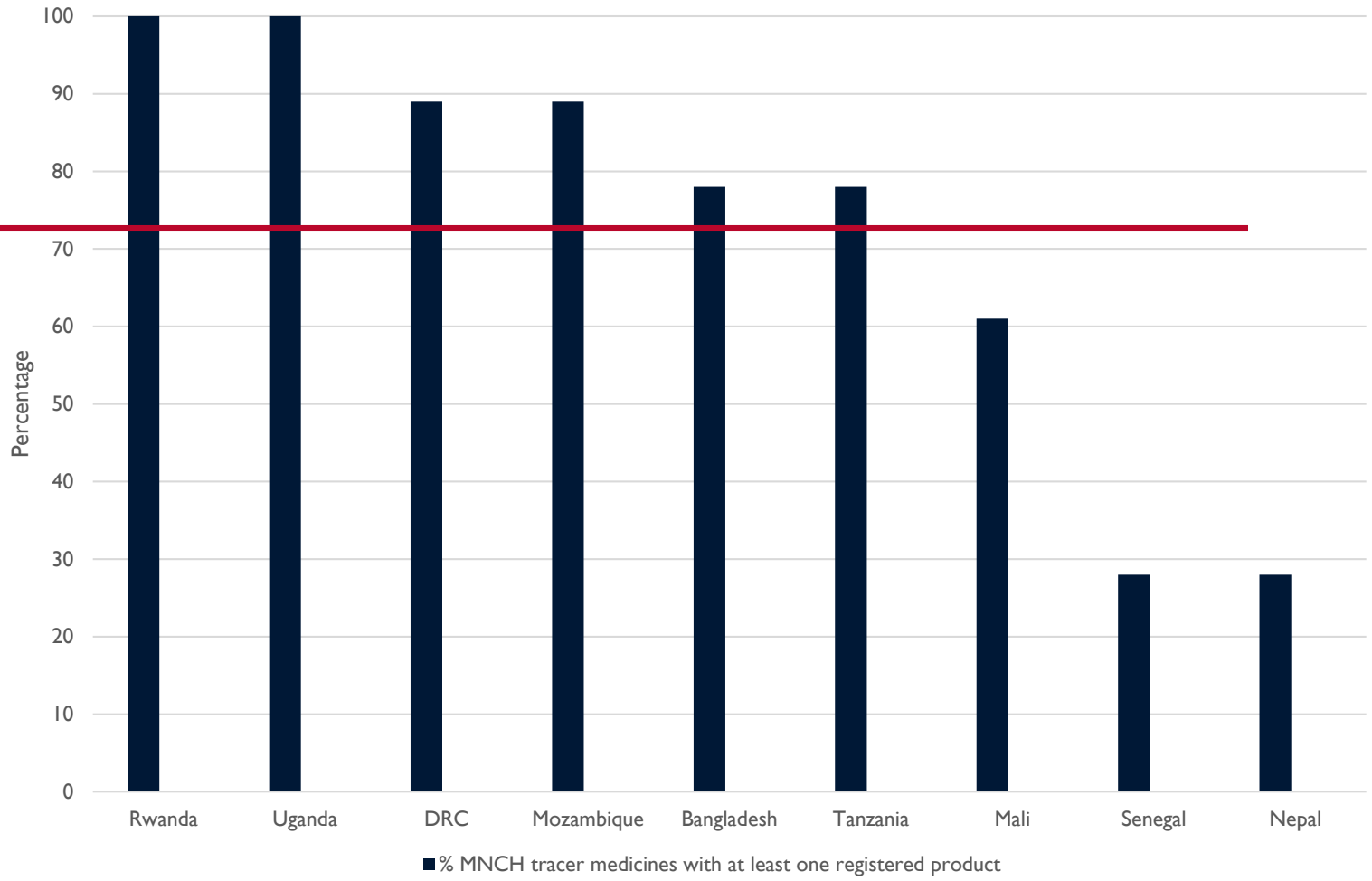
Registration Status of 18 MNCH Tracer Medicines Studied

1.	Oxytocin 10IU/ml inj.*	Postpartum hemorrhage
2.	Misoprostol 200mcg tab.*	Postpartum hemorrhage
3.	Tranexamic Acid 100mg inj. for IV	Postpartum hemorrhage
4.	Hydralazine 20mg amp.	Severe hypertension in pregnancy
5.	Methyldopa 250mg tab.	Severe hypertension in pregnancy
6.	Magnesium Sulphate 500mg/ml inj.*	Eclampsia and pre-eclampsia
7.	Calcium Gluconate 1g/10ml inj.	Eclampsia and pre-eclampsia (treatment of magnesium toxicity)
	Newborn and Child Health Medicines	
8.	Chlorhexidine 7.1% solution or gel	Newborn cord care
9.	Benzylpenicillin 600mg inj.	Possible serious bacterial infection
10.	Ceftriaxone 250mg inj. or Ceftriaxone 1g inj.	Possible serious bacterial infection
11.	Gentamicin 20mg inj. or Gentamicin 80mg inj.	Possible serious bacterial infection
12.	Procaine Benzylpenicillin 1g inj.	Possible serious bacterial infection
13.	Amoxicillin 125mg dispersible tab.	Pneumonia
14.	Amoxicillin 250 mg dispersible tab.	Pneumonia
15.	Amoxicillin 250mg/5ml syrup or suspension	Pneumonia
16.	ORS low osmolarity 20.5g/1L sachets or ORS flavored 200ml sachets	Diarrhea
17.	Zinc sulphate 20mg dispersible tab.*	Diarrhea


Photo credit: Mark Tuschman

Registration Status of Tracer MNCH Medicines

72%



Registration Status of MNCH Tracer Medicines

No.	Tracer Essential MNCH Medicines	Number of Registered Products								
		Rwanda	Uganda	DRC	Mozambique	Bangladesh	Tanzania	Mali	Senegal	Nepal
Maternal health medicines										
1	Hydralazine 20mg amp.	2	1	0	3	0	0	0	0	0
2	Magnesium Sulphate 500mg/ml inj.	5	1	1	2	5	0	0	0	0
3	Calcium Gluconate 1g/10ml inj.	3	1	1	1	9	0	1	0	0
4	Tranexamic Acid 100mg inj. for IV	3	4	0	2	18	5	0	0	1
5	Oxytocin 10IU/ml inj.	8	4	2	1	3	3	6	0	0
6	Methyldopa 250mg tab.	12	4	1	6	10	5	4	2	0
7	Misoprostol 200mcg tab.	6	5	3	8	20	4	3	0	1
Newborn and child health medicines										
8	Procaine Benzylpenicillin 1g inj.	6	3	1	0	0	1	0	0	0
9	Co-presentation of ORS/Zinc	2	3	2	0	0	1	1	0	0
10	Amoxicillin 250mg dispersible tab.	2	8	1	6	10	4	0	0	0
11	Amoxicillin 125mg dispersible tab.	3	3	1	2	0	3	0	0	1
12	Benzylpenicillin 600mg inj.	4	3	4	2	3	0	2	0	0
13	Zinc sulphate 20mg dispersible tablets	5	6	2	3	8	4	0	0	0
14	Gentamicin 20mg inj or Gentamicin 80mg inj	7	4	5	8	27	5	2	0	0
15	Chlorhexidine 7.1% solution or gel	1	1	1	0	2	1	1	1	1
16	Amoxicillin 250mg/5ml syrup or suspension	10	3	5	23	4	1	12	1	0
17	ORS low osmolarity 20.5g/1L sachets or ORS flavored 200ml sachets	3	4	2	1	4	7	2	1	0
18	Ceftriaxone 250mg inj or Ceftriaxone 1g inj.	25	31	15	12	253	37	20	6	2
	Total	**107**	**89**	**47**	**80**	**376**	**81**	**54**	**11**	**6**

Number of registered products	0		1-2		3+	

Number of Registered WHO-Prequalified Products for Each MNCH Tracer Medicine by Country

Tracer Essential MNCH Medicines	Rwanda	Uganda	DRC	Mozambique	Bangladesh	Tanzania	Mali	Senegal	Nepal
Oxytocin 10IU/ml inj.	0	0	0	0	0	1	0	0	0
Misoprostol 200mcg tab.	0	2	0	2	0	1	1	0	0
Magnesium Sulphate 500mg/ml inj.	0	0	0	1	0	0	0	0	0
Zinc sulphate 20mg dispersible tab.	0	1	0	1	0	1	0	0	0

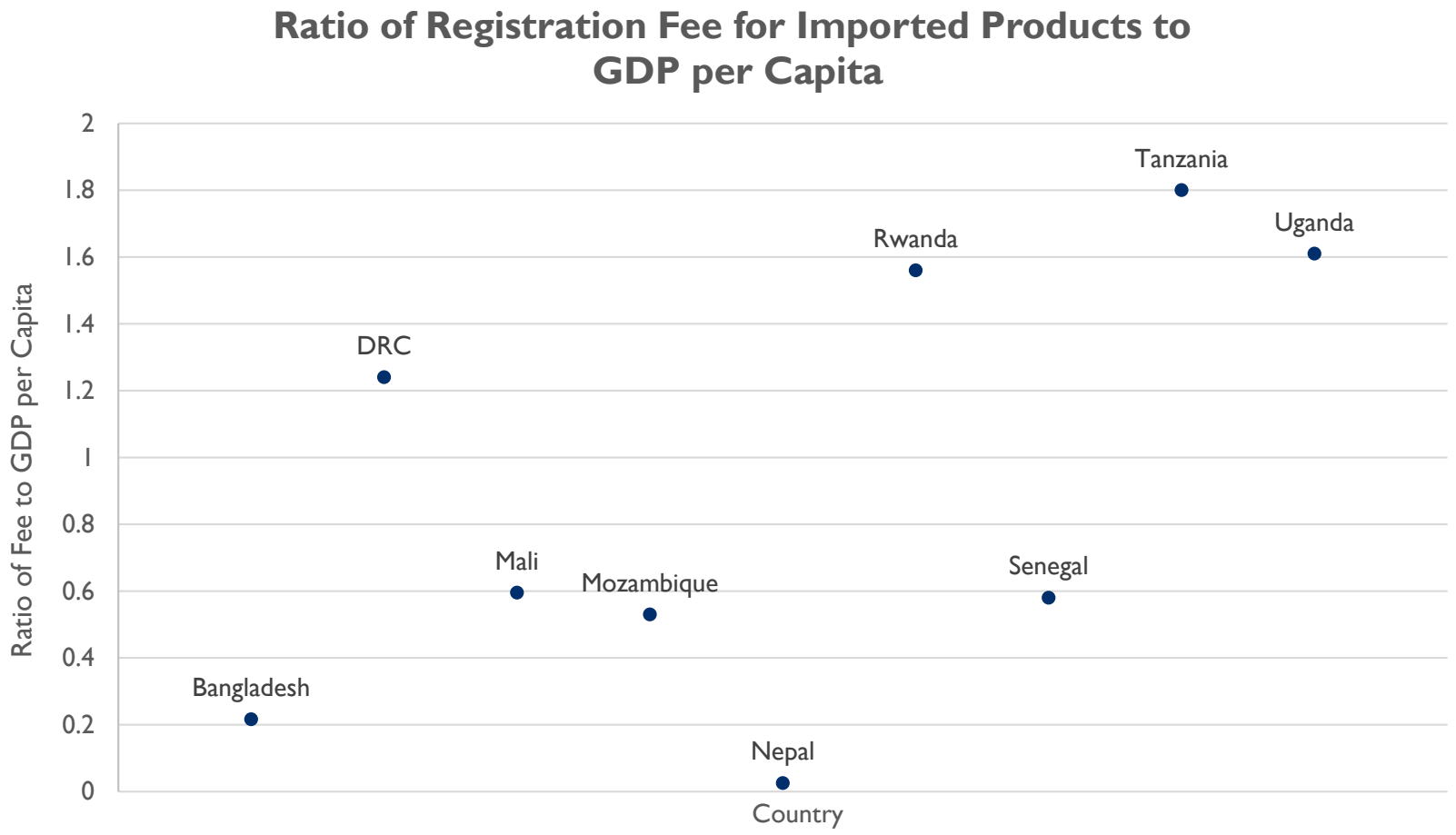
Mixed Policy and Regulatory Frameworks

- Adequate legal provisions for medicines:
  - National regulatory agencies (NRAs) have the mandate to perform registration activities
  - All medicines must be registered before entering the market
- Only 6 countries (Bangladesh, DRC, Nepal, Rwanda, Tanzania and Uganda) have the legal mandate for registration of medical devices
- Only 4 countries (Bangladesh, Rwanda, Tanzania and Uganda) have the legal mandate for registration of medical gases
- Lack of legal provisions for reliance

Registration Fees

Fees for imported products vary from 27US$ in Nepal to 2,000US$ in Tanzania

Fees for locally manufactured products range from 3US$ in Nepal to 675US$ in DRC



Key Observations

- Legal frameworks exist but do not include key provisions to support more efficient and effective regulation
- NRAs face inadequate funding and insufficient numbers of competent staff, which hinders a stable and functional regulatory system
- Long and inefficient registration process not utilizing reliance on other agencies for GMP inspection or recognition of registration status in other countries
- Efficacious and efficient regulation with the right incentives is even more important in a low-cost, low-profit context such as the market for MNCH medicines

Considerations to Facilitate the Registration of MNCH Medical Products

Streamlining the Registration Process

1. Amend legal provisions and regulations to:
   - advance reliance and to enable the NRA to formally recognize the registration decisions including GMP inspection outcomes of other reference NRAs and the WHO prequalification mechanism
   - include medical devices and medical gases
   - allow for priority registration of essential MNCH medical products as products of public health benefit
2. The NRA and the health ministry could advocate for the government to include an adequate budget line in the national budget and for greater financial autonomy as well as to increase fees where deemed low

Streamlining the Registration Process (2)

3. Align the medicine registration process with international standards and best practices
4. Improve communications with manufacturers by making an updated list of registered medicines available and creating transparency
5. Increase collaboration with regional/international bodies:
    - Use regional platforms to enlist MNCH medicines as part of the priority medicines for joint assessments and subsequent registration in the member states
    - Leverage regional counterparts and the best international practices as reference for development of a regulatory framework for medical devices and medical gases, including the use of model law and regional guidelines

Conclusions

1. Most of the MNCH tracer medicines are registered in the nine countries studied, but some countries (Senegal, Mali, and Nepal) have **lower levels of registered medicines**.
2. Streamlining the registration process will **mitigate disincentives for market entry for manufacturers** of quality-assured high volume-low cost/low profit MNCH medicines.
3. There is **a need for legal, organizational, and procedural changes** in registration. MTaPS is supporting these changes in Bangladesh, DRC, Nepal, Mozambique and Rwanda.
4. **Development partners have an important role to play** in supporting countries in their initiatives to improve the quality and efficiency of regulation for better access to safe, effective, and good quality medical products.

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MNCH Medical Products Registration in Mozambique

Denylson Namburete

MTaPS Country Lead

April 27, 2021

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Presentation outline

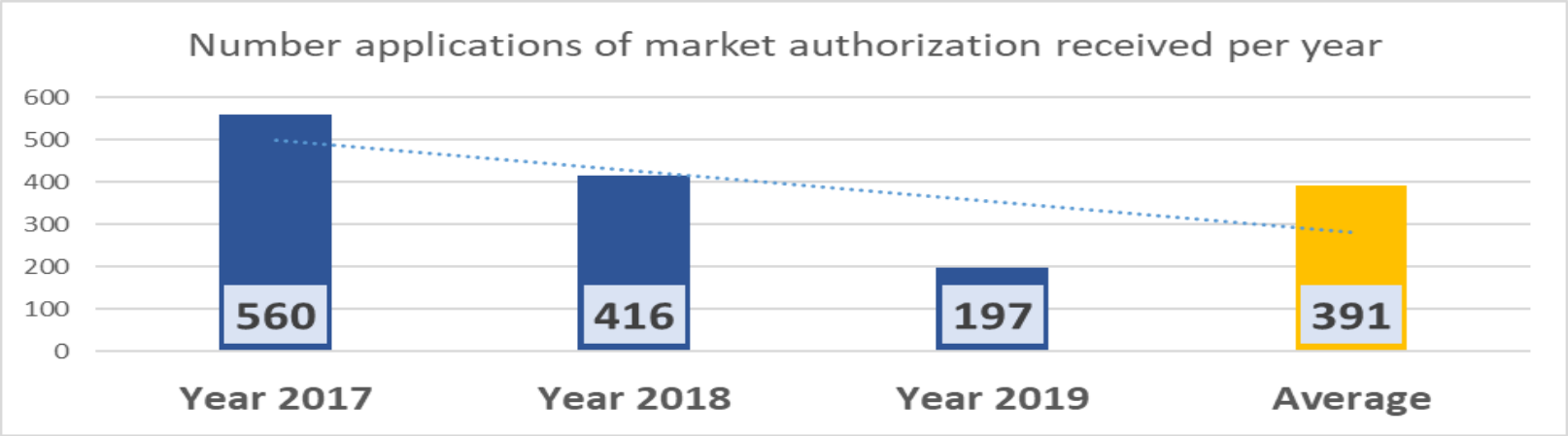
- Context
- Challenges in registration of MNCH medical products
- Streamlining registration process
- MTaPS support
- Next steps

Context

- The regulatory functions in Mozambique are currently performed by the DNF (Direcção Nacional de Farmácia) until the NRA is established and operational.
- DNF conducted a GBT in 2019 and has an Institutional Development Plan
- Legal framework in place for medicines but not yet for medical devices and medical gases
- Registration Department staffed by 15 technical personnel who need further capacity building for specialized areas, such as good review practices, evaluation of bioequivalence studies, medical devices, biologicals, and vaccines

Direcção Nacional de Farmácia (DNF)
Headquarters

Challenges in medical product registration



- Average of 391 medicines registration applications are received/year, i.e., 26 per assessor per year.
- Registration applications submitted in the standard CTD format, but SOPs are not updated; registration process can take up to a year.
- While priority/abbreviated processes based on public health benefit are possible under the legal framework, no priority registration is applied for essential MNCH medicines.
- The DNF participates in the WHO Collaborative Registration Procedure (CRP), which facilitates the registration of WHO prequalified products, including MNCH products (3 of 4 possible MNCH WHO prequalified medicines are registered). BUT MNCH medicines that are not WHO prequalified or approved by SADC, do not benefit from abridged registration procedures.

DNF: National Directorate of Pharmacy
SADC: Southern African Development Community
CTD: Common Technical Document

Specific MNCH Registration Findings and Implications

Indicator	Value
% MNCH tracer medicines with at least one registered product (valid registration status)	89% (16/18)
% MNCH tracer medicines with a locally in-country manufactured registered product	0
% MNCH tracer medicines with a registered WHO-prequalified product (n=4 since only 4 MNCH medicines -zinc, misoprostol, oxytocin, and magnesium sulphate- have been prequalified by WHO)	75% (3/4)
% of MNCH tracer medicines with one or more products with expired registration status	50% (9/18)
% marketing authorizations for the MNCH tracer medicines with one or more products with expired registration status	34% (41/121)
Source of specific MNCH registered products (%) (n= 80 non-expired registered products for the MNCH medicines listed)	India= 65% (52/80) Europe = 14% (11/80) China = 10% (8/80) Other = 11% (9/80)

Considerations to streamline registration for the country

- Support National Directorate of Pharmacy (DNF):
  - Allow reliance on registration decisions and GMP inspections from other NRAs even outside of SADC
  - Shorten process by reducing steps and allow timely decisions by DNF with target timelines
- Advocate for MNCH medicines to be added to the priority list for assessment at the DNF based on public health benefit.
- Implement good review practices to improve efficiency through guidelines and standard procedures (SOPs)
- Support full implementation of a Quality Management System for marketing authorization function to improve on efficiency and consistency of dossier evaluation for medical products.
- Use regional counterparts and international best practices as reference for registration of medical devices and medical gases.

Current support from MTaPS to the DNF

- Review and update of the regulatory framework for medical products registration
- Capacity building of DNF assessors in application of Good Review Practices
- Implementation of Quality Management System (QMS) through raising awareness, capacity building, and conduct of internal audit; plan for ISO 9001:2015 certification

MTaPS training DNF assessors in application of Good Review Practices, September 2020

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MNCH Medical Products Registration in Nepal

Dr. Birna Trap

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PHOTO BY WARREN ZELMAN

Product Registration and Challenges

- 12,000 registered products
- NEW Registrations are valid for 2 years
- Renewed thereafter annually
- About 75 manufacturers
- 45 technical staff at NMRA
- 4 assessors + 1 pharmacologist
- High workload

Dossier Review and Product Registration

- New product registrations:
  - Completed product registration per year: about 50 per assessor per year
  - Time to process <1 month
  - Cost is $27 imported/$3 locally manufactured
  - Annual fee $12
  - Registrations valid for 2 years
  - Registration renewal annually

Registration Challenges

- Overwhelming workload with annual renewal requirement
- Recruitment by Public Services Commission
- Assessment and review process at low maturity level
- WHO best practices only partially implemented
- Hardcopy requirement and manual handling
- Data quality in electronic registration database/MIS poor and unreliable
- Medical devices and gases not registered
- No regional collaboration or harmonization

Hard copy file required for registration and renewal

Specific MNCH Registration Findings and Implications

MNCH Products	%
% MNCH tracer medicines that have at least one registered product (5/18)	28%
% MNCH tracer medicines with a registered WHO-prequalified product (N=4)	0%
% MNCH tracer medicines registered not renewed or registration expired (12/18)	67%
% MNCH tracer medicines locally manufactured registered product (2/18)	11%

All manufacturers inspected and certified to local GMP requirements and only half to WHO GMP requirements (on the rise)

Streamlining Registration in Nepal

- **Process and requirements**
  - Revise guidelines and procedures
  - Increase renewal validity
  - Increase autonomy
  - Implement WHO dossier review
  - Shift to Pharmadex. Increase data quality and use

- **Local production**
  - GMP training - NMRA & industry
  - Inspection requirement by WHO standards
  - Pharmadex inspection module
  - SEARN collaboration

MTaPS Activities in Nepal

1. **Assessment**
   - GBT and IDP
2. **Reorganization**
   - New roles and responsibilities and revision of job description
   - Reorganization workshop
   - Decentralization and autonomy
   - HR plans, norms, capacity, and retention plans
3. **Quality Management System (QMS) implementation**
   - ISO 9001-2015 certification
   - Staff capacitation in QMS
   - Quality manual started
4. **Legal and regulatory revision**
   - Zero draft law
5. **Good dossier review practices**
   - Revision of process flows
   - Involvement of experts and committees
   - Revision of guidelines and SOP and documentation
   - Capacitation of assessors (e-learning)
6. **Management information system (MIS)**
   - SRS and customization to Nepal
   - Implementation of Pharmadex, including training of staff and stakeholders
   - Setting KPI and monitoring and tracking of performance
7. **Harmonization and collaboration**

Way Forward

Problems:

- WHAT, HOW, and WHY is known

Solution:

- Increase financial resources
- Increase human resources
- Increase autonomy
- Revise framework, practices, procedures and structures

Moving forward through collaboration and donor support to strengthen medicines registration system

Photo Credit: MSH Staff

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Thank You

Questions?

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Resources

Learn more about this initiative:

http://bit.ly/MTaPsCommodities

Engage with the Commodities subgroup **co-chairs**:

- Smita: smkumar@usaid.gov
- Ken: klegins@unicef.org

Subgroup information, recordings and presentations from previous webinars and meetings are available on the subgroup page of the Child Health Task Force website: www.childhealthtaskforce.org/subgroups/newborn
**The recording and presentations from this webinar will be available on this page later today*

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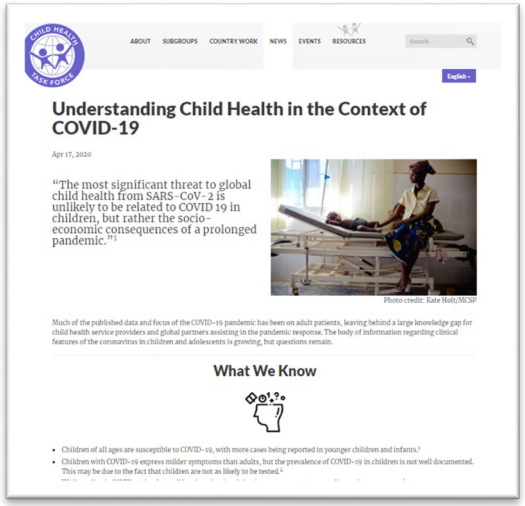

Check out the Task Force Child Health & COVID-19 web page for additional resources!

Suggestions for improvement or additional resources are welcome. Please email childhealthtaskforce@jsi.com.