AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

World Health Organization

Strengthening Quality Control Laboratories in Fighting Substandard and Falsified Medicines

Timothy Nwogu
Senior Technical Advisor, Regulatory Systems Strengthening
PQM+, USP

6th Scientific Conference on Medicines Regulation in Africa
5-7 December 2023

USAID
FROM THE AMERICAN PEOPLE

AMRH
African Medicines Regulatory Harmonisation Programme

Promoting the Quality of Medicines Plus (PQM+)

For more than 200 years, USP has been advancing its vision of a world where all have access to safe, quality medicines

As a scientific, international nonprofit organization, we have more than 200 years of experience increasing the supply of safe, effective medicines, vaccines, and trusted diagnostics.

USP strengthens health systems and delivers end-to-end pharmaceutical services that champion equitable access to quality medical products. Our work improves supply chain resilience, protects patients from poor-quality medicines, & combats antimicrobial resistance

.

200 usp
The standard of trust

Global Health within USP

Working with Underserved Populations and Resource-Constrained Governments

Promoting the Quality of Medicines (PQM)-Flagship Program

Helping low-and middle-income countries address critical pharmaceutical challenges with funding from the United States Agency for International Development (USAID)

Global Health Projects

Non-USAID funded projects to help low-and middle-income countries address critical pharmaceutical challenges

Preferential Access for Regulators (PAR)

Supporting the capacity of Official Medicines Control Laboratories for sustainable impact

USP-Ghana

Providing workforce development and technical training to regulatory professionals and bodies

South-South Collaboration

Promoting South-South Collaboration to support resource sharing and regional harmonization

About PQM+

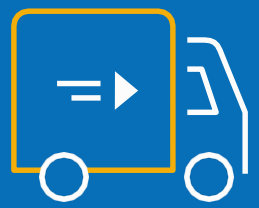
The Promoting the Quality of Medicines Plus (PQM+) program, funded by the U.S. Agency for International Development (USAID) and implemented by the U.S. Pharmacopeial Convention, works to improve systems that assure the quality of essential medical products in low- and middle-income countries (LMICs) to help prevent maternal and child deaths, control the HIV epidemic, and combat infectious diseases through high-performing health systems.

The PQM+ Program Objectives

1

Improve **governance** for medical product quality assurance systems

2



Improve country and regional **regulatory systems** to assure the quality of medical products in the public and private sectors

3

Optimize and increase **financial resources** for medical product quality assurance

4

Increase **supply** of quality-assured essential medical products of public health importance

5

Advance global global medical products quality assurance **learning and operational agenda**

The PQM+ program is funded by USAID and implemented by USP

Strengthening Quality Control Laboratories in Fighting Substandard and Falsified (SF) Medicines

USAID FROM THE AMERICAN PEOPLE

AMRH African Medicines Regulatory Harmonisation Programme

Promoting the Quality of Medicines Plus (PQM+)

Fighting SF…

It is a public health imperative…

Access to quality, safe and efficacious medical products…

SDG Target 3.8 |

Achieve universal health coverage, including financial risk protection, access to quality essential health care services and **access to safe, effective, quality, and affordable essential medicines and vaccines for all**

The NRA Market Control Function Is Key to Fighting SF

- Establishing a program for monitoring the quality of medical products on the market
  - ✓ Law, regulation, policy
  - ✓ Management through a technical working group,
  - ✓ Guidelines, SOPs

04:Market Surveillance and Control Thematic areas			
control of import activities	**prevention and detection of and response to SF** **(PMS)**	**Market surveillance program** **(PMS)**	Control of promotional, marketing and advertising activities

Fighting SF…
(Protocol, sampling, testing, and enforcement actions)

- Implementing a risk-based PMS – developing a sampling and testing plan for detection of SF from vulnerable geographic locations
  - Application of risk management principles for risk estimations (medicine, geographical areas, and outlets)
  - Sample size calculations, stratification, and random
  - Randomization of outlets
  - Sample collection, handling, training
  - Risk-based sample testing (the three-level approach: visual, screening and compendial)

- Result dissemination and risk-based regulatory actions when SF is found

The Quality Control (QC) Lab Plays a Critical Role in Fighting SF

QC Labs conduct quality tests for

- PMS samples
- Import control samples
- Inspection (GDP or GMP) samples
- Complaint samples

PQM+ Support

The USAID-funded PQM+ program is strengthening technical capacity for …

- PMS activities in **16+ African** countries
- QC labs in **13+ African** countries

Helping QC labs progress toward ISO accreditation or WHO PQ

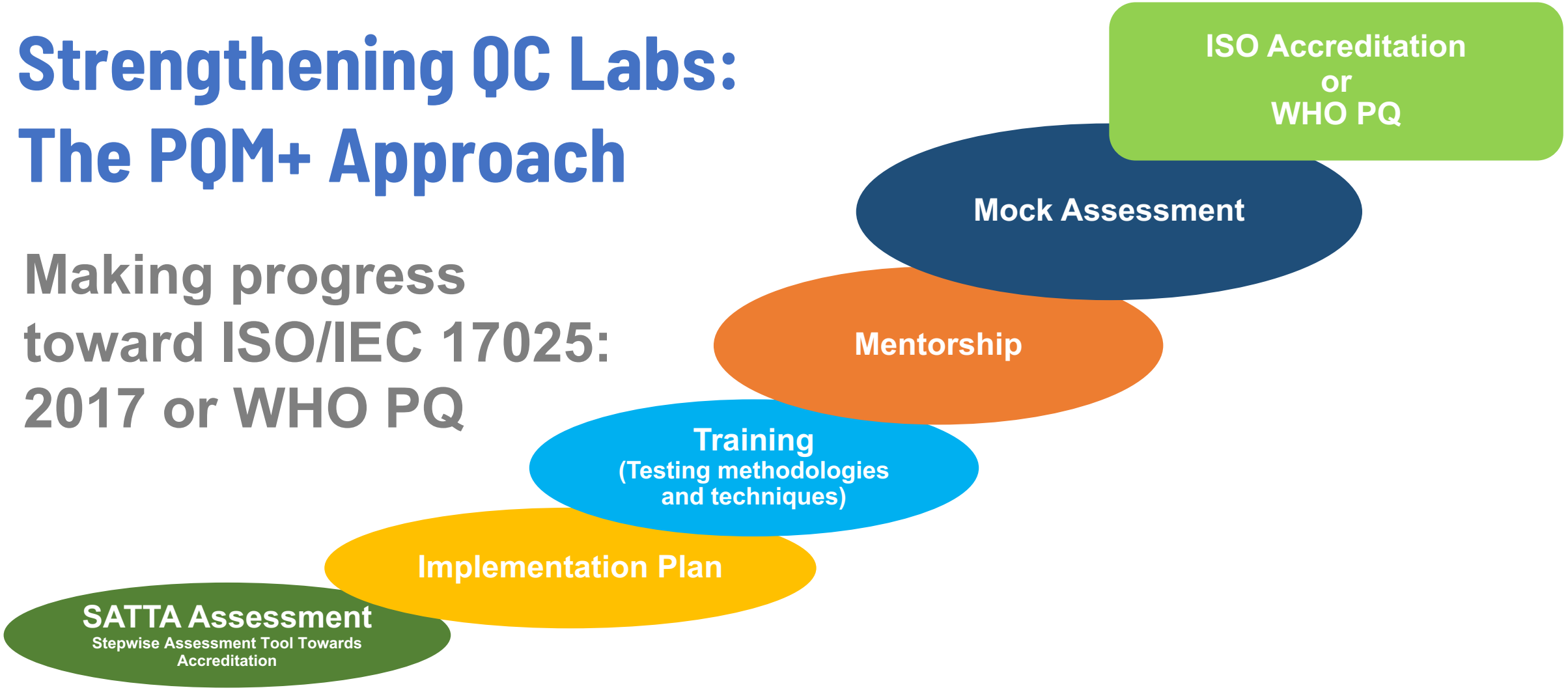
USAID FROM THE AMERICAN PEOPLE

AMRH African Medicines Regulatory Harmonisation Programme

Promoting the Quality of Medicines Plus (PQM+)

Strengthening QC Labs: The PQM+ Approach

Making progress toward ISO/IEC 17025: 2017 or WHO PQ



USAID FROM THE AMERICAN PEOPLE

AMRH African Medicines Regulatory Harmonisation Programme

Promoting the Quality of Medicines Plus (PQM+)

Strengthening QC Laboratories

Laboratory results must be accurate and reliable

The WHO GBT provides key indicators for QC lab

- Legal backing, provisions, regulations
- Organization and governance
- Establishment of a QMS for lab activities
- Adequate and trained human resources
- Well maintained and equipped lab
- Established guidelines and SOPs for laboratory testing activities
- Established mechanism for transparency and communication
- Performance and data trending – (trend analysis, participation in PT)
- Measures for occupational health and safety
- Management of outsourced QC activities

Building QMS Capacity Is Key

Between 2019-2023, globally PQM+ has

- Conducted 109 trainings on laboratory testing
- Conducted 174 quality assurance systems trainings
- Supported proficiency testing across
- Mock assessments

Training Topics include

- ISO/IEC 17025:2017
- WHO TRS 957 Annex 2
- WHO TRS 961 Annex 2
- Management system documentation
- Standard operating procedure writing
- Document management
- Record management
- Training program implementation
- Internal auditing
- Auditor
- Root cause analysis | corrective action
- Data integrity
- Management review
- Non-conforming work
- Use of standard methods
- Measurement techniques
- Good laboratory practices
- Good weighing practice
- Good pH measurement practice
- Solution preparation
- Loss on drying
- Dissolution
- Chromatography
- Spectrophotometry
- Measurement uncertainty
- Method validation
- Method verification
- Trend analysis
- pH meter calibration and PM
- Oven calibration and PM
- Dissolution tester calibration and PM
- HPLC calibration and PM
- UV-vis calibration and PM
- Good reagent storage practices

Sample Testing for PMS

A risk-based approach to PMS sample testing

The Three Level Approach (3LA) for RB-PMS Sample Testing

Level 1

Visual and physical inspection

Initial check of registration status, expiration date, labeling, packaging, appearance, physical and organoleptic properties, use of track and trace technologies

Level 2

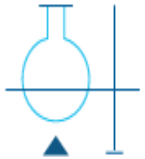
Field-based screening

Use of field-based screening technologies which may test for identity, content and other quality attributes

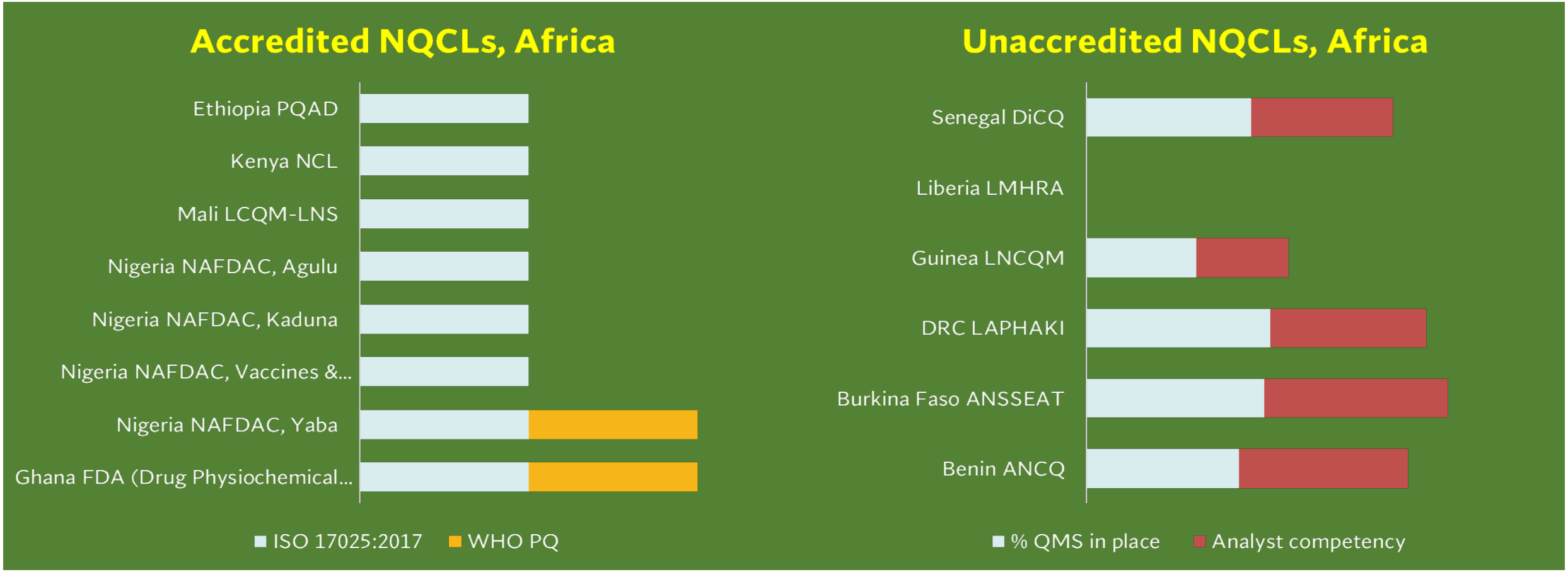
Level 3

Compendial testing

The prioritization and use of pharmacopeial methods or other validated methods approved by the NMRA



Achievements by Some Supported Labs



USAID FROM THE AMERICAN PEOPLE

AMRH African Medicines Regulatory Harmonisation Programme

Promoting the Quality of Medicines Plus (PQM+)

Some Achievements in LSS in Africa

COUNTRY	ACHIEVEMENT	DONOR/SPONSOR	SUPPORT PROVIDED	NEXT PRIORITY
BENIN	ISO/IEC 17025 roadmap implementation	USAID	Assessment Training TA to strengthening QMS Equipment Maintenance ILT/PT support	Audit planned in 2024
BOTSWANA	ISO/IEC 17025 roadmap implementation	Government	Assessment Training TA to strengthening QMS Equipment Maintenance	Audit date TBD
BURKINA FASO	ISO/IEC 17025 roadmap implementation	USAID	Assessment Training TA to strengthening QMS Equipment Maintenance Equipment calibration and qualification ILT/PT support	Audit planned in 2023

Some Achievements in LSS in Africa

COUNTRY	ACHIEVEMENT	DONOR/SPONSOR	SUPPORT PROVIDED	NEXT PRIORITY
CHAD	ISO/IEC 17025 roadmap implementation	World Bank	Assessment Training TA to strengthening QMS	Audit date TBD
DRC	ISO/IEC 17025 roadmap implementation Audit planned in 2023	World Bank USAID	Assessment Training TA to strengthening QMS Equipment Maintenance Equipment calibration ILT/PT support	Audit planned in 2023
GUINEA	ISO/IEC 17025 roadmap implementation	USAID	Assessment Training TA to strengthening QMS Equipment Maintenance Equipment procurement	Audit date TBD

Some Achievements in LSS in Africa

COUNTRY	ACHIEVEMENT	DONOR/SPONSOR	SUPPORT PROVIDED	NEXT PRIORITY
LIBERIA	ISO/IEC 17025 roadmap implementation	USAID	Assessment Training TA to strengthening QMS Equipment procurement	Audit date TBD
NIGER	ISO/IEC 17025 roadmap implementation	World Bank	Assessment Training TA to strengthening QMS	Audit date TBD
NIGERIA	ISO/IEC 17025 Accreditation NAFDAC (4 Labs) & NIPRD Lab	USAID	Assessment Training TA to strengthening QMS Calibration, PT & ILT	Reaccreditation Support WHO PQ 2023 (for NAFDAC)

Some Achievements in LSS in Africa

COUNTRY	ACHIEVEMENT	DONOR/SPONSOR	SUPPORT PROVIDED	NEXT PRIORITY
MALAWI	ISO/IEC 17025 roadmap implementation	Global Fund	Assessment Training TA to strengthening QMS Equipment Maintenance	Audit date TBD
MALI	ISO/IEC 10725 accreditation achieved	USAID	Assessment Training TA to strengthening QMS Equipment Maintenance Equipment calibration and qualification ILT/PT support	Accreditation scope expansion
SENEGAL	QA/QC Capacity building	USAID	Assessment Training TA to strengthening QMS Equipment Maintenance Equipment calibration	Audit date TBD

Some Challenges Remain

- NQCL technical staff attrition
- Tangible commitment from some NQCL leadership wavering at times
- Inability to maintain QMS and meet requirement without external technical or financial support
- Timely dissemination of PMS results and regulatory actions

Thank you!

Contact:
Timothy Nwogu
tyn@usp.org
PQM+, USP. Rockville MD, USA

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

AMRH
African Medicines Regulatory Harmonisation Programme

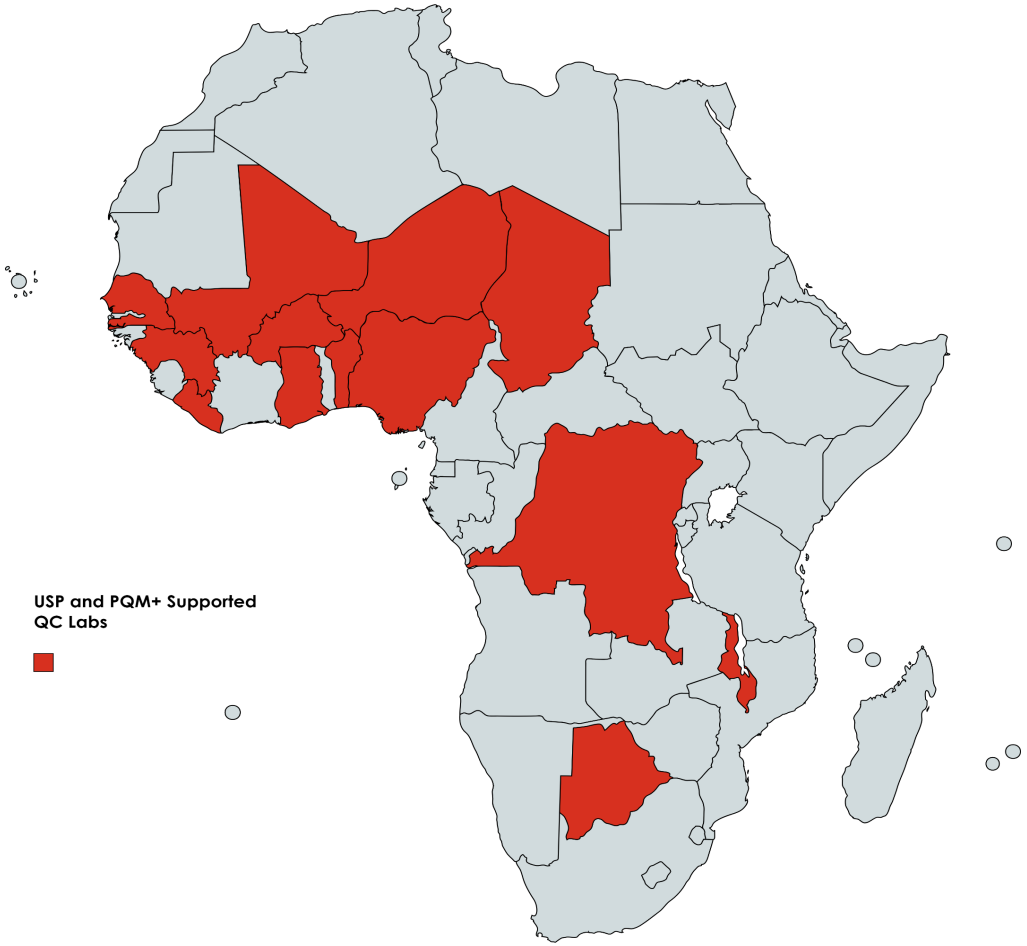
World Health Organization

Data from Sampling Activities by 11 NRAs (names withheld) conducted 2021-2023

298 out of 3557 samples collected did not meet quality specification (substandard)

1,015 samples were unregistered

Supported QC Labs and NRAs for PMS

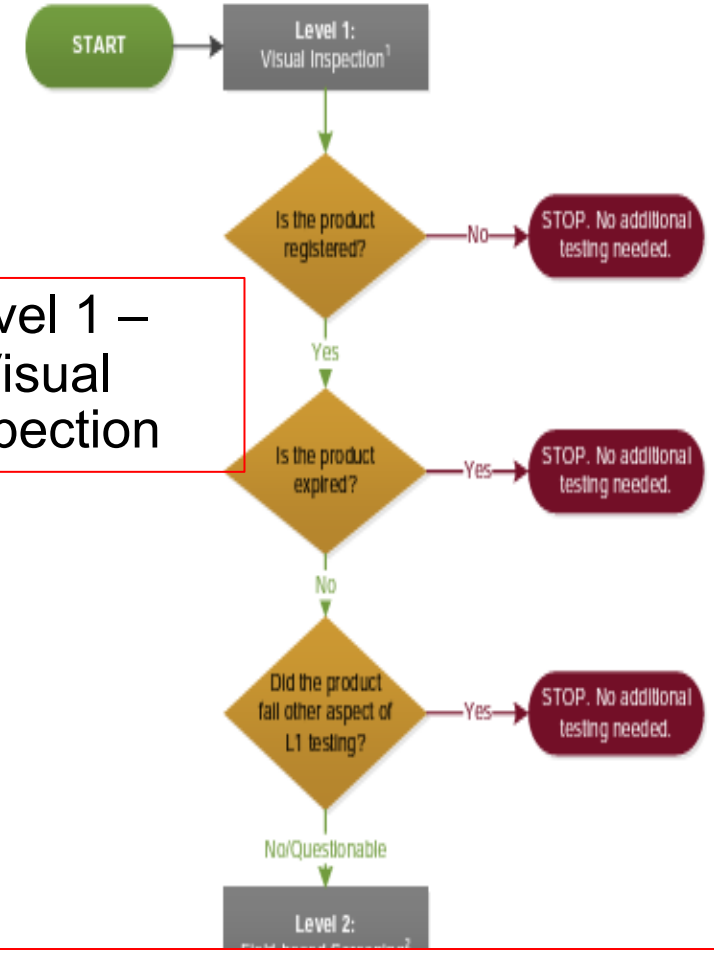


Created with mapchart.net

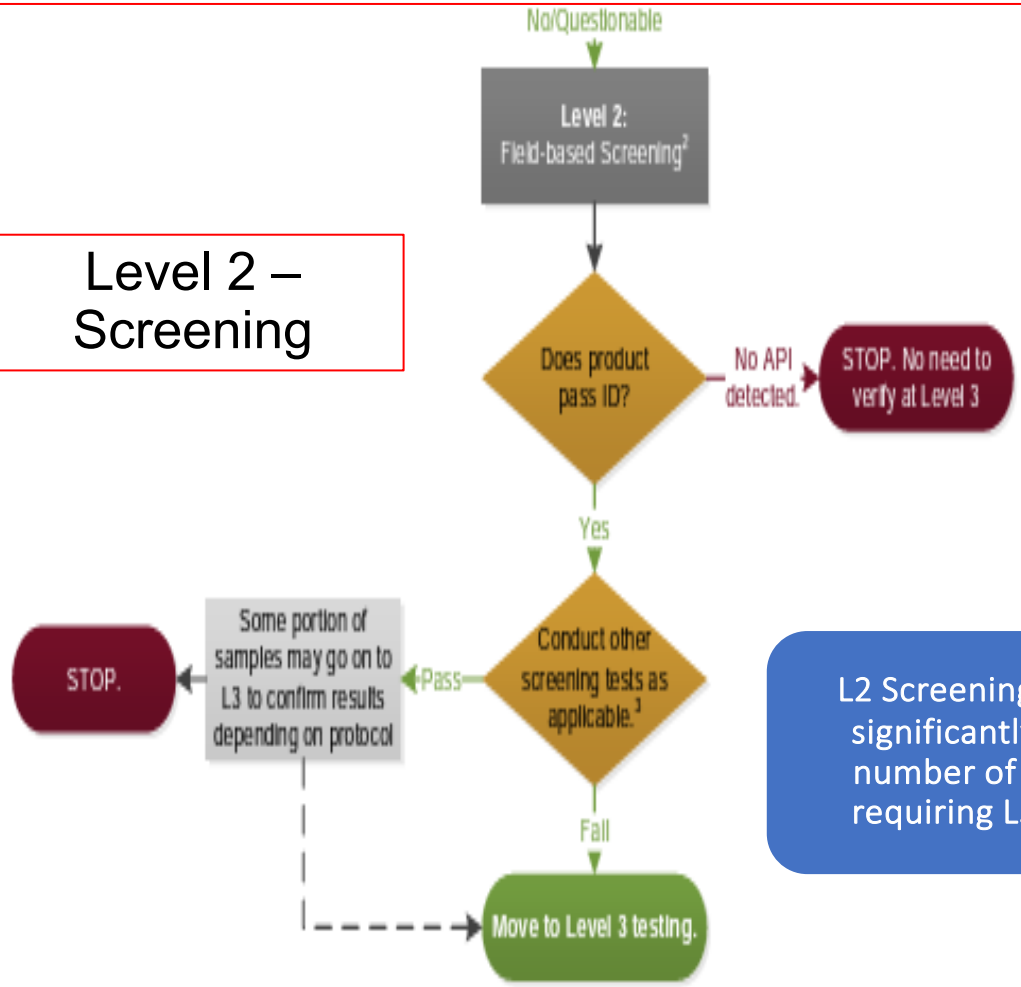
Created with mapchart.net

Risk-Based Testing for PMS

Level 1 – Visual Inspection

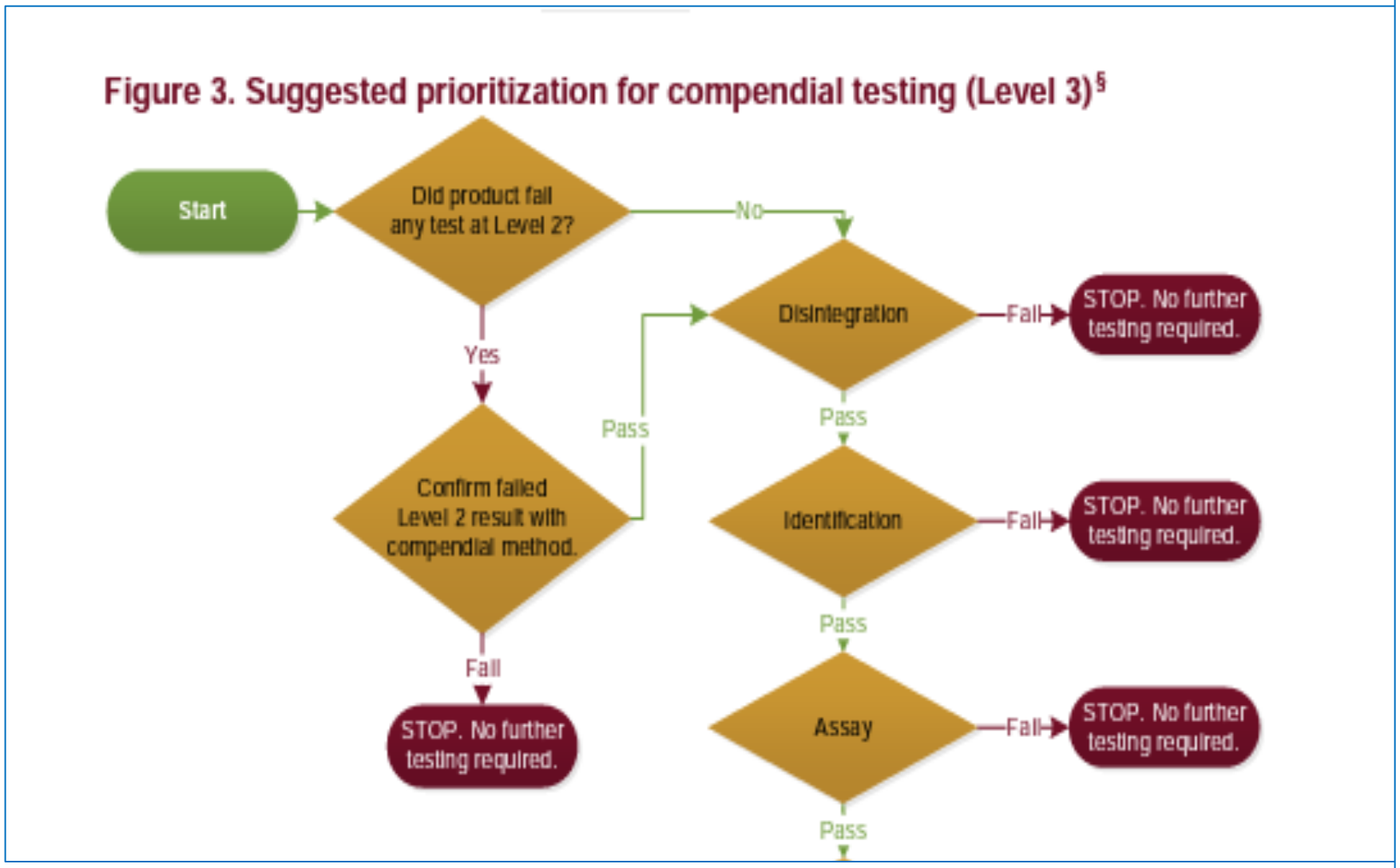


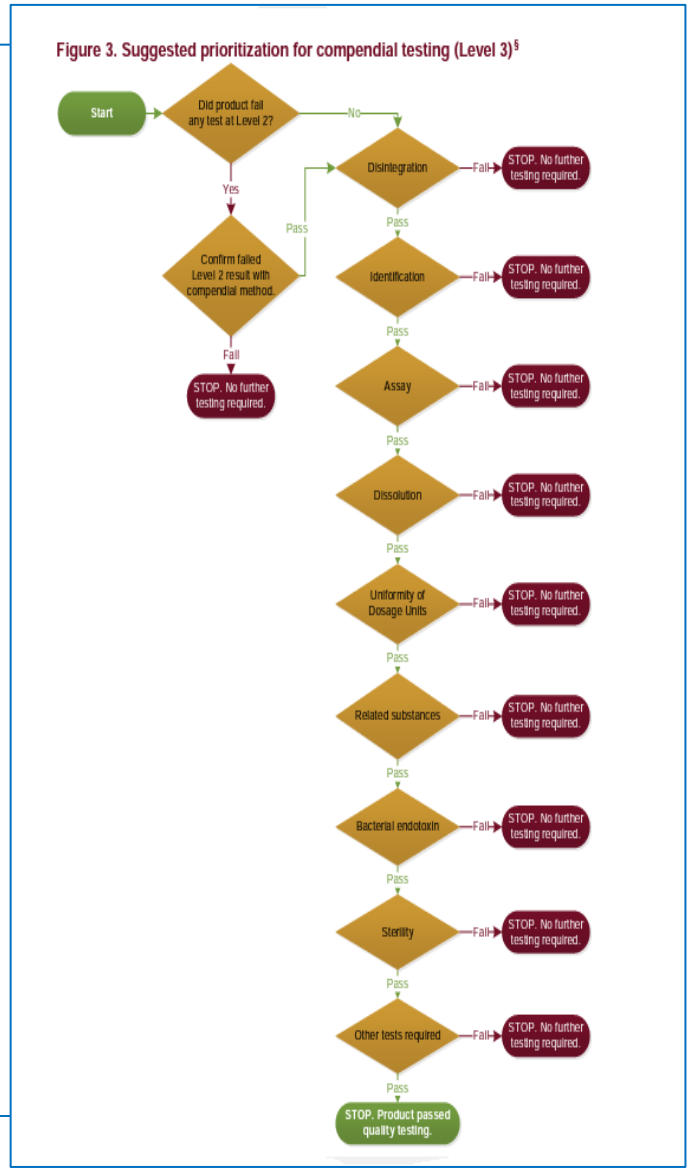
Level 2 – Screening



L2 Screening helps to significantly reduce number of samples requiring L3 testing

Risk-Based Testing - Level 3 (Laboratory Testing)





USP Review for Six Screening Technologies

- **Technologies reviewed**
  1. Global Pharma Health Fund-Minilab™ – chromatography and disintegration
  2. Paper analytical device – chromatography and wet chemistry
  3. Raman spectroscopy
  4. Near Infrared (NIR) spectroscopy
  5. Fourier Transform Infrared (FTIR) spectroscopy
  6. Portable Respirometer (Speedy Breedy – for sterility)

https://www.usp.org/global-public-health/technology-review-program

USP Technology Review Reports/Publications

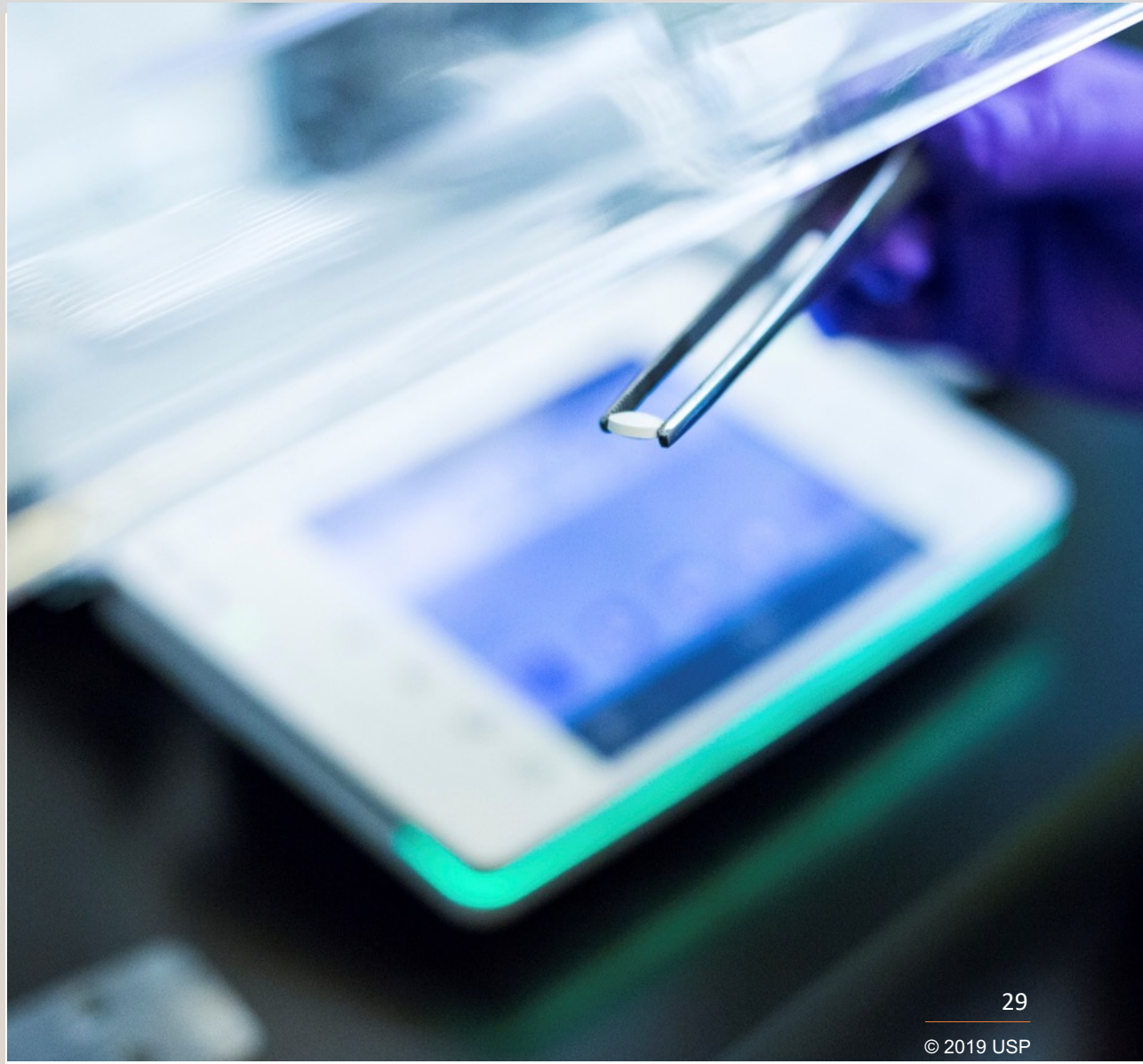
https://www.usp.org/global-public-health/technology-review-program

https://www.usp.org/sites/default/files/usp/document/our-work/global-public-health/rbpms-resources-english.pdf

Screening Technologies

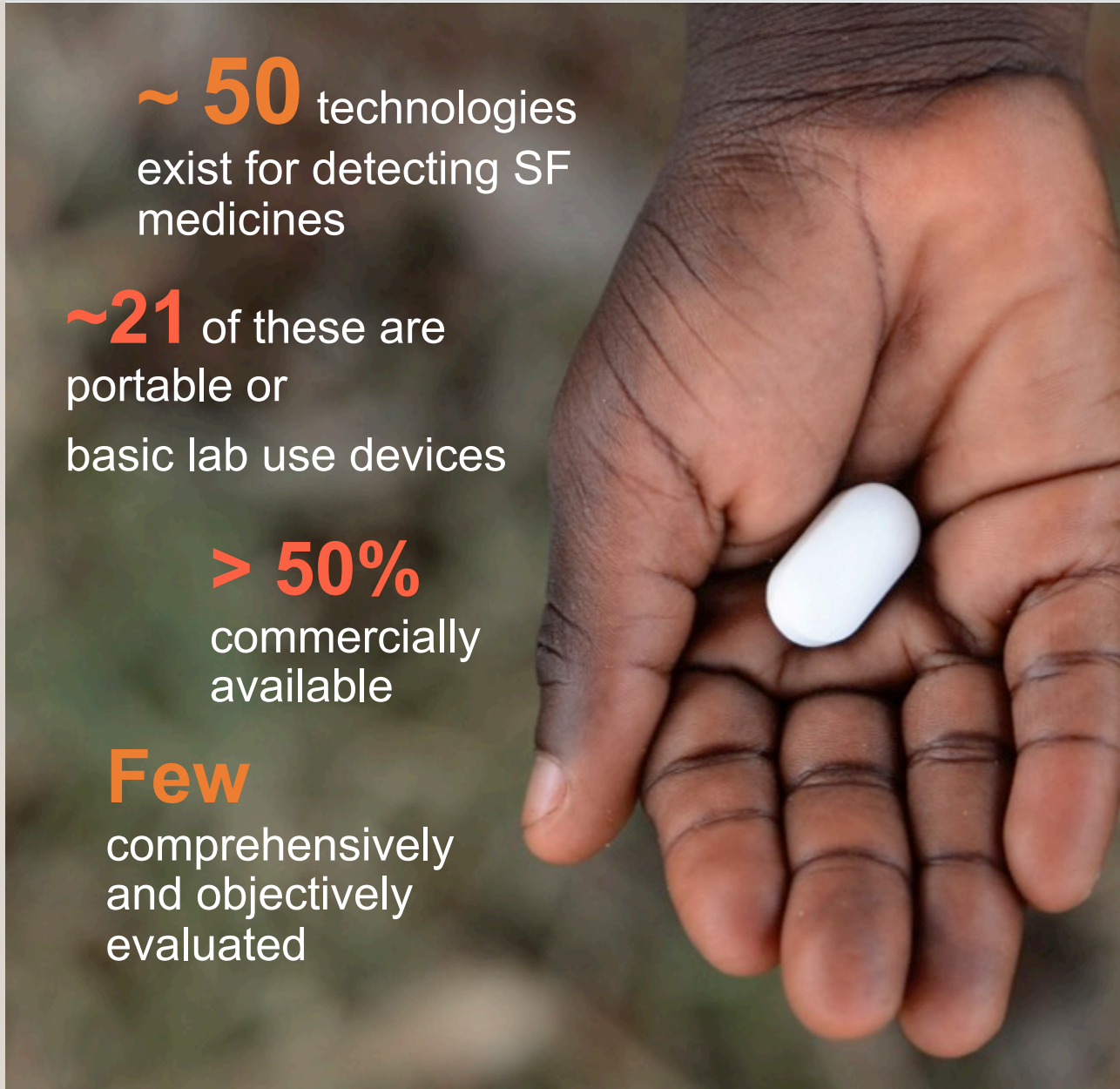
- Technologies that can help rapidly detect SF medicines
- Does not replace need for compendial laboratory testing

- **Application of screening technologies**
  - Manufacturing controls
  - Supply chain screening
  - Border control
  - Customs inspection
  - Post-market quality surveillance or regulatory monitoring
  - Point-of-care screening



Characteristics of Screening Technologies

- Relatively Inexpensive
- Portable / Handheld
- Easy to use
- Requires minimal training
- Non-invasive
- Reliable and robust
- Rapid methods
  - Identification
  - Quantitation
  - Disintegration
  - Sterility



How Can I Deploy a Screening Technology in PMS?

Where?

- Sentinel Sites
- Laboratories
- Ports of Entries

Savings example

- For a typical RB-PMS conducted by a country

✓ Assuming 380 samples were collected and only 100 required further lab testing (lab) after screening using GPHF-Minilab™ ;

✓ Cost savings may be up to ~ $224,000 (if approximately 280 samples are not subjected to lab testing. Assuming a cost of $800/sample (range $500-1,300) for full compendial test by third-party labs)

GPHF-Minilab™ (Commonly Used in LMICs for PMS)

- Screening method assembled as a self-contained kit ready-packed with a set of secondary reference standards
- Minilab can analyze 100 different drug substances prevailing in low- and middle-income countries for priority infectious diseases
- Minilab can be used for chemical (thin-layer chromatography) and physical (visual inspection checklist, weight verification, and disintegration) analysis
- TLC separates components in a sample according to differences in polarity, as the components interact between mobile and stationary phases (ID and semi-quantitative analysis)
- Quantification is performed by visually comparing the size and intensity of the spot of the sample solution with that of the standard solution at specific percentages of the nominal concentration

GPHF-Minilab™

Strengths

- ✓ Ability to detect different drug substances in multiple dosage forms
- ✓ Ability to analyze drug substances in co-formulated products
- ✓ Ability to carry semi-quantitative analysis
- ✓ Ability to estimate of the number of impurities in a formulation
- ✓ Relatively inexpensive compared to other screening technologies especially spectroscopy

Limitations

- ✓ Minilab methods typically use reference standard solutions at 80% and 100% of the nominal concentration
- ✓ Impurities levels not quantifiable
- ✓ Personnel may need to have some basic science and laboratory knowledge
- ✓ Requires sample preparation
- ✓ Safe handling and disposal of chemicals

Paper Analytical Device (PAD)

- A fast chromatography paper with 12 lanes containing reagents, which react with specific chemical functional groups to produce a color reaction in response to different drug products.
- Sample is applied in a line across the lanes and the card is placed on its edge in water. The water is drawn up the card by capillary action and mixes the reagent with a sample to start 12 color reactions.
- The outcomes of the 12 color tests form a color bar code. Test results are evaluated by comparing the color bar code to images of quality samples.

Paper Analytical Device (PAD)

Strengths

- ✓ Ability to detect falsified products
- ✓ No consumables or reagents are needed to perform an analysis except water
- ✓ Sample preparation and development takes a short time: 5 to 10mins
- ✓ Training: Very short duration <5 days
- ✓ Cost: $2 + shipping costs

Limitations

- ✓ Inability to detect substandard products (up to 50%)
- ✓ Single use per sample
- ✓ Color challenges especially for people who are color blind
- ✓ Only useful for solid dosage forms, e.g., tablets, capsules, or powdered injection

Raman Spectroscopy

- Raman measures the light scattered inelastically from excited chemical species; provides a "**spectral fingerprint**" for chemical identification
- Raman signal is most intense for nonpolar bonds enabling analysis in the presence of water, unlike FTIR and NIR
- Raman employs a match score identification (ID) metric, which scales from 0 to 1 by comparing the spectra of a known quality product against the sample

Raman Spectroscopy

Strengths

- ✓ High specificity; Ability to reliably & accurately identify APIs in various single drug products
- ✓ Multiplexing capability
- ✓ Quick analysis time requiring no sample preparation
- ✓ User friendly and easy operation; short training required
- ✓ Easy to interpret results through match factor; pass/fail binary response
- ✓ Suitable for field settings; handheld and battery operated

Limitations

- ✓ Mostly useful for solid dosage forms
- ✓ Relatively low sensitivity (but can be overcome using enhanced Raman technologies)
- ✓ Fluorescence and opaque packaging interference
- ✓ Relatively expensive

Near Infrared (NIR) Spectroscopy

- NIR instruments measure the absorption of near infrared radiation diffusely reflected from samples
- The NIR penetration depth for solid dosage form medicines can extend ~ 1–5 mm, enabling a more representative bulk evaluation of the drug product composition than FTIR or Raman
- The larger penetration depth and lower absorption of NIR radiation compared to FTIR also

Near Infrared Spectroscopy

Strengths

- ✓ Ability to reliably identify APIs in various single drug products
- ✓ Enable accurate API quantification
- ✓ Short run time per sample
- ✓ Short training required
- ✓ Suitable for field settings; handheld and battery operated

Limitations

- ✓ Mostly useful for solid dosage forms
- ✓ Unable to detect the presence of APIs in water-based formulations e.g., injections
- ✓ Affected by particle size/packing variability and opaque packaging
- ✓ Challenge in identifying the presence of multiple APIs in co-formulated products; require chemometric modeling
- ✓ Relatively expensive

Portable Fourier Transform Infrared (FTIR) Spectrometer

- FTIR instruments measure the absorption of IR radiation. IR spectroscopy is most sensitive to polar bonds, lending this technique most responsive to functional group
- FTIR instruments employ diamond attenuated total reflection (ATR) due to its robustness and ease-of-use
- Target-ID employs a correlation coefficient (CC) match factor identification (ID) metric, which scales from 0 to 1, with 1 being a perfect match and 0 being a perfect mismatch

Portable Fourier Transform Infrared (FTIR) Spectrometer

Strengths

- ✓ Ability to reliably identify several of the APIs in single drug products
- ✓ An intuitive, easy-to-operate user interface
- ✓ Easy to use and interpret result, through match factor and overlay of spectra on the screen

Limitations

- ✓ Mostly useful for solid dosage forms
- ✓ Unable to detect the presence of APIs in water-based formulations e.g. injections
- ✓ Challenge in identifying the presence of multiple APIs in co-formulated products
- ✓ The low penetration depth of IR instrumentation inhibits through package (coatings, capsules, or blister packs) analysis)
- ✓ Requires sample preparation (minimal)

Portable Respirometer (Speedy Breedy)

- Portable respirometer able to detect bacterial contamination in sterile liquids
- The equipment measures pressure change in a vessel filled with a liquid sample to determine whether or not the sample has been contaminated with microbes
- Detection is observed through pressure transients relating to gaseous exchanges within a 50 mL closed culture vessel as a result of microbial respiration

Portable Respirometer (Speedy Breedy)

Strengths

- ✓ Ability to detect microbial contamination in sterile liquids
- ✓ Reproducible down to 1 CFU
- ✓ Short training period
- ✓ Faster than a traditional lab test
- ✓ No preparation required
- ✓ Ability to dispose non-spore-forming bacteria through pasteurization cycle up to 65°C

Limitations

- ✓ Protocols require 24h run time
- ✓ Require continuous power for the entirety of the run/operate, limiting its use in remote setting with no electricity