Member States Briefing on WHO coordinated efforts for regulatory systems strengthening, local production and assistance, and prevention, detection and response to substandard and falsified products

11 April 2023

WHO Regulation and Prequalification Department

World Health Organization

Agenda

1. **Welcoming remarks**
   Dr Hanan Balkhy, Assistant Director General a.i, Access to Medicines and Health Products Division

2. **Affordable, timely and equitable access to quality-assured medical products**
   Dr Rogerio Gaspar, Director Regulation and Prequalification Department

3. **Regulatory System Strengthening**
   Hiiti B. Sillo, Unit Head, Regulation and Safety

4. **Local Production and Assistance**
   Dr Jicui Dong, Unit Head, Local Production and assistance

5. **Substandard and Falsified medical products**
   Rutendo Kuwana, Team Lead, Incidents and Substandard and Falsified medical products

6. **Questions & Answers**

Expand **access to quality assured medicines and health products**

Ensure that quality essential medicines and health products are available in **sufficient quantities and affordable** to the population through functioning regulatory and procurement systems

3 GOOD HEALTH AND WELL-BEING

1 in 10

observed failure rate
of medicines samples in low- and middle-income countries

Child deaths

estimated 72 430–169 271 deaths caused by substandard and falsified antibiotics in children under 5 suffering from pneumonia*

Malaria

estimated 31 000–116 000 deaths caused by substandard and falsified antimalarials in sub-Saharan Africa*

US$ 38.5 million
estimated spending on substandard and falsified antimalarials in sub-Saharan Africa**

This costs

US$ 30.5 billion

estimated spending on substandard and falsified medicines in low- and middle-income countries, based on wholesale level sales

Source:
Public health and socioeconomic impact study 2017
https://apps.who.int/iris/handle/10665/331690

* University of Edinburgh
** London School of Hygiene and Tropical Medicine

“End-to-end” health products’ management: shared responsibilities

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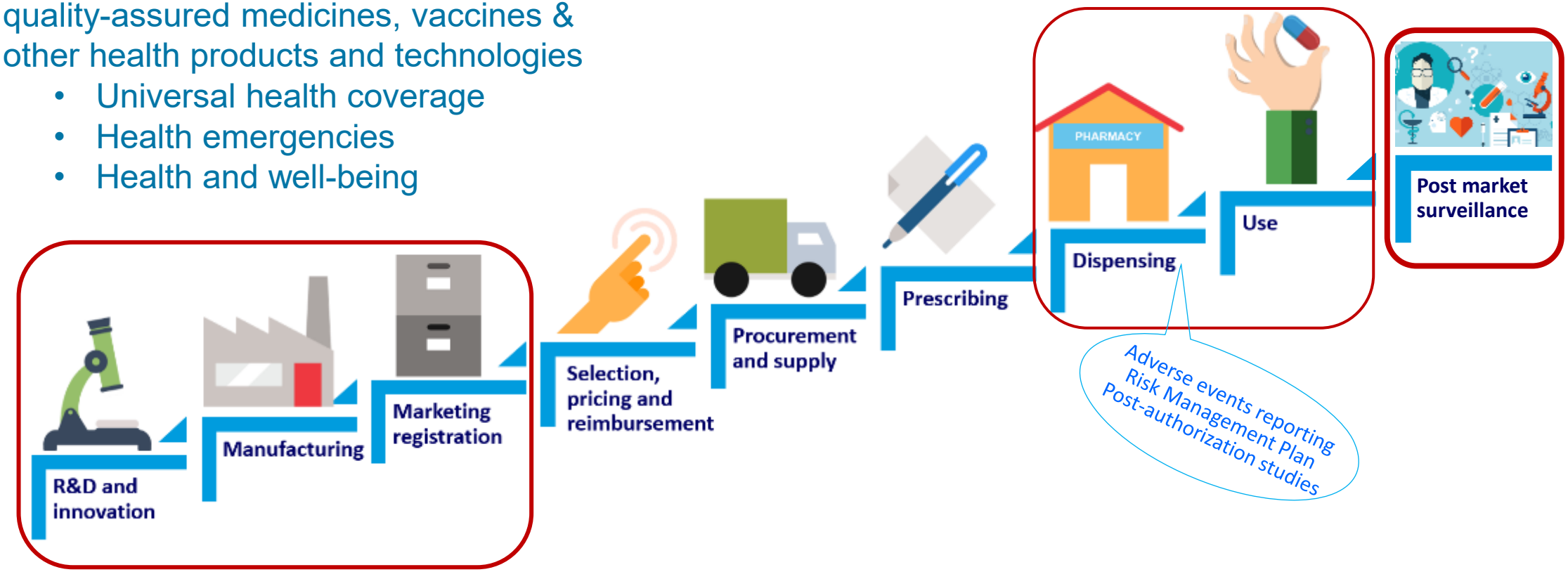
Legislation, regulation, governance, monitoring

Affordable, timely and equitable access to quality-assured medicines, vaccines & other health products and technologies

- Universal health coverage
- Health emergencies
- Health and well-being



Joint reviews & assessments of clinical trials

Long term Good Regulatory Practice

Regulatory Reliance, Collaboration and Harmonization

Regulatory system strengthening

Hiiti B. Sillo

Unit Head, Regulation and Safety

World Health Organization

Background to WHO regulatory strengthening activities

- Strong regulatory capacity is an essential component of a well-functioning healthcare system (Resolution WHA 67.20, 2014)
- Globally, >70% of countries have weak national regulatory systems
  - ✓ Only 57 countries (29%) have regulatory systems at GBT maturity level 3/4
    - See: https://www.who.int/initiatives/who-listed-authority-reg-authorities
- WHO regulatory systems strengthening programme responds to this challenge
  - ✓ Benchmarking to document strengths and identify gaps
  - ✓ Capacity building, including on regulatory preparedness & response
    - In collaboration with partners through the Coalition of Interested Parties (CIP)
  - ✓ Promoting smart regulation – good regulatory and reliance practices
    - Implementation of WHO Listed Authorities framework

WHO Regulatory Action Plan: 2019-2023 (2025)

Four strategic priorities

1. Strengthen country and regional regulatory systems
2. Improve regulatory preparedness for public health emergencies
3. Reinforce and expand WHO prequalification & product risk assessment
4. Increase the impact of WHO regulatory support activities

- Guiding WHO regulatory strengthening activities
  - ✓ Benchmarking and technical assistance to address regulatory gaps
  - ✓ Promoting regulatory convergence, harmonization, work-sharing and reliance mechanisms
  - ✓ Improving countries' ability to carry out risk-based post-marketing surveillance to securing supply chains against substandard and falsified products & safety monitoring of authorized products (vigilance)
    - Includes strengthening national quality laboratories
  - ✓ Promote and support sustainable and quality-assured local production through technical assistance

https://www.who.int/medicines/news/2019/strong-reg-systems-to-reach-UHC/en/

WHO Regulatory Activities

Ensuring normative and technical excellence drives impact at country level

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Technical Standards & Specifications

- Set global norms and standards (written & physical) and nomenclatures
- Increase common understanding on regulatory requirements by authority & manufacturer
- Standardize approach used by quality control labs

Prequalification

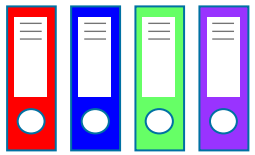
- Assure safety, quality efficacy & appropriateness of medical products used in LMICs, including medicines, vaccines, medical devices, cold chain equipment, vector control products & in vitro diagnostics
- Increase competition to shape the market

Regulation & Safety

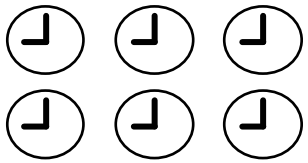
- Strengthen regulatory systems in countries and regions
- Promote regulatory cooperation, convergence and transparency through networking, work-sharing and reliance
- Mitigate risks and protect against substandard / falsified products

Local production & assistance

- Provide holistic & coordinated support to strengthen local production and technology transfer
- including
  - guidance tools, situational analyses for sustainable quality local production
  - strengthening local production, capacity building and specialized technical assistance



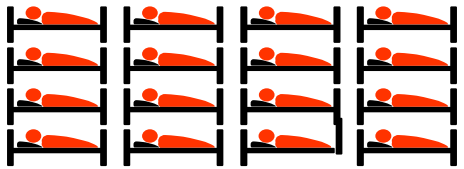
Decreased regulatory burden



Reduced time for regulation

Increased regulatory capacity in LMIC

Decreased cost of regulation

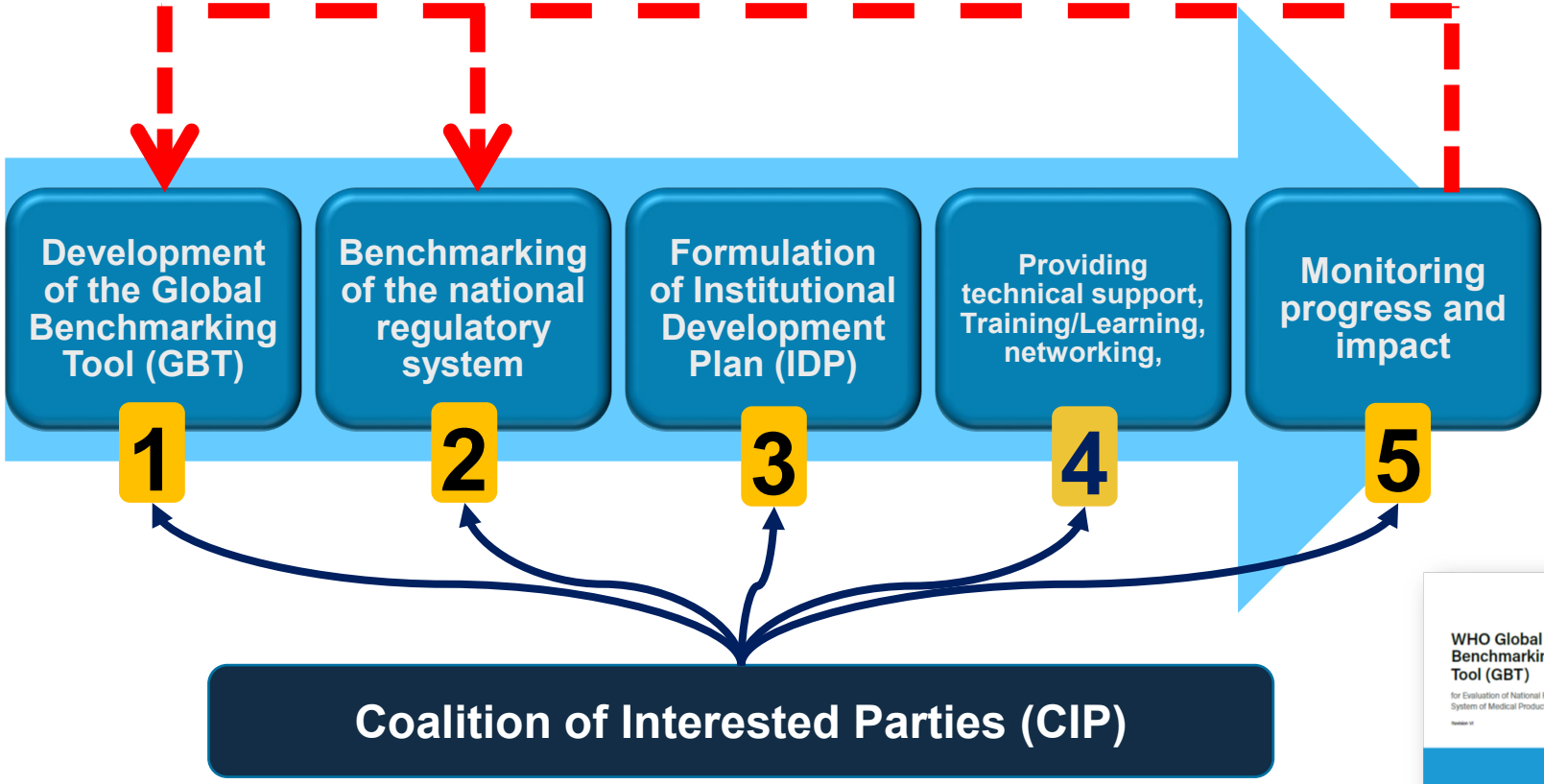


Reduced mortality and morbidity

WHO Five-Step Capacity Building Model for National Regulatory Authorities (NRAs)

World Health Organization

As per Resolution WHA 67.20 on Regulatory Systems Strengthening (2014)



- **Stable, well functioning and integrated regulatory system**
- **Eligibility for vaccine PQ**
- **WHO listed authorities (WLA)**

Link: https://apps.who.int/iris/handle/10665/341243

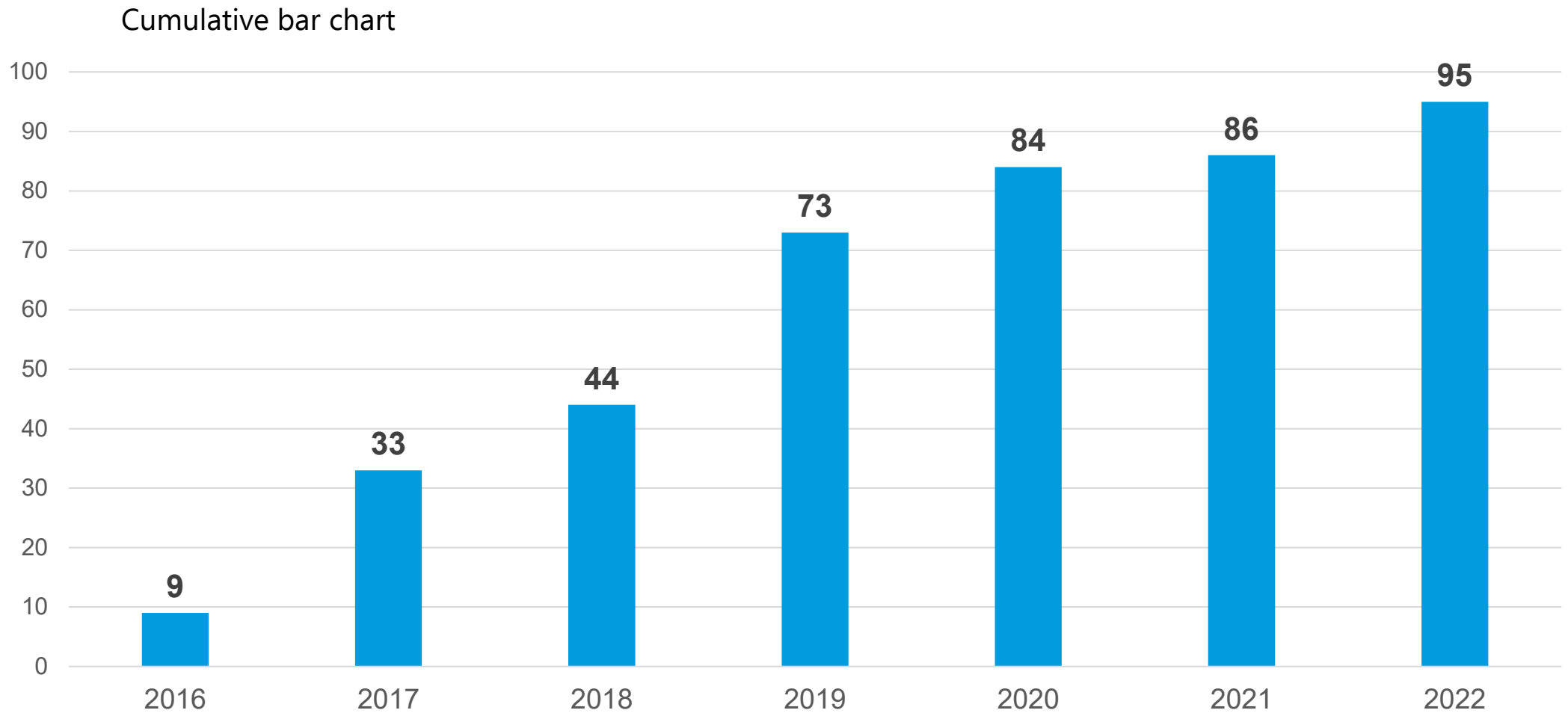
+

Blood (Nov 2019)

Medical Devices (Apr 2022)

Link: https://www.who.int/tools/global-benchmarking-tools

Number of Member States benchmarked by GBT by year



WHO Regulatory System Strengthening Programme
Global status of benchmarking of regulatory systems (2016 – Mar 2023)

Self Benchmarking

1. Algeria
2. Afghanistan
3. Albania
4. Angola
5. Benin
6. Bhutan
7. Bolivia
8. Bosnia and Herzegovina
9. Botswana
10. Burkina Faso
11. Cameroon
12. Cape Verde
13. Central African Republic
14. Chad
15. Comoros
16. Democratic Republic of the Congo
17. Costa Rica
18. Cote d'Ivoire
19. Djibouti
20. Ecuador
21. Equatorial Guinea
22. Eswatini
23. Gabon
24. Gambia
25. Guatemala
26. Guinea
27. Guinea-Bissau
28. Honduras
29. Iraq
30. Islamic Republic of Iran
31. Jordan
32. Kyrgyzstan
33. Lebanon
34. Liberia
35. Madagascar
36. Malawi
37. Malaysia
38. Maldives
39. Mali
40. Mauritania
41. Mauritius
42. Mongolia
43. Montenegro
44. Namibia
45. Nepal
46. Nicaragua
47. Niger
48. North Macedonia
49. Pakistan
50. Panama
51. Peru
52. Philippines
53. Republic of Congo
54. Senegal
55. Seychelles
56. Sierra Leone
57. Syrian Arab Republic
58. Togo
59. Tunisia
60. Ukraine
61. Zambia

World Health Organization

95 = 74%

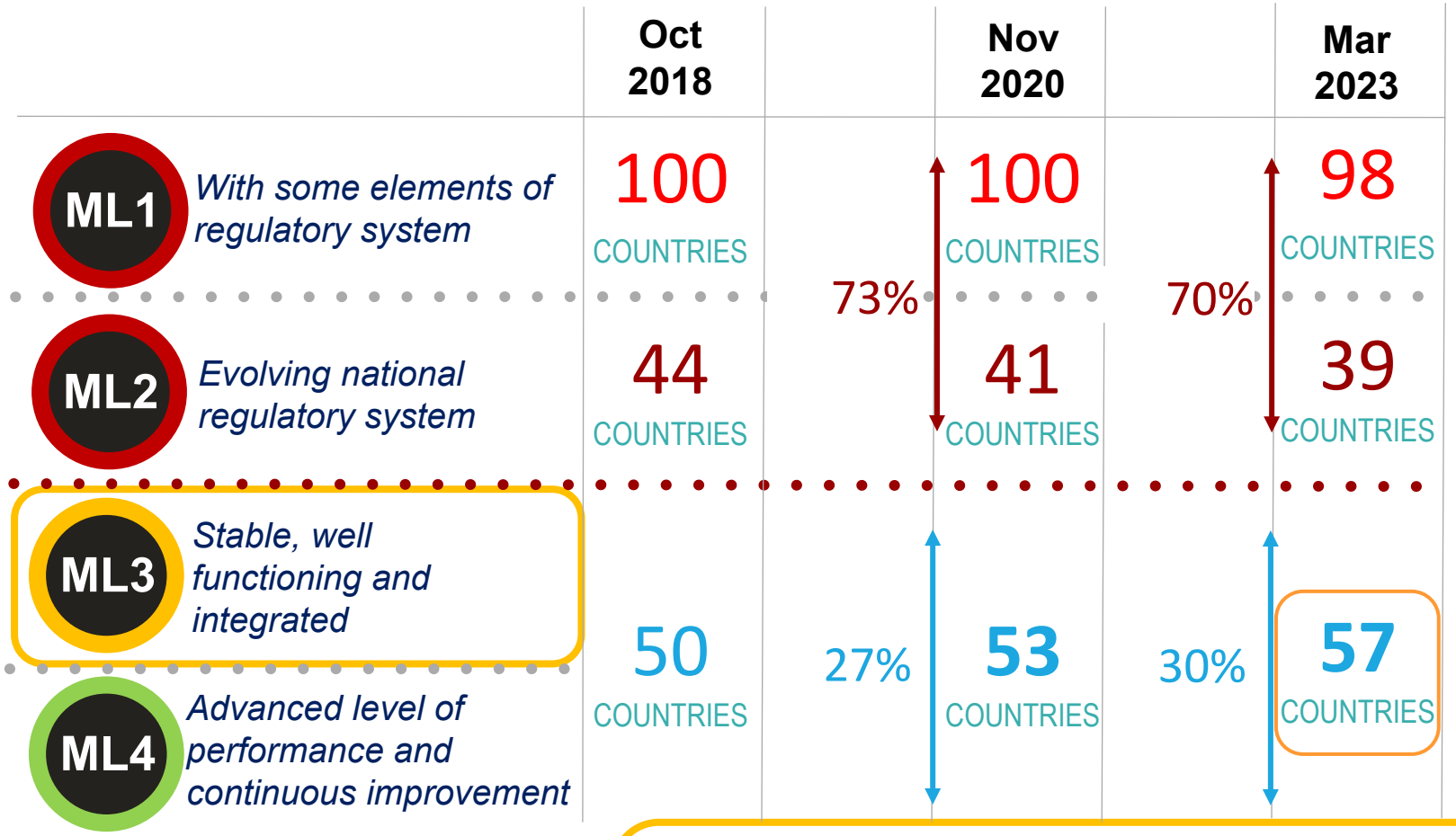
Member-states World population

Benchmarking

1. Bangladesh
2. Burundi
3. Cambodia
4. People's Republic of China
5. El Salvador
6. Egypt
7. Eritrea
8. Ethiopia
9. Ghana
10. India
11. Indonesia
12. Kazakhstan
13. Kenya
14. Lao People's Dem Rep
15. Mozambique
16. Nigeria
17. Papua new guinea
18. Rwanda
19. Saudi Arabia
20. Serbia
21. Singapore
22. Somalia
23. South Africa
24. South Korea
25. South Sudan
26. Sri Lanka
27. Sudan
28. Türkiye
29. United Republic of Tanzania
30. Thailand
31. Timor-Leste
32. Uganda
33. Viet Nam
34. Zimbabwe

Maturity levels of national regulatory systems

WHO GBT (for medicines and vaccines: as of Mar 2023)



Vaccines developed in countries with weak regulatory systems, i.e., ML1/ML2, are not eligible for WHO EUL or Prequalification

In 2022 alone, 6 countries achieved ML 3/M4 in medicines and vaccines reg systems

- **Singapore ML 4 (medicines)**
- **Republic of Korea ML 4 (medicines & vaccines)**
- **Egypt, China and South Africa ML 3 (vaccines)**
- **Nigeria ML 3 (medicines)**

ML3 **GOAL of WHA Resolution 67.20**

ML: *(regulatory system) maturity level*

Coalition of Interested Parties (CIP) Network
launched in 2021, now with 20 members

World Health Organization

Purpose:

To establish and promote a unified strategic and coordinated approach to strengthening national and regional regulatory systems

Aim:

To increase the effectiveness of collective efforts and desired impact in countries and regions.

A voluntary Network established by the WHO

Interested entities need to apply to become a member of the CIP Network

The CIP Network's activities span the lifecycle of regulatory system strengthening efforts

The WHO five-step capacity building model will guide the roles and activities of the CIP members

The nature and scope of collaboration between the NRA & the CIP member(s) will be set forth in an agreed Terms of Reference & Support Plan

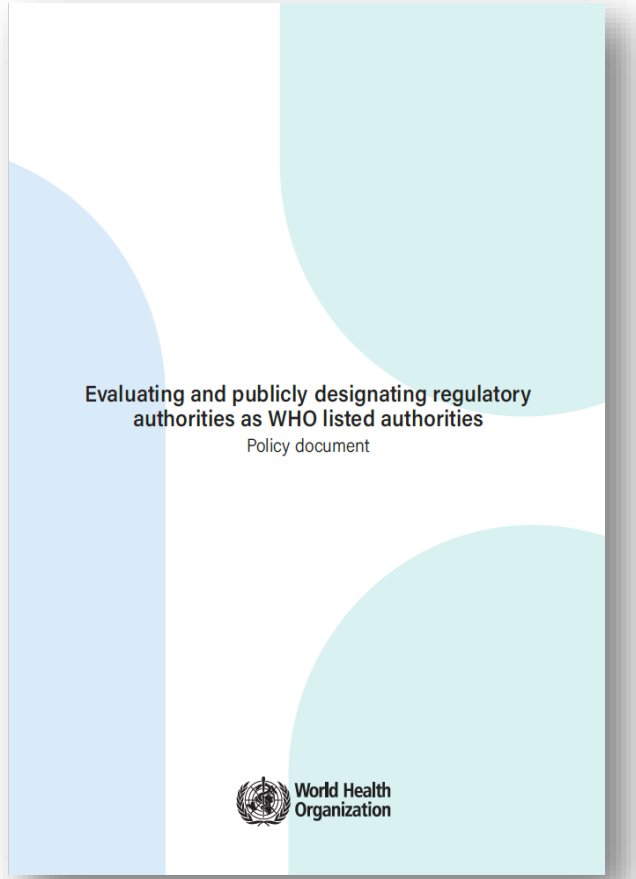
Contact the CIP Secretariat: **cip_network@who.int**

Joining the CIP Network

- Eligible entities need to submit an **Expression of Interest (EOI) form** via the CIP web platform: https://www.cip-network-rss.org/
- Follow the link, click on the "**Join Us**" tab and then complete and submit the EOI form.
- Following the submission of the EOI form, an **application form** will be sent to the applicant by the CIP Secretariat.
- The completed application form must be submitted via email to the CIP Secretariat.
- Applications are reviewed against the eligibility criteria set forth in the CIP TOR & the WHO Framework for engagement with Non-State actors (FENSA)

WHO Listed Authorities (WLA)

- Framework for designating and publicly listing a regulatory authority as a WLA
  - Transparent and evidence-based pathway for regulatory authorities operating at an advanced level of performance
  - Replacing the procurement-oriented concept of stringent regulatory authorities
  - Promote access and supply of safe, effective and quality medical products.
  - Provides for the optimal use of limited resources by facilitating reliance on the work products and decisions of trusted agencies in the decision-making of regulatory authorities, the WHO PQ Programme and procurement agencies
  - Fostering regulatory cooperation, thus contributing to the improvement in good regulatory and reliance practices.
- Launched in March 2022 - 3 pilots advanced and full implementation Q2/2023



- **Key resources**
  1. Policy document (2021): https://www.who.int/publications/i/item/9789240023444
  2. Transitional list (tWLA) (2022): https://www.who.int/publications/m/item/list-of-transitional-wlas
  3. Interim Operational Guidance (2022): https://www.who.int/publications/m/item/wla-interim-operational-guide-combined
  4. Interim manual for the performance evaluation (2022): https://www.who.int/publications/m/item/a-framework-for-evaluating-and-publicly-designating-regulatory-authorities-as-who-listed-authorities-wla

Facilitated Regulatory Pathways (FRP)
A solution to NRAs

World Health Organization

FRPs, as a solution for NRAs and public health

What are Facilitated Regulatory Pathways (FRPs)?

FRP are a type of regulatory pathways available to NRAs, which are meant to facilitate and accelerate the regulatory decisions and the introduction of quality-assured products in countries, through the use of the concepts of reliance and collaboration.

When well implemented:

- NRAs leverage on the work performed by others, improving efficiency of the regulatory systems by avoiding duplication of regulatory efforts and work;
- NRAs optimize the use of human and financial resources and increase expertise and build capacities
- NRAs reduce the time nedeed to process a product application and reduce workload and backlog at NRAs;
- NRAs perform science-based and transparent regulatory decision-making, while maintaining national independence on their decisions;
- NRAs ensure timely access to quality-assured products in countries.

FRPs, such as the Collaborative Registration Procedure, to be used not only during emergencies but also in the regular and routine regulatory activities of countries to improve efficiency of the regulatory systems and ensure registration of quality-assured products

WHO efforts to facilitate good quality decisions based on reliance

Internationally, by participation and contribution in regional and sub-regional regulatory networks and initiatives

ICH harmonisation for better health

IPRP International Pharmaceutical Regulators Programme

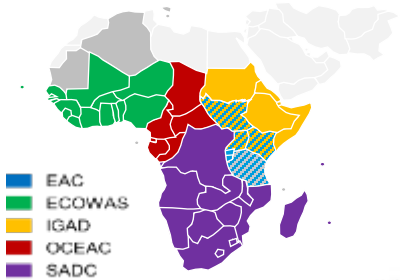
PIC/S

IMDRF International Medical Device Regulators Forum

IGDRP International Generic Drug Regulators Programme

ICMRA

AMRH



ASEAN SIAHR Project

APEC Asia-Pacific Economic Cooperation

Regulatory Harmonization Steering Committee

APEC Life Sciences Innovation Forum

Caribbean Public Health Agency CARPHA

SEARN SOUTH-EAST ASIA REGULATORY NETWORK

RED PARF PANDRH

PANDRH

WESTERN PACIFIC REGIONAL ALLIANCE of NRAS for Medical Products

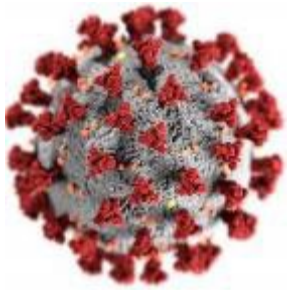
Example: Reliance supported national decision making during COVID-19 pandemic, mostly in Africa

COVAX

With a fast-moving pandemic, no one is safe, unless everyone is safe

COVAX is co-led by CEPI, Gavi and WHO, alongside key delivery partner UNICEF. In the Americas, the PAHO Revolving Fund is the recognized procurement agent for COVAX.

CEPI Gavi unicef World Health Organization




Reliance is key to effective access and oversight of medical products in case of public health emergencies

Agnes Saint-Raymond, Marie Valentin, Nobumasa Nakashima, Nick Orphanos, Gustavo Santos, Georgios Balkamos & ...show all

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Expert Review of Clinical Pharmacology
https://www.tandfonline.com/doi/full/10.1080/17512433.2022.2088503

Facilitation of EUL process

31 December 2020, first WHO EUL for a COVID-19 vaccine (BNT162b2 mRNA vaccine); 10 days after EMA scientific opinion

In-country authorizations for use

- **First roll-out in Feb-March 2021** ChAdOx1 vaccine
- **Approvals/import permits in 101 out of 145 countries (70%) within 15 days** of WHO EUL (15 February 2021)

Reliance in Lifecycle/all reg functions
Authorization, Pharmacovigilance, Batch/Lot Release, Post Authorisation

Overall, over **2 billion vaccines doses** allocated in over **160 countries/territories** involving close to **5,000 regulatory approvals** as of August 2022

Local production and assistance

Dr Jicui Dong
Unit Head, Local Production and Assistance Unit

World Health Organization

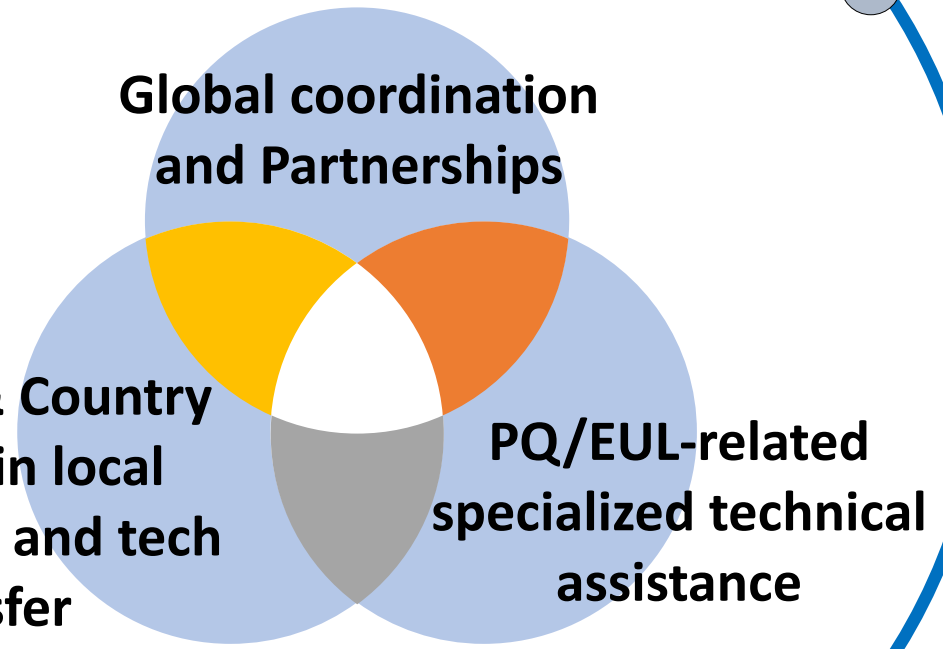
LPA Unit's mandates in strengthening quality and sustainable local production to improve access

Further strengthened by Resolution WHA74.6:

World Local Production Forum (WLPF) Interagency statement etc.

Ecosystem assessments for quality and sustainability

Strategy/roadmap setting and implementation



Global resources on local production and technology transfer

Facilitation of technology transfer

Capacity building and technical assistance to achieve quality, sustainability and WHO PQ/EUL

EUL: Emergency use listing
PQ: Prequalification

For more information: https://www.who.int/teams/regulation-prequalification/lpa

World Local Production Forum

Enhancing access to medicines and other health technologies

World Health Organization

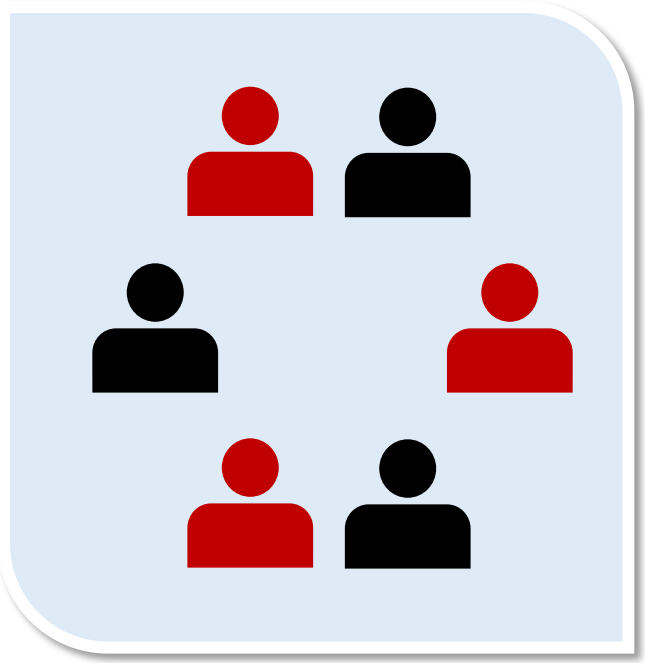
- New WHO initiative to foster global coordination, synergy and partnerships
- Sustainable, global platform for Member States, industry, experts, academia, UN agencies, international organizations, etc.
- High-level collective action to address challenges, harness opportunities and shape strategies and the direction of local production globally

Nov 2023

2nd World Local Production Forum (WLPF) will be convened in the Netherlands as the hosting country

https://www.who.int/initiatives/world-local-production-forum

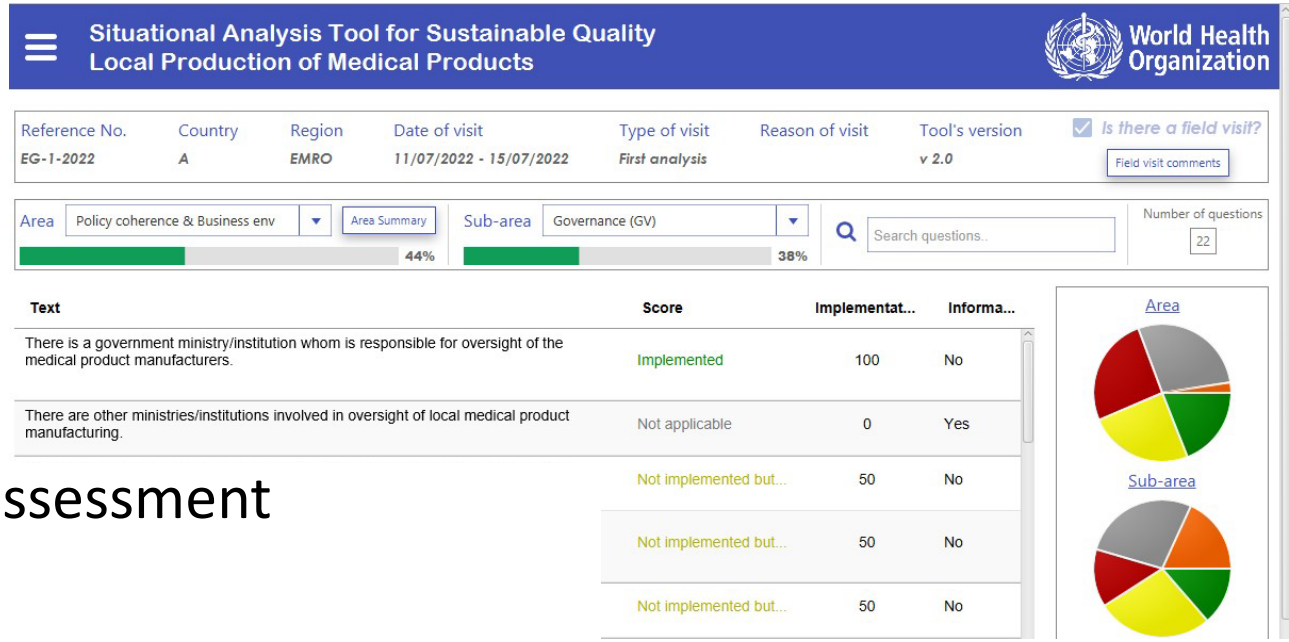
Technical Advisory Group on Local Production and Technology Transfer of Health Products (TAG-LPTT)



- Established in 2022, following recommendation of the 1st World Local Production Forum
- Provide **strategic** and **technical advice** to WHO on promoting and strengthening sustainable local production and technology transfer

Situational analysis tool for ecosystem assessments

Ecosystem assessments build MS' understanding of the ecosystem affecting quality and sustainability of local production



Situational analysis tool:

- Standardizes the approach to conduct an assessment
- Provides evidence:
  - for MS to prioritize actions to address gaps that hinder achieving quality and sustainability
  - for WHO to provide tailored support and capacity building, including attaining WHO PQ/EUL
  - to inform the development of holistic, national strategy/roadmap

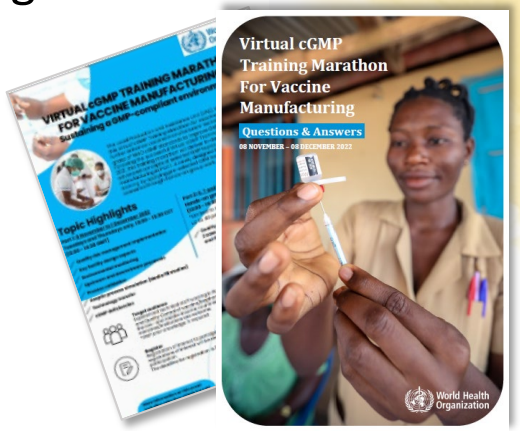
E-version of the tool has been developed and is under piloting in countries (7 countries thus far)

Comprehensive approach toward capacity building to ensure quality

Virtual cGMP Training Marathon for Vaccine Manufacturing (Nov-Dec 2022)

An annual global event to improve understanding on WHO cGMP standards, facility design, tech transfer, etc. and improve compliance for quality manufacturing

Q&A Booklet is published and available at WHO website



Virtual workshop on Vaccine CTD/CMC Requirements for WHO PQ/EUL (Jun 2022)

A global event to improve understanding of vaccine quality and dossier requirements and improve the quality of dossiers to facilitate the review and hasten attainment of PQ/EUL

In 2022, total of >2000 vaccine & biopharmaceutical manufacturers and regulators from six WHO regions were successfully trained on WHO standards & requirements to achieve quality and compliance

PQ/EUL-related specialized technical assistance (TA) to facilitate WHO PQ/EUL and improve access

Who is eligible for PQ/EUL-related specialized TA

Manufacturers:

- produce a priority medicine, vaccine or IVD which is eligible for WHO prequalification (PQ) or emergency use listing (EUL)
- intend to submit the product for WHO PQ or EUL
- located in low- and middle-income countries (LMICs) are prioritized for specialized TA

Contract Research Organizations:

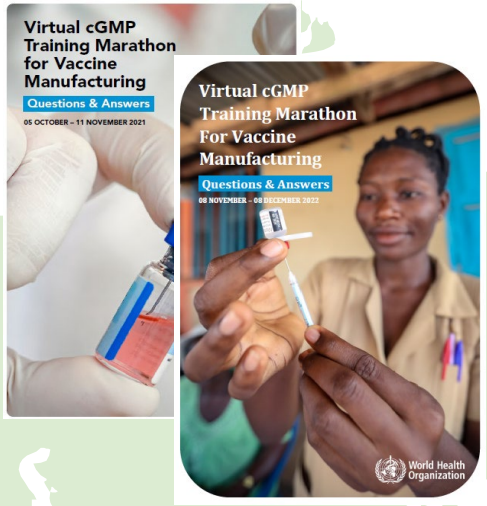
- conduct bioequivalence/clinical studies for manufacturers in LMICs and with the product that is eligible for WHO PQ/EUL

More information on eligibility for specialized TA and prioritization is available:
https://www.who.int/teams/regulation-prequalification/lpa/technical-assistance-for-who-prequalification

Global resources and technical products on local production and technology transfer

Updated WHO Guidelines on Technology Transfer in Pharmaceutical Manufacturing

WHO Technical Report Series No. 1044 (2022)



Two Virtual cGMP Training Marathon for Vaccine Manufacturing: Questions and Answers

Over 500 questions from manufacturers & regulators around the world on key GMP topics for vaccine manufacturing

Other technical products:

Situational analysis tool (described earlier)

Model strategy for strengthening local production (draft under development)

Strategy for hands-on training for quality local production (draft under development)

Situational studies on the local production of vaccines (drafts under development)

Linkage with mRNA technology transfer hub

Bangladesh, Kenya, Nigeria, Pakistan, Serbia, Senegal, Tunisia

Note: Arrows are representative only.

Substandard and falsified products

Rutendo Kuwana

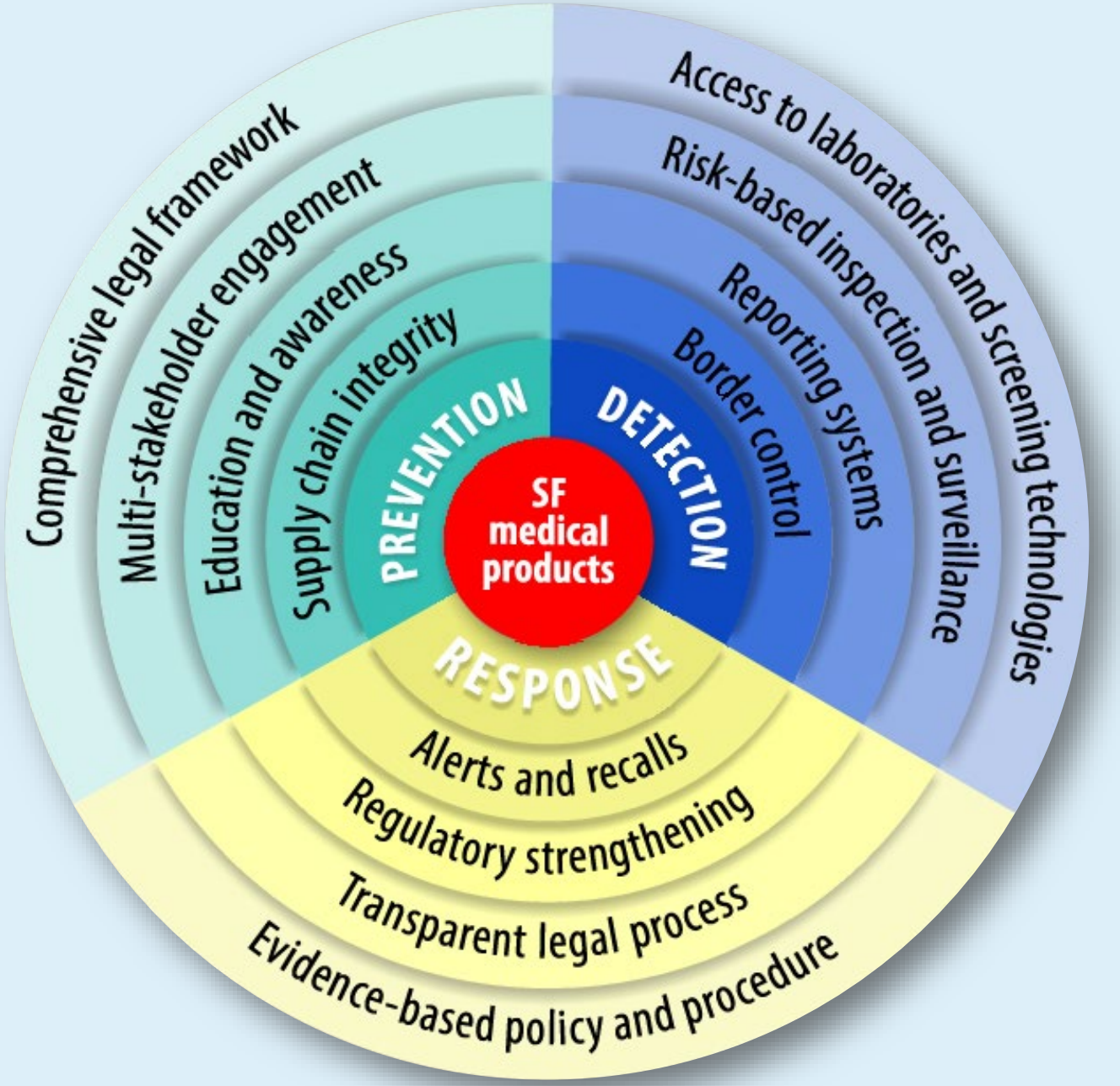
Team Lead, Incidents and Substandard and Falsified medical products

World Health Organization

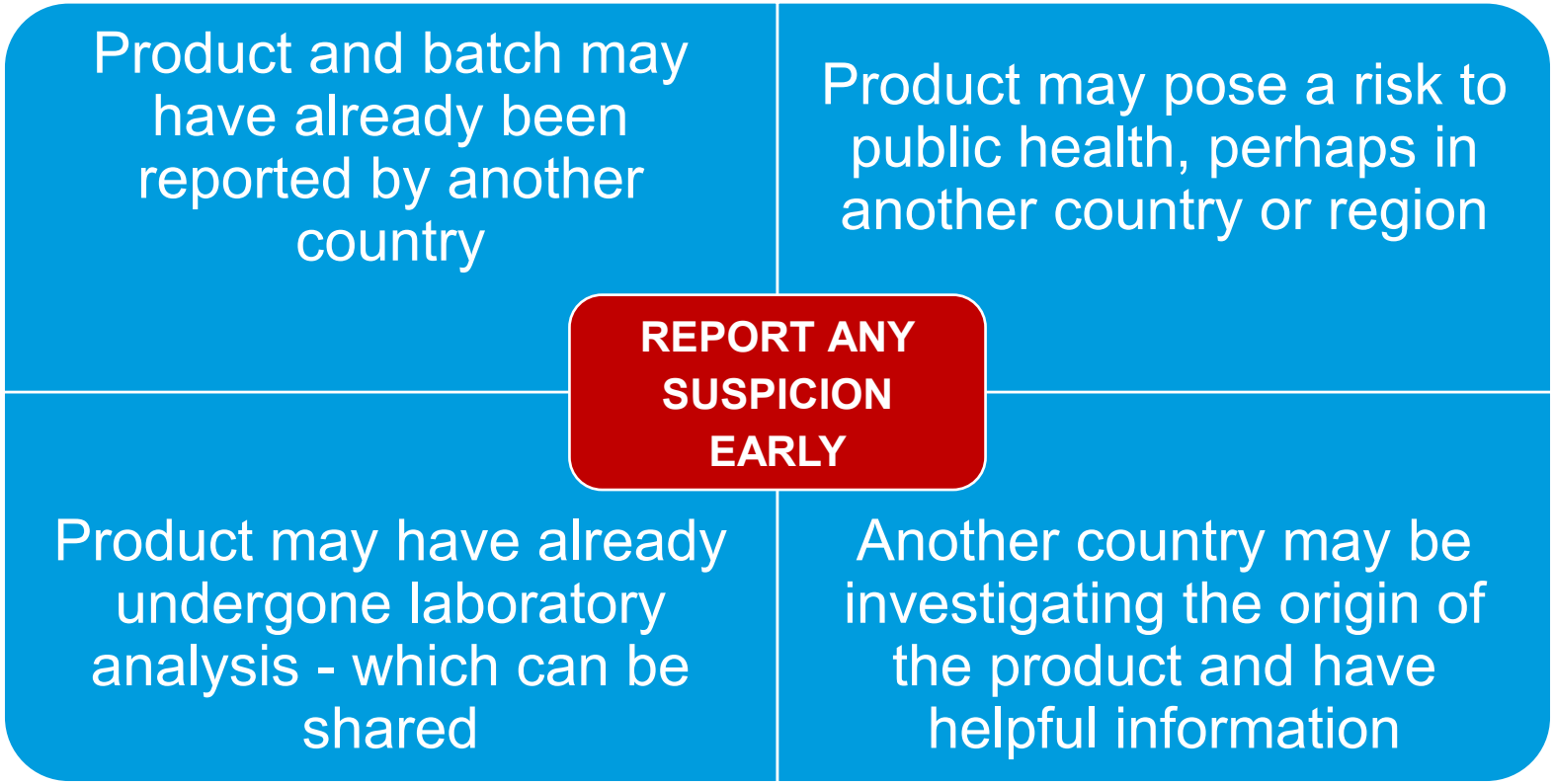
WHO's prevent-detect-response strategy

- WHO supports NRAs
  - Conduct investigations
  - Conduct sampling and testing for market surveillance
- WHO issues risk communications
  - Global Medical Product Alerts
  - Targeted Market Surveillance
  - WHO information notices for IVD users
- WHO develops normative guidance
  - National action plans for SF
  - Selecting technologies to screen/detect SF
  - Handbook for introducing SF into pharmacy school curriculum

World Health Organization



WHO Global Surveillance and Monitoring System



The WHO GSMS is

- A global database of SF medical products; AND
- A network of national regulatory focal points, plus others (private sector, implementing partners, etc.)
- **REPORT ANY SUSPICIONS TO** rapidalert@who.int

WHO Member State Mechanism

Established by WHA Resolution 65.19 to address SF medical products

Led by a Steering Committee chaired by Australia and supported by 11 Vice Chair from all WHO Regions

WHO Member States agree on a 2-year workplan; current prioritized activities ar for 2022-2023 and include work on:

- Regulatory capacity-building for prevention, detection and response (le by Brazil)
- Global networks (led by Eritrea)
- Detection technologies (led by Montenegro) and traceability (led by Nigeria)
- Competencies and good governance
- Risk communication (led by Zambia)
- Impact and awareness (led by Australia)
- Internet distribution and sales (led by Colombia)
- Informal markets (led by the United States of America)

"The goal of the Member State Mechanism is to protect public health and promote access to affordable, safe, efficacious, and quality medical products, and to promote through effective collaboration among Member States and the Secretariat, the prevention and control of substandard and falsified medical products and associated activities."

WHO call to action 23 January 2023

World Health Organization

Regulators

Ensure that all medicines are **approved for sale** by competent authorities and obtainable from authorized/licensed suppliers;

Improve and increase **risk-based inspections** of manufacturing sites;

Increase market surveillance including **risk-based targeted testing** for medicines; and

Enact and **enforce legal provisions** that help to combat the manufacture, distribution and/or use of substandard and falsified medicines

Manufacturers

Only purchase **pharmaceutical grad**e excipients from qualified suppliers;

Conduct **testing upon receipt of supplies and before use** in manufacture of finished products;

Provide assurance of product quality including through **certificates of analyses**; and

Keep a**ccurate, complete and proper records** of purchase of materials, testing, manufacture, and distribution to facilitate traceability during investigations in case of incidents.

WHO urges action to protect children from contaminated medicines

In conclusion

- Globalization and regional economic integration
  - ✓ Facilitating regulatory harmonization, convergence and work-sharing in development and regulation of medical products
- Collaboration and partnerships – Covid-19 demonstrated the importance of international cooperation and partnerships
  - ✓ Role of CIP in regulatory strengthening activities
- Buy-in from countries to invest in regulatory strengthening activities
  - Publication of outcomes of benchmarking of NRAs
- High Member States commitment to strengthen local production capacity to ensure health security and timely access
- WHO built a strong network and credibility among partners and mechanisms have been established for supporting Member States on local production and technical assistance
- Evaluation of the Member State Mechanism on SF medical products, 10 years since its establishment in 2012

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World Health Organization