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Workshop

Drug lifecycle control in Subsaharan Africa

From production to responsible safe disposal and elimination in wastewater treatment plants

(Med4Africa)

ENSURING QUALITY OF MEDICINES: EXPERIENCE FROM TANZANIA

Drug Lifecycle Control in Subsaharan Africa

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OUTLINE

TMDA

- Background
- Regulatory functions
- Legal & Regulatory Framework
- PMS Objectives
- Approaches
- Results
- Regulatory Actions
- Conclusion

TMDA Background

TMDA's Vision

To be the leading Regulatory Authority in ensuring safe, quality and effective, medicines, medical devices, diagnostics and other health related products for all.

TMDA's Mission

To protect and promote public health by ensuring quality, safety and effectiveness of medicines, medical devices, diagnostics and other health related products.

TMDA – Executive Agency under the MoH

- Established under the Tanzania Medicines and Medical Devices Act, Cap 219

The Act;

Mandate TMDA to regulate quality, safety, andefficacy of Medicines, Medical Devices and ***In-vitro diagnostics***

Accreditations

ISO 9001:2015

WHO Maturity LEVEL 3

ISO 17025 ACCREDITED LABORATORY

Regulatory functions

TMDA –

- Conducting PMS of the registered medicines to monitor quality, safety & efficacy
- It is also a continuation of the regulated health product review process initiated in the pre-approval areas of the product development process.

Key Roles

LEGAL & REGULATORY FRAMEWORK

- **Legislation**
  - ✓ Tanzania Medicines and Medical Devices Act, Cap 219
- **Regulations**
  - ✓ **Tanzania Medicines and Medical Devices, (Registration of Medicinal Products) Regulations, 2015. - section 9 (2) (e) & section 18(1) (2) (3). GN 314**
  - ✓ **Tanzania Medicines and Medical Devices (Pharmacovigilance) Regulations, 2018.**
- **Guidelines**
- **SOPs**
- **Reporting tools**
- **Quality Management System**
- **TMDA Strategic Plan (5Yrs)**
- **Regional collaboration (EAC) & SADC**

OBJECTIVES

☐ Main objective

❖ To ensure quality conformity of medicines with the accepted product specifications as declared in the registration dossier.

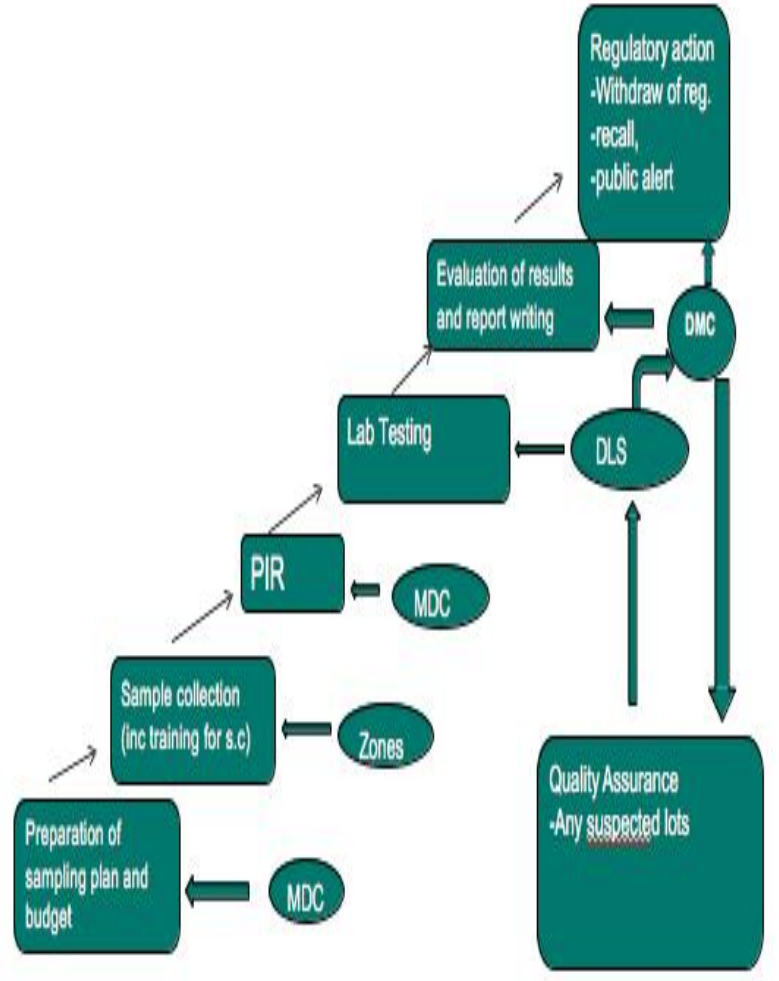
☐ Specific objectives

- ✓ To monitor the quality of registered medicines
- ✓ To combat the spread of falsified/substandard medicines
- ✓ To investigate complaints received
- ✓ To develop medicine information databank on quality of medicines circulating in the market
- ✓ To disseminate information on quality of medicines to stakeholders involved in medicines regulation, procurement, distribution and use.

PMS Approaches:

There are a number of approaches in PMS that can be used to ensure the continued quality of medicinal products;

Approaches	Medicines quality monitoring system
Methods	➢ Routine Drug Quality Assurance Program with emphasize of conducting primary screening of medicines ➢ Structured PMS Programs with focus on sampling and testing based on risks. ➢ Complaints Handling (poor quality forms)



Methodology (1)

Programme

3 Years

Daily QA

Sampling Sites

Different pharmaceutical outlets , different regions:

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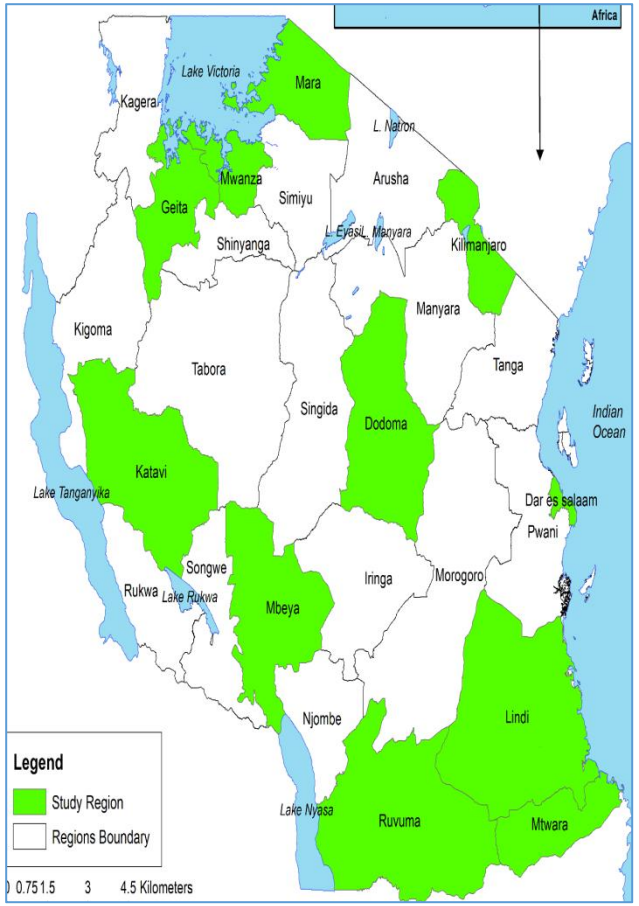
Selection criteria

- Highly populated regions,
- bordering other countries,
- regions with advanced urbanization,
- regions reported to have medicines quality problems
- those which were not included in the previous PMS programmes.



Criteria for selection of medicines

- Medicines that are used for treating diseases of economic importance eg anti-retroviral, anti-malarial and anti tuberculosis;
- diseases of common occurrence in the certain regions;
- for priority endemic diseases;
- for common chronic diseases or life-threatening illnesses such as anti-diabetics, anti-hypertensive and anti-asthmatics;
- which have indicated poor quality performance;
- used by special group at risk such as children and pregnant women;
- irrationally prescribed and dispensed;
- First line medicines with complicated dosage regimen;
- Medicines which require prolonged administration to a larger population and a number of them are used in combination;
- Medicines that are candidates for possible counterfeiting; and
- Medicines which are potentially dangerous, unstable or difficult to formulate.

Methodology…..

Product Information review (PIR)	Tier 1 Laboratory screening	Confirmatory test
Involve visual examination of 1 & 2nd pack, PIL, product appearance	samples are subjected to preliminary quality screening – • Visual Inspection • Simple disintegration test & • identification by TLC	Not screened, failed, suspicious & 10% passed screening test Parameters: appearance, identification, disintegration, related substance, weight variation & assay
Approved information	using GPHF mini-lab Kits	BP. EP, IP, USP
Data Management and Analysis ➢ processed & analyzed using Microsoft office, Excel Spreadsheet , results were expressed in %		

What has been done? (1)

PMS PROGRAMME	2007 – 2009	2011 - 2013
Human Medicines	ARVs, Anti-malarial, Analgesics Antibiotics	Quinine, Sulphamethoxazole + Trimethoprim, Erythromycin tabs, Cloxacillin, Abacavir, Ampiclox, Sulfadoxine + Pyrimethamine, Azithromycin, Tenofovir, Paracetamol, ALu., Sulphamethopyrazine + Pyrimethamine, Duo-cotecxin, Lopinavir + Ritonavir, Efavirenz, TLE, Lamivudine, Stavudine + lamivudine + nevirapine, Tenofovir+Emtricitabine, Lamivudine + Zidovudine, Zidovudine + lamivudine + nevirapine, Zidovudine
Veterinary medicines		Oxytetracycline 10% + 20%,
Outcome	15% of antimalaria (quinine and SP tablets) did not comply with quality test (assay and dissolution)	❖91% of Sulfadoxine/pyrimethamine failed dissolution test ❖32% of all samples failed to comply with labelling requirement

What has been done? (2)

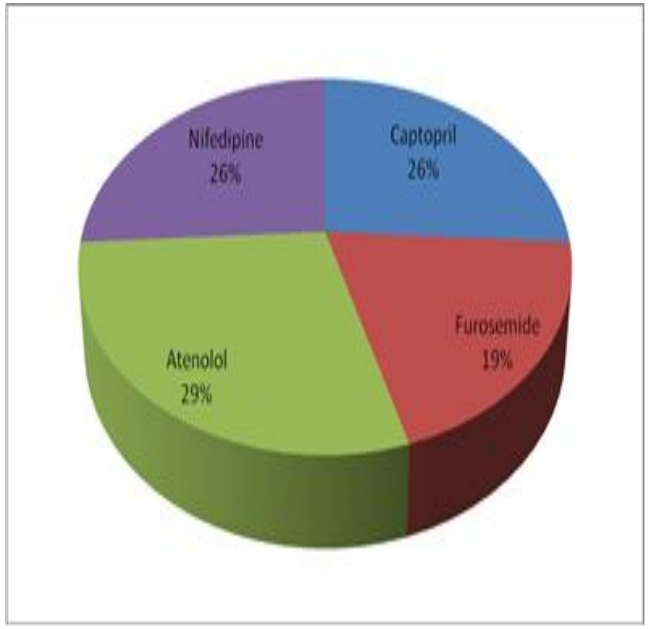
TYPE	PMS PROGRAMME		
	2014 - 2017	**2017 - 2020**	**2020 - 2023**
Human Medicines	Chloramphenicol, Atenolol, Diclofenac + Paracetamol, Misoprostol, Nifedipine, Dexamethasone + Neomycin, Phenoxymethyl Penicillin, Metronidazole, Albendazole, Ergometrine	Atorvastatin, Glimepiride, Procaine benzyl penicillin inj, Cloxacillin inject, Amoxicillin dispersible tablets, Ergometrine inj, Oxytocin, Artemether inj, Ciprofloxacin, Clotrimazole V.P, Furosemide Dihydroartemisinin/piperaquine phosphate	Azithromycin tabs, metronidazole susp, Metformin, Telmisartan/hydro chlorthiazide, cefalexin,ampicillin+cloxacillin, nifedipine
Veterinary medicines	Oxytetracycline 10% & 20%, Diminazene, Isometamidium, Amprolium, Levamisole	Sulfamethoxazole/Trimethoprim powder, Ivermectin inj, Isometamidium powder for inj, Diminazene diaceturate tetrahydrate powder for inj, Enrofloxacin oral solution, Albendazole oral suspension	Levamisole Inj, Norfloxacin, Albendazole bolus
Outcome	83% (609/737) H & 92% (219/238) V medicine failed labelling 1.5% of HM failed assay test (Phenoxymethyl Penicillin, Chloramphenicol), 100% of Ergometrine inj. failed assay test 20% of the VM failed assay tested (Isometamidium and Diminazine)	1 sample (1/3) of Glimepiride (33%) failed dissolution test 1 sample (1/52) of albendazole VM failed (0.02%) identification & assay	ON GOING

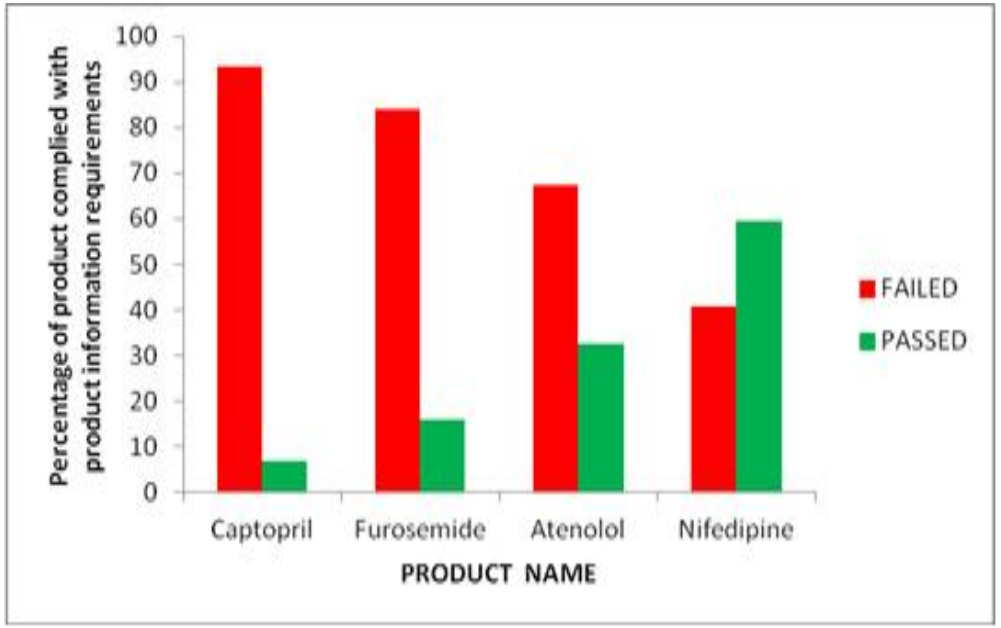
Routine QA

Year	No. of falsified medicines found	No. of substandard medicines found
2005	5	2
2006	1	0
2007	4	8
2008	1	0
2009	5	5
2010	3	17
2011	7	17
2012	7	29
2013	11	16
2014	10	40
2015	10	34
2016	4	8
2017	5	5
2018	3	6
2019	11	17
2020	7	21
2021	2	4
TOTAL	**96**	**229**

ANTI HYPERTENSIVE

- **PIR:** A total of 63.5% (108/170) samples failed to comply with product information requirements.





Antihypertensive

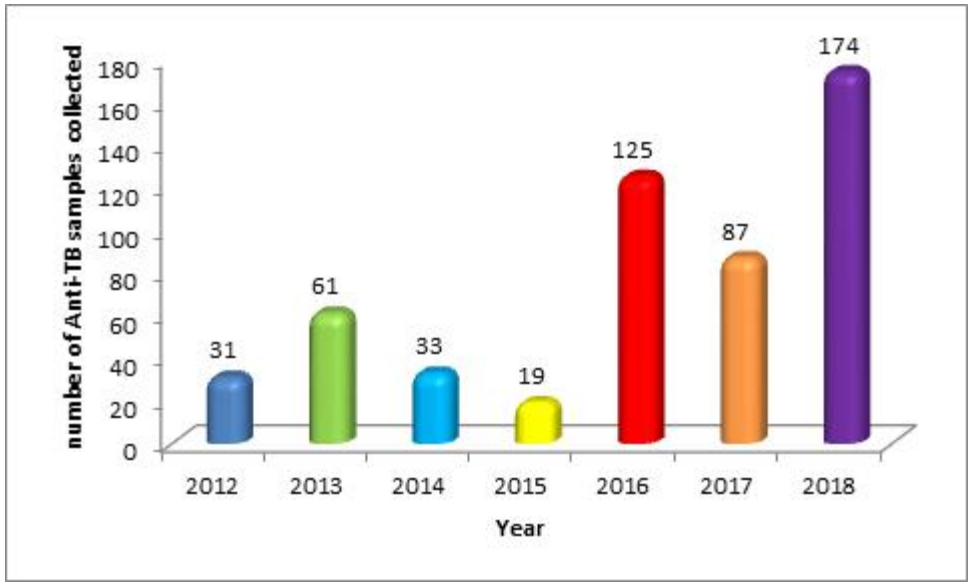
- **Confirmatory test:** A total of 90 samples (32) atenolol, (7) nifedipine, (27) captopril and (24) furosemide medicines were subjected to the test
  - Tested for appearance
  - Identification
  - Content uniformity
  - Disintegration
  - Assay
  - Related substance (Captopril)

❖ All samples passed all tested parameters with exceptional of Nifedipine – failed assay test by 14.3% (1/7). Repeated – 4 samples results ranged 69.4 – 79.5% (Limit 90% - 110%)

❑ The failure in assay could be a result of:

- ➢ degradation of the active ingredient attributed by light sensitivity nature of the active ingredient (inline with different studies conducted in Rwanda – Twagirumukiza et al, Dinarvand et all)
- ➢ less light protection capacity of the primary container.
- ➢ fault in manufacturing process of the product.

ANTI-TB



Samples of Anti-TB collected from port of entry between 2012 and 2018

- Streptomycin Sulphate powder for injection
- Isoniazid tablets
- Rifampicin/Isoniazid tablets
- Rifampicin/Ethambutol tablets
- Rifampicin/Isoniazid/Pyrazinamide tablets
- Rifampicin/Isoniazid/Ethambutol tablets
- Rifampicin/isoniazid/Pyrazinamide/Ethambutol tablets

PIR evaluation

Year	Evaluated	Complied	Not complied	% non-compliance
2012	157	6	151	96.2
2013	0	0	0	0
2014	48	35	13	27.1
2015	42	30	12	28.6
Total	247	57	176	71.3

Conclusion

All passed screening and confirmatory testing

71.3% failed PIR

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Quality Surveillance of Anti-Tuberculosis Medicines in Tanzania, 2012-2018

Kissa W. Mwamwitwa[1*], Betty A. Maganda[2], Seth Kisenge[1], Sophia A. Mziray[1], Henry Irunde[1], Yonah H. Mwalwisi[1], Adam M. Fimbo[1], Wilbroad Kalala[2], Adelard Mtenga[1], Akida M. Khea[1], Adonis Bitegeko[1], Danstan H. Shewiyo[1] and Blandina T. Mbaga[3]

ARVs

- Sampling: 2,630 ARVs samples b/n 2012 and 2018 from POEs and medicine distribution outlets
- 83.7% (2,200/2,630) were collected from POEs
- PIR - 25.6% (110/430) did not comply
- Screning: 3.3% (14/430) of the samples from the distribution outlets, failed disintegration test; - FDC of lopinavir/ritonavir tablets (7/430) and lamivudine/zidovudine/nevirapine tablets (7/430).
- Confirmatory:3% (3/100) failed confirmatory test . The failed samples were of FDC of stavudine/lamivudine/nevirapine 3% (3/100) which failed disintegration test 2% (2/100) and assay test 1% (1/100), having low content of stavudine (86.6%) of the specified amount (limit 90% - 110%).

Medicines tested

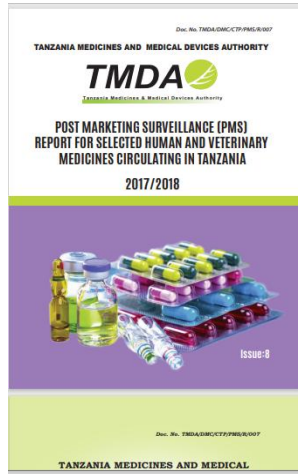
Mono: efavirenz, nevirapine, lamivudine, zidovudine, abacavir sulphate, tenofovir disoproxil fumarate and fixed dose combination (FDC) containing tenofovir disoproxil fumarate /emtricitabine, lamivudine/zidovudine/nevirapine, lamivudine/stavudine/nevirapine, tenofovir/lamivudine/efavirenz, tenofovir/ emtricitabine/efavirenz and lopinavir/ritonavir.

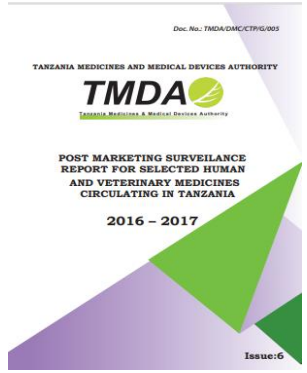
Conclusions

- The quality of majority of ARVs was good,
- However, significant deficiencies on labelling and packaging were observed.

Regulatory action

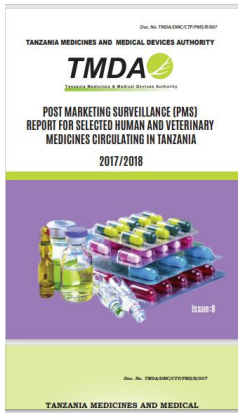
- The failed batches were recalled from the market
- Manufacturer was directed to conduct thorough investigation and importation was suspended
- Manufacturers for those products failed PIR, were directed to comply with labeling requirements





Achievements

- Regulatory actions: withdraw/recall of poor quality medicines from the market, de-registration of the products, legal action
- Joint PMS activities with EAC states : Amoxicillin caps, Amoxicillin/Clavulanic acid, Sulfamethaxazole/ trimethoprim
- Effectively Implementation of four (4) PMS programmes
- Collaboration with WB to strengthening PMS activities for the veterinary vaccines
- Publications: Post Marketing Surveillance of Anti-malarial Medicines in Tanzania (Pharmaceutical Regulatory Affairs: Open Access), Quality of antihypertensive, Quality of anti-TB
- WHO Maturity level 3



Conclusion

- Improved quality of medicines
- Presence of some substandard and falsified medicines signifies the need for continuous monitoring of the quality of medicines post registration

Thank you