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

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

Long term Good Regulatory Practice
Regulatory Reliance, Collaboration and Harmonization
Regulatory system strengthening

Hiiti B. Sillo
Unit Head, Regulation and Safety
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

**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

WHO Regulatory Activities
Ensuring normative and technical excellence drives impact at country level

- **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

**Reduced mortality and morbidity**

**Reduced time for regulation**

**Increased regulatory capacity in LMIC**

**Decreased cost of regulation**
WHO Five-Step Capacity Building Model for National Regulatory Authorities (NRAs)

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

1. Development of the Global Benchmarking Tool (GBT)
2. Benchmarking of the national regulatory system
3. Formulation of Institutional Development Plan (IDP)
4. Providing technical support, Training/Learning, networking,
5. Monitoring progress and impact

Coalition of Interested Parties (CIP)

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

[Links are not shown in the natural text representation.]
Number of Member States benchmarked by GBT by year

Cumulative bar chart

- 2016: 9
- 2017: 33
- 2018: 44
- 2019: 73
- 2020: 84
- 2021: 86
- 2022: 95
WHO Regulatory System Strengthening Programme
Global status of benchmarking of regulatory systems (2016 – Mar 2023)

<table>
<thead>
<tr>
<th>Self Benchmarking</th>
<th>Benchmarking</th>
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<tbody>
<tr>
<td>1. Algeria</td>
<td>1. Bangladesh</td>
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<td>2. Afghanistan</td>
<td>2. Burundi</td>
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<td>3. Albania</td>
<td>3. Cambodia</td>
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<td>5. Benin</td>
<td>5. El Salvador</td>
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<td>7. Bolivia</td>
<td>7. Eritrea</td>
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<td>8. Bosnia and Herzegovina</td>
<td>8. Ethiopia</td>
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<td>10. Burkina Faso</td>
<td>10. India</td>
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<td>11. Cameroon</td>
<td>11. Indonesia</td>
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<td>12. Cape Verde</td>
<td>12. Kazakhstan</td>
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<td>15. Comoros</td>
<td>15. Mozambique</td>
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<td>Democratic Republic of the Congo</td>
<td>16. Nigeria</td>
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<td>17. Costa Rica</td>
<td>17. Papua new guinea</td>
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<td>18. Cote d’Ivoire</td>
<td>18. Rwanda</td>
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<td>20. Ecuador</td>
<td>20. Serbia</td>
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<td>22. Eswatini</td>
<td>22. Somalia</td>
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<td>23. Gabon</td>
<td>23. South Africa</td>
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<td>24. Gambia</td>
<td>24. South Korea</td>
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<td>25. Guatemala</td>
<td>25. South Sudan</td>
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<td>27. Guinea-Bissau</td>
<td>27. Sudan</td>
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<td>29. Iraq</td>
<td>29. United Republic of Tanzania</td>
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<td>30. Islamic Republic of Iran</td>
<td>30. Thailand</td>
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<td>32. Kyrgyzstan</td>
<td>32. Uganda</td>
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<td>33. Lebanon</td>
<td>33. Viet Nam</td>
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<td>34. Liberia</td>
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<td>35. Madagascar</td>
<td>35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46.</td>
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<td>36. Malawi</td>
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<td>37. Malaysia</td>
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<td>38. Maldives</td>
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<td>39. Mali</td>
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<td>40. Mauritania</td>
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<td>41. Mauritius</td>
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<td>42. Mongolia</td>
<td>78. 79. 80. 81.</td>
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<td>43. Montenegro</td>
<td>82. 83. 84. 85.</td>
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<td>44. Namibia</td>
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<td>45. Nepal</td>
<td>90. 91. 92. 93.</td>
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<td>46. Nicaragua</td>
<td>94. 95. 96. 97.</td>
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95 member-states represent 74% of the world population.
## Maturity levels of national regulatory systems

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

### Maturity Levels

- **ML1**: With some elements of regulatory system
- **ML2**: Evolving national regulatory system
- **ML3**: Stable, well functioning and integrated
- **ML4**: Advanced level of performance and continuous improvement

### GOAL of WHA Resolution 67.20

ML: (regulatory system) maturity level

### Progress:

<table>
<thead>
<tr>
<th>Month</th>
<th>ML1 Countries</th>
<th>ML2 Countries</th>
<th>ML3 Countries</th>
<th>ML4 Countries</th>
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<tbody>
<tr>
<td>Oct 2018</td>
<td>100</td>
<td>44</td>
<td>50</td>
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<tr>
<td>Nov 2020</td>
<td>100 (73%)</td>
<td>41 (70%)</td>
<td>53 (30%)</td>
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<td>Mar 2023</td>
<td>98 (70%)</td>
<td>39 (30%)</td>
<td>57 (70%)</td>
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### 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)

### Note:

Vaccines developed in countries with weak regulatory systems, i.e., ML1/ML2, are not eligible for WHO EUL or Prequalification.
Coalition of Interested Parties (CIP) Network

launched in 2021, now with 20 members

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.

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

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)

Contact the CIP Secretariat: cip_network@who.int

Interested entities need to apply to become a member of the CIP Network
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
2. Transitional list (tWLA) (2022): https://www.who.int/publications/m/item/list-of-transitional-wlas
Facilitated Regulatory Pathways (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 needed 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
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)

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

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

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

Dr Jicui Dong
Unit Head, Local Production and Assistance Unit
LPA Unit’s mandates in strengthening quality and sustainable local production to improve access

Further strengthened by Resolution WHA74.6:

- Global coordination and Partnerships
- PQ/EUL-related specialized technical assistance
- 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

World Local Production Forum (WLPF)
Interagency statement etc.
Ecosystem assessments for quality and sustainability
Strategy/roadmap setting and implementation

For more information: https://www.who.int/teams/regulation-prequalification/lpa
World Local Production Forum
Enhancing access to medicines and other health technologies

- 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

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

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

Nov 2023
Established in 2022, following recommendation of the 1\textsuperscript{st} World Local Production Forum

Provide \textbf{strategic} and \textbf{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

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

Situational studies on the local production of vaccines (drafts under development)
Linkage with mRNA technology transfer hub
Bangladesh, Kenya, Nigeria, Pakistan, Serbia, Senegal, Tunisia

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)

Note: Arrows are representative only.
Substandard and falsified products

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

<table>
<thead>
<tr>
<th>Product and batch may have already been reported by another country</th>
<th>Product may pose a risk to public health, perhaps in another country or region</th>
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<tbody>
<tr>
<td>REPORT ANY SUSPICION EARLY</td>
<td>Another country may be investigating the origin of the product and have helpful information</td>
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</table>

Product may have already undergone laboratory analysis - which can be shared. Product may pose a risk to public health, perhaps in another country or region. Another country may be investigating the origin of the product and have helpful information.
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 are for 2022-2023 and include work on:

- Regulatory capacity-building for prevention, detection and response (led 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)
WHO call to action 23 January 2023

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 grade 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 accurate, 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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