WHO Update
UNICEF Vaccine Industry Consultation
17 September 2019, Copenhagen

Emer Cooke
Director, Regulation and Prequalification
Overview

- **WHO 5-year Action Plan to Help Build Effective and Efficient Regulatory Systems**
  - Regulatory systems strengthening activities
  - Collaborative Registration Procedures
  - Accelerating convergence and harmonization of regulatory requirements

- **Update on EUAL process: considerations for supply and procurement**
WHO Transformation

Major reorganization of WHO to deliver the mission and strategic priorities of the 13th General Programme of Work

Mission

• Promote Health
• Keep the World Safe
• Serve the Vulnerable

Strategic Priorities

Division: Medicines & Health Products

Health Products Policy and Standards

• Assistive technologies
• Blood Products
• Expert Committees
• INN
• Medical devices
• Pricing policy

Regulatory and Prequalification

• Regulatory Systems Strengthening
• Safety and vigilance related activities
• Prequalification
• Local production

“Together for a healthier world”

Dr Tedros Adhanom Ghebreyesus

13th General Programme of Work
2019-2023
Regulatory activities ensure normative and technical excellence to drive impact at country level

<table>
<thead>
<tr>
<th>Technologies, Standards and Norms</th>
<th>Regulatory Systems Strengthening</th>
<th>Prequalification Team</th>
<th>Safety &amp; Vigilance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Set global norms and standards (written &amp; physical) and nomenclatures</td>
<td>• Set effective and efficient regulatory systems in LMICs through collaborative &amp; harmonized approaches with reliance principles</td>
<td>• Assure safety, quality, appropriateness &amp; efficacy of medical products used in LMICs: medicines, vaccines, medical devices, cold chain equipment, vector control products &amp; in vitro diagnostics</td>
<td>• Increase knowledge and coordinate actions against adverse events following immunization (AEFI)</td>
</tr>
<tr>
<td>• Increase common understanding on regulatory requirements by authority &amp; manufacturer</td>
<td>• Increase confidence in medical products produced in LMICs</td>
<td>• Increase competition to shape the market</td>
<td>• Mitigate risks and protect against substandard / falsified products</td>
</tr>
<tr>
<td>• Standardize approach used by quality control labs</td>
<td></td>
<td>• Contain antimicrobial resistance</td>
<td>• Decrease regulatory burden</td>
</tr>
</tbody>
</table>

Decreased regulatory burden  Reduced time for regulation  Increased regulatory capacity in LMIC  Decreased cost of regulation  Reduced mortality and morbidity
WHO 5-year action plan to improve the quality and safety of health products

- Identifying the best ways to achieve a safe and quality-assured supply of medicines, vaccines and other health products for all
- Responding to the need for global health partners to work together towards a common goal
- Adopting a universal health coverage approach to reach the sustainable development goal
- Striving for better use of donor money and aid effectiveness by aligning milestones and activities among internal and external stakeholders

WHO 5-year action plan to improve the quality and safety of health products

Four strategic priorities aligned with 13\textsuperscript{th} GPW

1) Strengthen country and regional systems in line with the drive toward UHC

2) Increase regulatory preparedness for public health emergencies

3) Strengthen and expand WHO prequalification and product risk assessment processes

4) Increase the impact of WHO’s Regulatory Supportive activities - efficiency, advocacy, knowledge sharing, joint planning

## Current Status of Regulatory Systems

### WHO Global Benchmarking (for medicines and vaccines: as of February 2019)

<table>
<thead>
<tr>
<th>ISO 9004</th>
<th>WHO GBT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td><strong>No formal approach</strong></td>
</tr>
<tr>
<td></td>
<td>Some elements of regulatory system exist</td>
</tr>
<tr>
<td></td>
<td>Can ensure the quality of products if rely on ML3 / ML4 regulatory systems</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td><strong>Reactive approach</strong></td>
</tr>
<tr>
<td></td>
<td>Evolving national regulatory system that partially performs essential regulatory functions</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td><strong>Stable formal system approach</strong></td>
</tr>
<tr>
<td></td>
<td>Stable, well-functioning and integrated regulatory system</td>
</tr>
<tr>
<td></td>
<td>Target of WHA Resolution 67.2</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td><strong>Continual improvement emphasized</strong></td>
</tr>
<tr>
<td></td>
<td>Regulatory system operating at advanced level of performance and continuous improvement</td>
</tr>
<tr>
<td></td>
<td>Advanced/reference Regulatory Authorities</td>
</tr>
</tbody>
</table>

**Target of WHA Resolution 67.2**: Can ensure the quality of products if rely on ML3 / ML4 regulatory systems.
Strategic priority 1: focus on actions with vaccine implications

Strengthen country and regional systems in line with the drive toward UHC

- Global Benchmarking Tool version VI published December 2018
- WHO Listed Authorities concept nearing finalization – consultation meeting this week
- Local production joint statement- 5 UN (including UNICEF) and Global Fund partners
- Consultation towards Policy on traceability of health products
- Support for countries transitioning out of GAVI and Global Fund
- WHO’s network of laboratories avoiding duplicative lot testing
A new proposal aimed at promoting reliance:
WHO Listed Authority (WLA):

• Term ‘Stringent Regulatory Authority (SRA)’:
  o defined as original ICH member/observer,
  o developed to guide procurement decisions

• Widely used and recognized

• However growing concerns with term SRA:
  o with the fact that ICH doesn’t have remit or competence to assess regulatory capacity;
    coupled with expanding membership

• WHO expert committee asked WHO to develop new proposal in October 2017 – based on Global Benchmarking Tool assessments

• Extensive discussions and consultations, concept note published May 2019, stakeholder meeting 23 September
WLA – Why and when?

- Provides pathway for regulatory authorities to be globally recognized and thereby help guide procurement decisions on medical products, including for products not eligible for prequalification
- Provides a robust framework to promote trust, confidence and reliance, enabling efficient use of regulatory resources
- Encourages investment in and continuous improvement of regulatory systems
- Expands the pool of regulatory authorities contributing to efficiency of Prequalification program through increased use of abridged procedure
- Creates an enabling regulatory environment for innovation and local production
- Policy document to be finalized this week, more details on operationalization under development
Accelerated registration through Collaborative Registration Procedures (CRP)

Objectives:

• to facilitate the assessment and accelerate national registration of Prequalified products

• to accelerate registration of health products that have already received approval from a “stringent regulatory authority”

Principles: ✓ Voluntary ✓ Co-operation
✓ Sovereignty ✓ Reliance
✓ Identicality ✓ Monitoring and maintenance

Sovereignty: Participating NRAs agree to respect principles, but national requirements still apply, decision remains national decision

Reliance: WHO PQT share the assessment reports, inspection reports and laboratory results with participating NRAs
Median time to registration for medicines

*Including regulatory time and applicant time

As at 26 Aug 2019

Calendar Days

<table>
<thead>
<tr>
<th>Year</th>
<th>Median</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>81</td>
<td>15</td>
</tr>
<tr>
<td>2014</td>
<td>93</td>
<td>36</td>
</tr>
<tr>
<td>2015</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>2016</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>2017</td>
<td>93</td>
<td>125</td>
</tr>
<tr>
<td>2018</td>
<td>113</td>
<td>106</td>
</tr>
<tr>
<td>2019</td>
<td>114</td>
<td>33</td>
</tr>
<tr>
<td>All</td>
<td>93</td>
<td>456</td>
</tr>
</tbody>
</table>
### Collaborative Registration Procedure (CRP)

Countries participating to vaccines CRP

<table>
<thead>
<tr>
<th>Armenia</th>
<th>Eritrea</th>
<th>Mali</th>
<th>Sudan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azerbaijan</td>
<td>Georgia</td>
<td>Namibia</td>
<td>Tanzania</td>
</tr>
<tr>
<td>Belarus</td>
<td>Ghana</td>
<td>Nigeria</td>
<td>Thailand</td>
</tr>
<tr>
<td>Botswana</td>
<td>Kazakhstan</td>
<td>Pakistan</td>
<td>Uganda</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Kyrgyzstan</td>
<td>Philippines</td>
<td>Uzbekistan</td>
</tr>
<tr>
<td>Burundi</td>
<td>Madagascar</td>
<td>Sierra Leone</td>
<td>Zambia</td>
</tr>
<tr>
<td>*<strong>Caribbean Community (CARICOM)</strong></td>
<td>Malawi</td>
<td>South Africa</td>
<td>Zanzibar</td>
</tr>
<tr>
<td>Comoros</td>
<td></td>
<td>Sri Lanka</td>
<td>Zimbabwe</td>
</tr>
</tbody>
</table>

**Red: newly joined**

* CARICOM
  Member States: Antigua and Barbuda, Bahamas, Belize, Dominica, Grenada, Haiti, Jamaica, Montserrat, Saint Lucia, St. Kitts and Nevis, St Vincent and the Grenadines, Suriname and Trinidad and Tobago

* Associate Member States: Anguilla, Bermuda, British Virgin Islands, Cayman Islands and Turks and Caicos Islands

As at 26 Aug 2019
accelerating access to vaccines? an examples of collaboration predating CRP

MenAfriVac (2010) - How it worked:

- Regulatory support from Health Canada (HC) and Indian DCGI
- Fast track, expedited procedure, prequalification approach, using HC/DGCI assessment (PQed in 5 months)
- Workshop in AFRO for sharing of reports that were the basis for PQ

Benefits:

- Assessment resources saved and targeted to other activities, for example, strengthening post-marketing surveillance

Successful registration of MenAfriVac in 26 countries of the meningitis belt (2011)
<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Vaccine(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ukraine</td>
<td>2016</td>
<td>6 vaccines applied</td>
<td>5 registered in &lt; 12 months</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>2017</td>
<td>1 vaccine BCG (India)</td>
<td>Registration still pending</td>
</tr>
<tr>
<td>DRC</td>
<td>2017</td>
<td>1 vaccine DTwP-HepB-Hib (Korea)</td>
<td>Registration still pending</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>2017</td>
<td>1 Vaccine DTwP-HepB-Hib (Korea)</td>
<td>Registered About 6 months</td>
</tr>
</tbody>
</table>
Experiences of CRP for Vaccines:
2017: workshop in Accra on oral cholera vaccine

• CRP workshop on registration of PQed oral cholera vaccine manufactured in Korea

• Participating NRAs:
  Ghana, Nigeria, Tanzania, Uganda and representatives from CARICOM

• Oral Cholera vaccine registered in:
  Nigeria in June 2018 - < 3 months
  CARICOM* in April 2018 - < 5 months

* CARICOM
Member States: Antigua and Barbuda, Bahamas, Belize, Dominica, Grenada, Haiti, Jamaica, Montserrat, Saint Lucia, St. Kitts and Nevis, St Vincent and the Grenadines, Suriname and Trinidad and Tobago
Associate Member States: Anguilla, Bermuda, British Virgin Islands, Cayman Islands and Turks and Caicos Islands
2018 Experiences of CRP for Vaccines:

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Vaccine</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>2018</td>
<td>4 PQed vaccines successfully registered</td>
<td>Reduced registration times by more than 6 months, “excellent reports”</td>
</tr>
<tr>
<td>Ukraine</td>
<td>2018</td>
<td>Tetanus (Indonesia)</td>
<td>Documentation shared</td>
</tr>
<tr>
<td>Belarus</td>
<td>2018</td>
<td>DTwP-HepB-Hib (Korea)</td>
<td>Documentation shared</td>
</tr>
</tbody>
</table>

- Other “mature” authorities requesting reports, particularly for emergency products
Optimizing CRP for vaccines (1):

• Mapping of current regulatory pathways in countries critical to ensure efficient use of resources
  - Countries accepting PQed vaccines supplied through UN
  - Countries ready to accept CRP
  - CRP Agreements extended to vaccines if necessary and focal points designated

• Identification of possible constraints for implementation of the procedure in countries
  - Need for local agent in countries?
  - Understanding of inspection and testing requirements,
  - Interest from manufacturers to submit an application?
Focussing resources

• Need to define priority vaccines and countries: for example,
  o priority vaccines representing major public health benefits or vaccines to contain an outbreak or vaccines under shortages
  o countries with long timelines, specific national requirements

• PQ to improve preparedness for sharing reports

• Joint review option may also facilitate registration (not CRP)

But

• Dossiers need to be first submitted in countries
  o Interest from countries that will benefit from the review - future "champions"
  o Adjustments may be needed depending on knowledge base of countries
Focus on adapting CRP from medicines to vaccines world

- Medicines based on voluntary system
- For vaccines – a need to prioritize countries and products has been identified
- Also to build on successful experiences for MenAfriVac and Polio end-game strategy
- DCVMN and IFPMA working with WHO on exploring how best to take it forward
- Some notable successes, but more work to do!
Strategic priority 2: 

*Increase regulatory preparedness for public health emergencies*

- Roadmap for revision of emergency use procedures (EU(A)L) nearing finalisation
- Ebola Crisis DRC - accelerating access to vaccines
- Roadmaps for specific products (Merck and J&J vaccines, discussions with other vaccine developers ongoing)
- Facilitating additional evidence through additional clinical trials and expanded access
- Use of EUL for novel Polio vaccines
- Recommendation for release into the global polio stockpile of mOPV2 vaccines
- Vigilance preparedness
Update on EUAL vaccine related activities
WHO Regulatory work to prepare for Public Health Emergencies

- Support for WHO’s R & D Blueprint
- Technical guidelines and standards
- Regulatory Systems Strengthening (mapping of provisions and competences, table top exercise, support for guidelines and SOPs)
- Regulatory platforms to facilitate registration of drugs/vaccines through joint reviews
- Emergency Use (Assessment) and Listing (EU(A)L)
- Safety monitoring
- Communication and coordination
Assessment of Ebola vaccines

Emergency Use and Assessment Listing (EUAL): risk-based evaluations on quality, safety and efficacy data of investigational products under PHEIC

1. Merck vaccine: EUAL – positive scientific assessment
   • SAGE recommendation for use under Expanded access protocol (EAP)

2. J&J and Cansino:
   • Scientific assessments concluded
   • Additional efficacy data needed

Additional issues:
• Complexity DRC crisis and
• limited supply: Clinical trials
Accelerating access to Ebola vaccines: Roadmap and licensing

- Roadmap published on licensing of Merck’s Ebola vaccine (VSV-ZEBOV) in countries at risk
  

**Background and Development**

1) Initial discussions November 2018
2) Draft prepared January 2019
3) Consultation with FDA, EMA, AVAREF
4) Discussed at AVAREF TCC and SC February 2019
5) Revised version published May 2019

**Purpose of the Roadmap:**

- to facilitate the introduction and roll-out of a licensed Merck Ebola Vaccine in concerned African countries
- to describe the roles and responsibilities of different stakeholders
- to clarify the potential role of AVAREF as a platform
Challenges and Options

→ PHEIC declared 17 July 2019

Constraints:
  - Security situation in DRC limiting effectiveness of ring vaccination
  - Limited supply of Merck Vaccine

• Contract manufacture being explored
• Limited data and/or supplies on other vaccines
• How to get additional data on other candidate vaccines?
• Licensed vaccines a priority
• Post-deployment monitoring of AEFI{s critically important
Allocation of vaccines based on epidemiological information

Liaison with UN agencies and manufacturers

ICG approach?
Prequalification (PQ) Achievements

At the close of 2018, WHO had prequalified over 1770 products*

Diagnostics
- 88 IVDs
- 2 male circumcision devices

Medicines
- 663 FPPs
- 140 APIs
- 53 quality control labs

Vaccines
- 333 vaccines
- 413 immunization device & cold chain equipment

Vector Control
- 76 vector control products (FPPs & APIs)

Through PQ, WHO has made available numerous quality-assured products to Member State markets

*: cumulative numbers of products since inception
Strategic priority 3:

Strengthen and expand WHO prequalification and product risk assessment processes

- PQ pilot for Biosimilars launched – exploring Human insulin
- First antivenom listed following risk assessment – May 2019 for Workshop
- IVDs – Syphilis and HBV viral load assays – new eligibility criteria for In-Vitro Diagnostics
- Reproductive health? Other Cancer medical products? Antibiotics?
- Ongoing collaboration with IVB on vaccines at all stages of development
- Use of information from WHO Listed Authorities (WLA) to facilitate prequalification
Strategic priority 4:

*Increase the impact of WHO’s Regulatory Supportive activities - efficiency, advocacy, knowledge sharing, joint planning*

- Improve our business processes – Quality Management System
- Increase impact and efficiency – IT system, KPIs
- Step-up cross functional collaboration and communication and increase our cooperation across WHO
- Increase awareness of WHO support during product development
- Streamline policy and PQ processes, particularly for innovative products
- Increase regulatory support and focus on transitioning countries
Highlights 2019-2023 – what we promise

• Roll out of WLA process
• 60 countries with improved regulatory systems by 2023 – 2024 to reach at least ML3
• 30 countries with risk-based approach for medical devices and IVDs
• Launch of Coalition of Interested Partners
• Countries in transition – focus on regulatory and supply chain aspects
• 10 countries better prepared for emergencies, including adapted pharmacovigilance system
• Expanded scope of PQ and new routes to prequalification (WLA)
Key messages

- Strong and efficient Regulatory systems use concepts such as reliance, work-sharing and international collaboration
- Rich portfolio of concepts, tools, networks and enablers now exist – e.g.
  - Good Regulatory Practices
  - Collaborative Registration Procedures
  - Joint reviews, Regional networks...
- More work needed to translate into practical realities for vaccines
- “Political will” and understanding as well as “regulatory will” are crucial
  - the power of the patient and stakeholder voice
  - the role of regulatory champions
- Opportunities to streamline in other areas, e.g., post approval changes/variations and inspections
A world where every child, man and woman has access to the quality essential medicines, vaccines and other health products they need to lead a healthy and productive life.

Emer Cooke
Director, Regulation and Prequalification