Working together to build effective & efficient regulatory systems

Improving affordable & equitable access to quality-assured medical products

DCVMN-AGM2022
Session on Innovation in Regulatory & PQ

Rogério Gaspar | Director, Department of Regulation and Prequalification (RPQ)
WHO’s Regulatory Strategic Priorities: 2019-2023

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

These strategic guide WHO regulatory 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 SF products
  - Includes strengthening national quality laboratories
- Broaden the prequalification programme
- Leverage political attention and commitment to advance accountability
- Promote and support sustainable and quality-assured local production through technical assistance

WHO PQP has a Return on Investment of 30-40 to 1

USD Mn

- PQ costs: 28
- PQ savings: 826 – 1,074

| Limited unit price drop given each diagnostics method has 1 MNC with > 50% market share |
| Conservative value as a limited time interval (2012-2014) and only HIV diagnostics is considered |
| Key driver is high volume |
| DTP-HepB-Hib accounts for majority of savings |
| Rx-HIV and Rx-Malaria comprises > 80% of savings |
  - Rx-HIV key driver is high volume |
  - Rx-Malaria key driver is large unit price drop |
| No savings Rx-RH considered despite injectables price drop, however these are mostly supplied by MNCs (90%+) |
Snapshot of donations/allocations (15 Aug 2022)
4926 regulatory approvals in 175 countries/territories

- **AstraZeneca (incl. SII)**
  - 149 countries/territories
  - 2061 regulatory clearance
  - 8 DS sites
  - 3 DS sites
  - 12 DP sites
  - 7 DP sites

- **Johnson & Johnson**
  - 131 countries/territories
  - 1057 regulatory clearance
  - 3 DS sites
  - 2 DS sites

- **Moderna**
  - 96 countries/territories
  - 802 regulatory clearance
  - 2 DS sites
  - 3 DP sites

- **Pfizer**
  - 175 countries/territories
  - 723 regulatory clearance
  - 4 DS sites
  - 10 DP sites

- **Sinopharm**
  - 96 countries/territories
  - 96 regulatory clearance
  - 1 DS/DP site

- **Sinovac**
  - 77 countries/territories
  - 129 regulatory clearance
  - 1 DS/DP site

- **Novavax**
  - 58 countries/territories
  - 58 regulatory clearance
  - 1 DS/DP site
Revised guidance EUL document*
30 March 2022

• Posted on 30 March 2022, following discussions with regulators and with the WHO R&D Blueprint Team
• The revised document
  • Acknowledges applications for EUL based on immunobridging
  • Indicates that careful choice of comparators is important
  • Indicates that additional nonclinical and immunogenicity data may be required
  • Indicates that demonstration of efficacy by in-deployment clinical trials or of (more likely to happen in practice) effectiveness by post-deployment observational studies will also be needed as a post-listing commitment

Avoids being too prescriptive
  Is aligned with the
  - revised WHO Target Product Profiles (TPP) for COVID-19 vaccines
  - draft R&D Blueprint Team “Framework” document

* Considerations for evaluation of COVID-19 vaccines: Points to consider for manufacturers of COVID-19 vaccines. Revised version, 30 March 2022
The WHO TAG-CO-VAC continues to monitor and assess the evidence on the genetic and antigenic characteristics of SARS-CoV-2 Variants of Concern (VOC), including descendent lineages of VOCs.

In their latest statement\(^1\), TAG-CO-VAC advised that it may be prudent for manufacturers seeking to pursue an updated composition of current COVID-19 vaccines, to seek to achieve broader immunity against circulating and emerging variants, while retaining protection against severe disease and death:

- viruses or sequences closely related to Omicron BA.1 are some of the most antigenically distant from the index virus

The USA FDA issued a recommendation for COVID-19 vaccine composition to include Omicron BA.5 in an attempt to increase and extend protection by better matching the vaccine composition with circulating variants:

- mRNA vaccines which include BA.5 may be available in the USA by the Northern Hemisphere fall, pending regulatory approval.

A statement from ICMRA\(^2\) indicates that adapted mRNA vaccines, which incorporate an Omicron variant, can increase and extend protection, when used as a booster dose, but gives no indication as to which Omicron lineage should be included.

The MHRA has approved\(^3\) the use of the Moderna bivalent vaccine product (index virus + Omicron BA.1) as a booster dose in the UK.

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Locations of Covid-19 Vaccine Manufacturers

Source: Global Health Centre – Graduate Institute Geneva [https://www.knowledgeportalia.org/covid19-vaccine-manufacturing](https://www.knowledgeportalia.org/covid19-vaccine-manufacturing)
Local Production and Assistance

WHO VACCINE MANUFACTURING WORKSHOP for SOUTHEAST ASIAN and WESTERN PACIFIC REGIONS

MEMBER STATE SUPPORT IN STRENGTHENING LOCAL PRODUCTION DZA, EUC, EGY, ETH, GHA, KAZ, NGA, SEN, SRB, etc.

ONGOING PQ/EUL-RELATED SPECIALIZED TECHNICAL ASSISTANCE

IMPLEMENTATION OF WORLD LOCAL PRODUCTION FORUM RECOMMENDATIONS
Global status of national regulatory systems, April 2022

<table>
<thead>
<tr>
<th>ML1</th>
<th>Oct 2018</th>
<th>100 COUNTRIES</th>
<th>Nov 2020</th>
<th>100 COUNTRIES</th>
<th>Apr 2022</th>
<th>98 COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>With some elements of regulatory system</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>ML2</th>
<th>Oct 2018</th>
<th>44 COUNTRIES</th>
<th>Nov 2020</th>
<th>41 COUNTRIES</th>
<th>Apr 2022</th>
<th>40 COUNTRIES</th>
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<tbody>
<tr>
<td>Evolving national regulatory system</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ML3</th>
<th>Oct 2018</th>
<th>50 COUNTRIES</th>
<th>Nov 2020</th>
<th>53 COUNTRIES</th>
<th>Apr 2022</th>
<th>56 COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable, well functioning and integrated</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>ML4</th>
<th>Oct 2018</th>
<th>50 COUNTRIES</th>
<th>Nov 2020</th>
<th>53 COUNTRIES</th>
<th>Apr 2022</th>
<th>56 COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced level of performance and continuous improvement</td>
<td></td>
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</tr>
</tbody>
</table>

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

Singapore medicines regulator world’s first to achieve the highest maturity level (ML4) following assessment (28 Feb 2022).

Nigeria and Egypt announced as ML 3 in March 2022.
How does the collaborative procedures work?

WHO
PQ

SRA
Medicines & Healthcare products Regulatory Agency

NRA

Submission
NRA
Marketing authorisation

90 days TARGET

World Health Organization
CRP in facilitating in-country regulatory approval of medical products

As of August 2022

1. CRP PQ-ed Medicines and vaccines
   - 56 NRAs, plus 1 REC
   - 1400 submissions and 717 registrations (283 medicines)

2. CRP PQ-ed vaccines
   - 30 NRAs, plus 1 REC
   - 120 submissions and 22 registrations (33 different vaccines)

3. SRA CRP
   - 44 NRAs, 1 REC (SADC) and 4 SRAs: (EMA, Swissmedic, Dutch MEB and MHRA)
   - Approximately 200 submissions and 80 registrations (33 medicines)
Reliance is “implanted” in facilitated regulatory pathways

- Vaccines: 2004
- Medicines: Started in 2012
- FDA-WHO joint pilot to accelerate access to HIV medicines (CRP-lite)
- Diagnostics: Pilot 2019
- Vector control: Pilot 2020

- Initiated in 2015
- European Medicines Agency (EMA)
- UK Medicines and Healthcare Products Regulatory Agency (MHRA)
- 20 African NRAs

WHO PQ collaborative registration procedure

“SRA” collaborative registration procedure

Regional regulatory harmonization initiatives and networks

African Medicines Regulatory Harmonization Initiative (AMRH)

ASEAN SIAHR Project
Benefits of WHO-Listed Authority (WLA) framework

**Enable efficient use of regulatory resources**
by providing a robust framework to promote trust, confidence and reliance

**Encourage continuous improvement of regulatory systems and regulatory convergence**

**Help procurement decisions**
on medical products by UN and other agencies, as well as countries (especially LMICs)

**Contributes to WHO PQ programme**
by expanding the pool of trusted regulatory authorities

**Fosters health equity**
by enabling an environment for innovation and local production, and accelerating access to medical products
Access to quality medicines and other health products requires an integrated approach with all stakeholders.
Back-up slides
### 5A 340-400 million more patients are accessible thanks to resources freed up by PQ

<table>
<thead>
<tr>
<th>Product stream</th>
<th>Freed up budget(^1) USD Mn (% of market(^2))</th>
<th>Treatment cost/year USD</th>
<th>Additional patients accessible(^3), Mn</th>
<th>Methodology</th>
</tr>
</thead>
</table>
| Rx-HIV         | 147 - 196, 28 - 37%                          | 93.35                   | 1.6 - 2.1                                | - Treatment cost per year = Total sales / total # treatments  
- Most ARVs require daily pills  
- CHAI estimates 94 USD/year in 2016 |
| Rx-Malaria     | 124 - 145, 39 - 45%                          | 0.68                    | 183 - 213                                | - Based on GF reference treatment pricing for largest product in 2018  
- Considered 1 adult dose treatment per year (twice daily for 3 days) |
| Rx-TB          | 13 - 19, 9 - 14%                             | 662                     | 0.0                                      | - Treatment cost per year is weighted average of FLDs and SLDs\(^3\) cost  
- Based on Global Drug Facility sales in 2017 |
| Rx-RH          | 0                                             | 3.60                    | 0                                        | - CHAI RH 2018 report for treatment pricing, using market value to determine average cost |
| Vx             | 337 - 382, 17 - 19%                          | 2.19                    | 154 - 174                                | - # doses for each of top 5 drugs according to WHO recommendation used to determine vaccination cost |
| Dx             | 3.4 – 7.7, 1 - 3%                            | 1.33                    | 2.5 – 5.8                                | - 1 unit is equal to 1 diagnosis  
- Considered 1 diagnosis per year  
- Average price of HIV diagnosis |

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Assuming a fixed donor market size for all products, calculated the share of the market represented by savings (i.e. the freed up budget). Treatment cost/year price only includes price of the product itself.
WHO Emergency Use Listing process

Step 1
Expression of interest
- Submission by company
- Assessment

If negative feedback
- Company to resubmit

Step 2
Pre-submission mtg
- Company to present product info
- Agree on rolling submission timelines

Step 3
Establish Product Evaluation Group (PEG)
- Roster expert + reviewers from NRAs (CMC/Non-clinical/clinical/RMP)

Step 4
Submission screened / PEG Assessment
- List of Qs
- Responses
- PEG report

- Review of data packages
- GMP inspection / recognition

Step 5
TAG assessment of PEG report & recommendation
TAG deliberation and recommendation

- Sharing approved version of RMP with PVG for implementation of post-listing activities

Step 6
Public assessment report
Outcome is announced

Step 7
Post-listing activities
- Updates
- Changes
- Surveillance reports
Clinical evidence is required for variant vaccines to be authorized and implemented in programmes

COVID-19 current vaccine development pipeline – Variants*

*Adapted from Cepi 5 Aug 22 - Based on publicly available information from vaccine candidates based on variants

**Broadly protective Beta coronavirus
## Variant-containing COVID-19 vaccines

As of 31 August 2022

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Variant-containing vaccine</th>
<th>Publicly available data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Animal model data</td>
<td>Clinical data</td>
</tr>
<tr>
<td>Moderna</td>
<td>mRNA1274.211 (Beta) monovalent</td>
<td></td>
<td>Yes&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>mRNA1274.211 (Beta) bivalent</td>
<td></td>
<td>Yes&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>mRNA1274.214 (Omicron BA.1) bivalent</td>
<td>Yes&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>mRNA1274.214 (Omicron BA.5) bivalent</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pfizer</td>
<td>BNT162b2 (Omicron BA.1) monovalent</td>
<td>Yes&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>BNT162b2 (Omicron BA.1) bivalent</td>
<td>Yes&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>BNT162b2 (Omicron BA.5) bivalent</td>
<td>Yes&lt;sup&gt;6&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Sanofi/GSK</td>
<td>Beta monovalent</td>
<td></td>
<td>Yes*</td>
</tr>
<tr>
<td></td>
<td>Beta + D614 bivalent</td>
<td></td>
<td>Yes*</td>
</tr>
</tbody>
</table>

*Shared with WHO; not in public domain

Under development: Novavax Omicron-containing product; Sinopharm Omicron-containing product
Adding variant adapted vaccines to portfolios as boosters potential additional operational complexity for countries

Source: Our World in data, WHO COVID-19 dashboard, Government websites; Press research

1. World Bank classification (2021) of 218 economies. Note: The term country, used interchangeably with economy, does not imply political independence but refers to any territory for which authorities report separate social or economic statistics.

<table>
<thead>
<tr>
<th>Countries &amp; economies using available vaccines, Cumulative number of different vaccines products used</th>
<th>DATA AS OF AUGUST 15, 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca - Vaxzevria / SII - Covishield</td>
<td>181</td>
</tr>
<tr>
<td>Pfizer BioNTech - Comirnaty</td>
<td>172</td>
</tr>
<tr>
<td>Moderna - mRNA-1273</td>
<td>123</td>
</tr>
<tr>
<td>Janssen - Ad26</td>
<td>123</td>
</tr>
<tr>
<td>Beijing CNBG - BBIBP-CorV</td>
<td>101</td>
</tr>
<tr>
<td>Gamaleya - Sputnik V</td>
<td>70</td>
</tr>
<tr>
<td>Sinovac - CoronaVac</td>
<td>68</td>
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<tr>
<td>Bharat - Covaxin</td>
<td>33</td>
</tr>
<tr>
<td>Novavax - Covavax</td>
<td>33</td>
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<tr>
<td>Bharat - Covaxin</td>
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<tr>
<td>CanSino - Convidecia</td>
<td>28</td>
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<tr>
<td>Adbala</td>
<td>4</td>
</tr>
<tr>
<td>Soberana02</td>
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</tr>
<tr>
<td>CIGB - CIGB-66</td>
<td>4</td>
</tr>
<tr>
<td>Wuhan CNBG - Inactivated</td>
<td>3</td>
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<tr>
<td>Anhui ZL - Zifivax</td>
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<tr>
<td>Julphar - Hayat-Vax</td>
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<tr>
<td>RIBSP - QazVac</td>
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<tr>
<td>SRCVB - EpiVacCorona</td>
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<tr>
<td>RIBSP - QazCovid</td>
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<tr>
<td>Biological E - Corbevax</td>
<td>1</td>
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<tr>
<td>Chumakov - Covi-Vac</td>
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<tr>
<td>IMB - Covidful</td>
<td>1</td>
</tr>
<tr>
<td>Shifa - COViran Barakat</td>
<td>1</td>
</tr>
<tr>
<td>Turkovac</td>
<td>1</td>
</tr>
<tr>
<td>Zydus - ZyCov-D</td>
<td>1</td>
</tr>
</tbody>
</table>

12 countries and economies are using 1 vaccine; 206 are using 2 or more vaccines

Source: Our World in data, WHO COVID-19 dashboard, Government websites; Press research