WHO evaluation strategy for COVID-19 Vaccines

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IPA, 6th Advanced GMP Workshop
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Department of Regulation and Prequalification (RPQ)
Current status of NRAs based on WHO GBT Performance Maturity Levels

- **ISO 9004**
  - **1**: No formal approach
  - **2**: Reactive approach
  - **3**: Stable formal system approach
  - **4**: Continual improvement emphasized

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- **WHO GBT**
  - **1**: Some elements of regulatory system exist
    - Can ensure the quality of products if rely on ML 3/ML 4 regulatory systems
    - 100 Countries
  - **2**: Evolving national regulatory system that partially performs essential regulatory functions
    - 41 Countries
  - **3**: Stable, well-functioning and integrated regulatory system
    - Target of WHA Resolution 67.20
    - 53 Countries
  - **4**: Regulatory system operating at advanced level of performance and continuous improvement
    - Advanced and well resourced regulatory systems
    - 27% Countries

- **Countries**
  - Total: 100
  - ML 3/ML 4: 41
  - ML 5: 53
  - Total percentage: 73%

5,484 M doses of COVID-19 vaccine have been administered\(^1\) in 217 countries, areas, territories & economies\(^2\)

**Total doses administered per 100 population\(^3\)**

<table>
<thead>
<tr>
<th>Doses administered per 100 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
</tr>
<tr>
<td>6-20</td>
</tr>
<tr>
<td>21-50</td>
</tr>
<tr>
<td>50+</td>
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</tbody>
</table>

5,484M vaccine doses\(^1\) have been administered

COVAX has shipped 236.6M doses to 139 participants\(^4\)

Immunization programmes have not yet started in 3 countries, economies & territories

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1. Source of data: WHO dashboard, Bloomberg; 2. Total of 220 countries, areas, territories & economies: 218 economies listed by World Bank + WHO Member states Cook Islands + Niue

Note: The designations employed and the presentation of these materials do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
Overview of % of total population fully vaccinated across WHO Member States

**Breakdown of WHO MS by percentage of total population fully vaccinated**

- **AFRO**
- **AMRO**
- **EMRO**
- **EURO**
- **SEARO**
- **WPRO**

<table>
<thead>
<tr>
<th>Percentage category</th>
<th># of Member States</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) 0-1%</td>
<td>25</td>
</tr>
<tr>
<td>2) 1-10%</td>
<td>47</td>
</tr>
<tr>
<td>3) 10-20%</td>
<td>25</td>
</tr>
<tr>
<td>4) 20-30%</td>
<td>27</td>
</tr>
<tr>
<td>5) 30%+</td>
<td>67</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>191</td>
</tr>
</tbody>
</table>

**WHO MS with percentages of total population fully vaccinated of less than 0.35%**

<table>
<thead>
<tr>
<th>Member State name</th>
<th>% pop. fully vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niger</td>
<td>0.35%</td>
</tr>
<tr>
<td>Madagascar</td>
<td>0.35%</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>0.34%</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>0.32%</td>
</tr>
<tr>
<td>Cameroon</td>
<td>0.29%</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>0.18%</td>
</tr>
<tr>
<td>Turkmenistan</td>
<td>0.16%</td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>0.15%</td>
</tr>
<tr>
<td>Chad</td>
<td>0.09%</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>0.06%</td>
</tr>
<tr>
<td>Yemen</td>
<td>0.04%</td>
</tr>
<tr>
<td>South Sudan</td>
<td>0.04%</td>
</tr>
<tr>
<td>Haiti</td>
<td>0.04%</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>0.01%</td>
</tr>
</tbody>
</table>

**Top 15 percentages of total population fully vaccinated**

- **Malta**: 93%
- **United Arab Emirates**: 91%
- **Palau**: 78%
- **Iceland**: 77%
- **Portugal**: 74%
- **Singapore**: 72%
- **Uruguay**: 71%
- **Denmark**: 71%
- **Niue**: 71%
- **Seychelles**: 71%
- **San Marino**: 70%
- **Spain**: 69%
- **Belgium**: 69%
- **China**: 67%
- **Ireland**: 67%

**DATA AS OF 31 AUGUST 05:37:54 UTC**

*Source: WHO weekly COVID-19 vaccine administration data | Notes: Three MS have not introduced a COVID-19 vaccine: 1) Burundi, 2) Eritrea, and 3) DPR Korea. Six MS report only total COVID-19 vaccine doses administered: 1) Bulgaria, 2) China, 3) Kuwait, 4) Moldova, 5) Tanzania, and 6) UAE. For these, a theoretical population coverage was calculated assuming all administered doses were part of a two-dose series.*
Prequalification Programme: International norms, standards and guidelines used to ensure wide applicability

Other guidelines e.g. ICH, ISO
Role of regulation: Promoting and protecting public health
WHO EUAL/EUL background

WHO Emergency Use Assessment and Listing (EUAL) mechanism developed in response to the 2014 - 2016 Ebola outbreak

Risk-based approach to expedite the availability of health products needed in public health emergency situations

It is intended to assist interested procurement agencies and Member States on the suitability for use of a specific health product, based on a minimum set of available quality, safety, and performance data

EUL status is time-limited
Types of COVID-19 candidate vaccines being developed

**Virus Vaccines**
- Weakened virus
- Inactivated virus

**Viral Vector Vaccines**
- Replicating viral vector
- Non-replicating viral vector

**Nucleic Acid Vaccines**
- DNA vaccine
- RNA vaccine

**Protein-Based Vaccines**
- Protein subunits
- Virus-like particles
Challenges and solutions

- Regulatory requirements
  - Development of criteria for evaluation TPP, EUL, ECBS
- Regulatory alignment
  - Regulatory Advisory Group
    - ICMRA
    - Regional regulatory networks
    - Vaccine cluster
- Facilitation in countries
  - Development of EUL roadmap
  - Ad Hoc support to member states
  - Briefing on outcome of review
- Resources
  - Prioritization mechanism: eligibility
  - Establishment of product evaluation group (PQ roster and NRA global level) and TAG
  - Collaboration agreements with NRA of reference for sharing information
WHO alignment activities for COVID-19 vaccines ongoing since Feb 2020

<table>
<thead>
<tr>
<th>Development criteria</th>
<th>Submission requirements</th>
<th>Assessment process</th>
<th>In-country approval for use &amp; post approval monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Target Product Profiles</td>
<td>✓ EUL and PQ guidance and Questions &amp; Answers</td>
<td>• Evaluation of candidates for EUL/PQ (incl. inspection, lot release process &amp; post-listing commitment)</td>
<td>• Country regulatory reliance on EUL/PQ*</td>
</tr>
<tr>
<td>✓ Expert Committee on Biological Standards guidance</td>
<td>✓ EUL/PQ Expressions of Interest (conditions &amp; evaluation criteria)</td>
<td>• Interactions &amp; agreements with NRAs/SRAs*</td>
<td>• Support for safety monitoring (based on safety preparedness manual)</td>
</tr>
<tr>
<td>✓ Regulatory guidelines</td>
<td>• Labelling &amp; packaging requirements</td>
<td>• Global assessment process* with region-designated national authority reps</td>
<td>• Tools for risk communication and strengthening response capabilities</td>
</tr>
</tbody>
</table>

- Roadmap* to enable product specific regulatory alignment (assessment process, in-country approval & post-listing monitoring)
- Alignment ongoing (Regulatory Advisory Group, ICMRA, regional regulatory networks, Vaccine cluster etc.)
- Regulatory updates and webinars
- Best practice principles for regulatory “agility”

* Elements of the Roadmap for WHO Assessment of vaccine x during the COVID-19 Public Health Emergency (model roadmap published on 30 Oct 2020)
WHO regulatory alignment roadmap for COVID-19 vaccines: overview of recognized pathways, and summary of related alignment activities

Submission requirements

- Data in dossier:
  - Efficacy
  - Safety
  - Quality

- Inspection data (GMP, GCP, GLP, GVP)

- Lot release data

- Etc...

Assessment process

- NRA / SRA in charge of oversight and (emergency) approval

- WHO EUL/PQ evaluation with Global Review Committee

In-country approval for use & post-listing monitoring

- SRA direct reliance (possible under COVAX mechanism)

- EUL/PQ direct reliance

- WHO roadmap process – facilitated by Regional champions (2-3 per region) & Regional networks (e.g. AVAREF, WPR Alliance)

- SRA

- Reliance on WHO EUL/PQ

- Interactions & agreements with NRAs/SRAs in charge of oversight early in process (incl. report sharing, aligned requirements)

- Global assessment with region-designated national authority representatives

In-country approval for use & post-listing monitoring

- Interactions & agreements with NRAs/SRAs in charge of oversight early in process (incl. report sharing, aligned requirements)

- Global assessment with region-designated national authority representatives

- Aligned requirements with NRA / SRA in charge of oversight

- Participant NRA requirements captured

- Single format for application submitted by manufacturers

- Transparent sharing of reports with all regulatory authorities for decision making process

- Promotion of reliance principles in countries based on facilitated pathways (direct, through regional networks, via regional champions/NRAs of reference)
Eligibility of candidate products

- The disease for which the product is intended is serious or immediately life threatening, has the potential of causing an **outbreak, epidemic or pandemic** and it is reasonable to consider the product for an EUL assessment, e.g., there are **no licensed products** for the indication or for a critical subpopulation (e.g., children);

- Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines);

- The product is manufactured in **compliance with current Good Manufacturing Practices (GMP)** in the case of medicines and vaccines and under a **functional Quality Management System (QMS)** in the case of IVDs; and

- The applicant **undertakes to complete the development of the product** (validation and verification of the product in the case of IVDs) and **apply for WHO prequalification** once the product is licensed.
At least 17 vaccines deployed to date, of which 7 with WHO EUL and SAGE recommendations

**At least 17 vaccines deployed to date…**
- Adabala
- Anhui ZL - Recombinant
- AstraZeneca - Vaxzevria
- Beijing CNBG - BBIBP-CorV
- Bharat - Covaxin
- CanSino - Convidecia
- Chumakov - Covi-Vac
- Gamaleya - Gam-Covid-Vac
- Janssen - Ad26.COVID-2-S
- Moderna - mRNA-1273
- Pfizer BioNTech - Comirnaty
- RIBSP - QazVac
- SII - Covishield
- Sinovac - CoronaVac
- Soberana02
- SRCVB - EpiVacCorona
- Wuhan CNBG - Inactivated

**… of which 7 with WHO EULs and SAGE recommendations**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>WHO EUL</th>
<th>SAGE Interim recs</th>
<th>Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer BioNTech</td>
<td>Dec 31 (2020)</td>
<td>Jan 5</td>
<td>June 14</td>
</tr>
<tr>
<td>AstraZeneca + SII</td>
<td>Feb 15</td>
<td>Feb 8</td>
<td>April 21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>July 30</td>
</tr>
<tr>
<td>Janssen</td>
<td>Mar 12</td>
<td>Mar 17</td>
<td>June 14</td>
</tr>
<tr>
<td>Moderna</td>
<td>Apr 30</td>
<td>Jan 25</td>
<td>June 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SINOVAC</td>
<td>June 1</td>
<td>May 24</td>
<td></td>
</tr>
</tbody>
</table>

**Further vaccines under evaluation**
- MFDS Korea EUL finalized Feb 15. EMA SK-Catalent followed Apr 16 and Wuxi (DS) Apr 30
- Source: WHO
Covid 19 vaccines

25 Covid 19 vaccines in the pipeline
12 vaccines listed
07 vaccines ongoing, (data expected)
06 vaccines planned

EUL listed vaccines

<table>
<thead>
<tr>
<th>Different platforms</th>
<th>Post EUL changes</th>
<th>Facilitation in countries:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different NRA oversight</td>
<td>Expansion capacity: New sites</td>
<td>Sharing dossier/reports &gt; 400</td>
</tr>
<tr>
<td></td>
<td>New storage conditions</td>
<td>&gt; 90 countries</td>
</tr>
<tr>
<td></td>
<td>New indications, new presentations</td>
<td>Briefing workshops</td>
</tr>
<tr>
<td></td>
<td>Shelf life updates</td>
<td>Ad Hoc consultation</td>
</tr>
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SAGE product specific policy recommendations

Indicates recent updates to recommendation

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Vaccine Platform</td>
<td>Messenger RNA</td>
<td>Viral Vector (Adenovirus)</td>
<td>Alum-adjuvanted inactivated whole virus vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy against symptomatic illness of any severity(^1)</td>
<td>95% (Israel, UK, US)</td>
<td>94%</td>
<td>61-79%</td>
<td>72%</td>
<td>56-79%</td>
<td>56-89%</td>
</tr>
<tr>
<td>Post-introduction vaccine effectiveness (w/out VOC)</td>
<td>&gt;90% (UK)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&gt;80% (Chile)</td>
<td></td>
</tr>
<tr>
<td>Storage requirements</td>
<td>Ultra cold chain -70°C ; -20°C (2 wks) 2 to 8°C (1 month)</td>
<td>Freezer -20°C ; 2 to 8°C (1 month)</td>
<td>Standard cold chain 2 to 8°C</td>
<td>Freezer &amp; Standard cold chain -20°C (24mos) ; 2 to 8°C (3mos)</td>
<td>Liquid formulation in single-dose vial or prefilled syringe, requires Standard cold chain (+2-8°C), supplied with VVM</td>
<td>Liquid formulation in multi-dose vial (40 doses), requires Standard cold chain (+2-8°C)</td>
</tr>
<tr>
<td>Dosage</td>
<td>2 doses (3-6 wk intrv.)</td>
<td>2 doses (4-6 wk intrv.)</td>
<td>2 doses (8-12 wk intrv.)</td>
<td>1 dose</td>
<td>2 doses (3-4 wk intrv.)</td>
<td>2 doses (2-4 wk intrv.)</td>
</tr>
<tr>
<td>Minimum age</td>
<td>12 years (once other priority groups cov’d)</td>
<td>18 years</td>
<td>18 years</td>
<td>18 years</td>
<td>18 years</td>
<td></td>
</tr>
<tr>
<td>Maximum age</td>
<td>None</td>
<td>None</td>
<td>None, though limited data for 60+ is acknowledged.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional updates</td>
<td>Mix and match – mRNA vax (i.e. Pfizer or Moderna(^2)) 2nd dose after 1st dose of AZ</td>
<td></td>
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</tbody>
</table>

1. Vaccine efficacy results are not comparable across vaccine products due to different case definitions of endpoints used in respective studies.
   For most recent official WHO recommendations, please refer to the SAGE Interim Recommendations, available online: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials

2. Pfizer policy updated on 14 June 2021; AZ policy update issued 30 July 2021; Moderna policy update in process
Country granting Emergency-use authorization (EUA) using reliance
- Regulatory approach based on reliance to WHO PQ EUL (or Stringent Regulatory Authority EUA)
- Some countries requested access by NRAs to documentation submitted by manufacturers to WHO PQ when applying for EUL, as well as respective assessment reports (issued by PQ).
- Few countries insisted on the submission of an application by a manufacturer.

“Import authorization” or other authorization for use under exceptional circumstances
- Requirement for regulatory authorization is "waived", relying on referring to the WHO EUL.
- Supply is based on an import authorization, without issuance of a national EUA.

Analysis: 101 participants clear regulatory within 15 days following WHO EUL (out of 145 total participants, allocated AZ or SII doses in first allocation round) (status: 3 March 2021)

Regulatory approaches adopted by countries under COVAX
Flexibilities to allow for continuation of mandate of PQT by performing:

- Remote real time inspections of BE sites, Vx sites, QCL, NCL, FPP
- Desk Reviews and reliance on work done by Mature NRA
- Joint inspections conducted with EMA Inspectors
- Extension of the WHOPIR validity from 3 years to 4 years
- EUL applications - Evaluation of QMS of manufacturing sites