Regulatory alignment and authorization of vaccines under EUL/PQ

Developing Countries Vaccine Manufacturers’ Network
21st Annual General meeting
“Vaccines, a healthy future”
Carmen Rodriguez Team lead vaccines Prequalification
Department of Regulation and Prequalification (RPQ)
05 November 2020
Goal of this WHO work: to optimize access & availability to safe, efficacious, quality-assured COVID-19 products by further aligning regulatory processes

Objectives of today’s presentation:

- Explain and update on WHO’s roadmap for aligning regulatory processes impacting access to COVID-19 vaccines
  
  [https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19](https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19)

- Ensure this approach is understood and communicated to stakeholders in a consistent manner (e.g. countries, manufacturers)

- Address specific issues of particular interest (e.g. labelling)
Overview of WHO’s end-to-end process for aligning the regulation of vaccines

Development criteria
- Efficacy
- Safety
- Quality
- Programmatic suitability

Submission requirements

Assessment process
- WHO EUL/PQ evaluation
- NRA/SRA independent assessment

In-country approval for use & post-approval monitoring

Decision on the basis of:
1. Independent assessment (e.g. EMA)
2. Recommendation from regional networks/body (e.g. EAC, Zazibona, ECOWAS)
3. Reliance on reference NRA that has done independent assessment (e.g. within PAHO region)
4. Reliance on WHO EUL/PQ (e.g. LMICs)
WHO alignment activities for COVID-19 vaccines ongoing since Feb 2020

- Evaluation of candidates for EUL/PQ (incl. inspection, lot release process & post-listing commitment)
- Interactions & agreements with NRAs/SRAs*
- Global assessment process* with region-designated national authority reps

### Development criteria
- ✓ Target Product Profiles
- ✓ Expert Committee on Biological Standards guidance
- ✓ Regulatory guidelines

### Submission requirements
- ✓ EUL and PQ guidance and Questions & Answers
- ✓ EUL/PQ Expressions of Interest (conditions & evaluation criteria)
- ✓ Labelling & packaging

### Assessment process
- Evaluation of candidates for EUL/PQ (incl. inspection, lot release process & post-listing commitment)
- Interactions & agreements with NRAs/SRAs*
- Global assessment process* with region-designated national authority reps

### In-country approval for use & post approval monitoring
- Country regulatory reliance on EUL/PQ*
- Support for safety monitoring (based on safety preparedness manual)
- Tools for risk communication and strengthening response capabilities

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- **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*
### Submission requirements: Labelling, Barcoding, QR codes

#### Current working position

<table>
<thead>
<tr>
<th><strong>Labelling</strong></th>
<th><strong>Progress on regulatory agreement on single label (model) – finalizing WHO/PQ &amp; EU alignment; WHO DG letter to countries?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Goes beyond regulatory processes; national exemptions from legal requirements will be needed</td>
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<tr>
<td>Bar codes on <strong>secondary packaging</strong> (i.e. carton) to support traceability</td>
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<tr>
<td><strong>Preferred characteristic</strong> by UNICEF¹</td>
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<tr>
<td>Bar codes on <strong>primary packaging</strong> (i.e. vials) to support traceability and monitoring</td>
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<tr>
<td><strong>Optional</strong> but not as a replacement for other printed label information</td>
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<tr>
<td><strong>QR codes in lieu of statutory labelling</strong> information printed on the <strong>vial and/or inserts</strong></td>
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<tr>
<td><strong>Not acceptable</strong></td>
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<tr>
<td><strong>QR codes in addition to statutory labelling</strong> information printed on the <strong>vial and/or inserts</strong></td>
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<tr>
<td><strong>Acceptable</strong></td>
<td></td>
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<tr>
<td><strong>Translated inserts</strong></td>
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<tr>
<td><strong>Expected</strong></td>
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1. UNICEF has not officially released their tender document, but it will be a "preferred product characteristic"
WHO working position on labelling and package inserts

- **Labelling models** being developed: generic vial label and carton label for all vaccine platforms & platform-specific package inserts

- **Single** language for vials & carton labels

- Exploring mechanisms (e.g. QR code) to allow *extension of expiry date* as more data becomes available (for shipment of initial batches)

- Exploring possibility for using *manufacturing date in lieu of expiry* (only for initial batches)

- Recommending possible **country actions** (e.g. take over printing of translated local language inserts)

- **Mechanisms to make insert information available** as early as possible to support development of training materials

- Country actions on **cold chain maintenance** when data available does not match any existing Vaccine Vial Monitor (VVM) category
Outline of risk areas and need for additional support outside the scope of regulatory interventions

**Risks**

**Specific legal exemption** required for acceptance of a single labelling model (& language) in many countries

**Lack of local language versions** posing potential risks to HCPs and subjects

**Undefined information behind QR codes** (when QR codes are proposed)

**Vulnerability to misuse and product diversion** (grey and black market)

**Lack of manufacturers understanding of requirements on inserts translation**

**Vaccine Vial Monitors** not possible

**Solution space**

- Letter from WHO DG/COVAX – part of T&C?
- Compensation by training – responsibilities need to be defined
- Clear definition and mechanism of what can be updated via the QR codes – e.g. expiry date, indications, take over printing of translated leaflets
- Printing expiry date on vials & **time-limiting** those without expiry date
- Communication to manufacturers
- **Manufacturer and country obligations** to be clearly communicated
Generic vial label

Name of vaccine
Type of vaccine
Method of administration
Multidose vial (X doses x X ml)
Store at XX °C
See package insert for details

Generic vaccine carton

Only package inserts will be platform-specific & translated in multiple languages
## WHO EUL/PQ submission requirements for evaluation of COVID-19 candidates & areas of specific guidance (examples)

### Non-clinical & Clinical assessment
- Non-clinical information
- Clinical development programme
- Ethics Committee approval of clinical trials
- Evidence of GLP/ GCP conduct
- Evidence for registration
- Clinical trial design
- Statistical Considerations
- Clinical trial end-point assays
- Vaccine lots used in clinical studies and lot-to-lot consistency studies
- Subject exposure to a new vaccine in trial

### Manufacturing, QC & labelling
- Characterization of cell banks
- Characterization of master and working seed organism(s)
- Process validation (incl. production lot consistency & post-listing commitments)
- Justified specifications
- Stability data
- GMP inspection reports
- Process change
- Labelling
- Comparability and impact of tech transfers

### Areas of COVID-19 specific guidance

### WHO’s assessment decision will be guided intra alia by status of clinical development, extent of the available quality, safety and efficacy data, evidence of compliance, process validation and reference NRA regulatory approvals

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)

**Alignment activities**
- Aligned requirements with NRA / SRA in charge of oversight
- Participant NRA requirements captured
- Single format for application submitted by manufacturers

- 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

- 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)
# In-country expedited approval for use & post-listing monitoring: the WHO regulatory alignment roadmap*

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<tbody>
<tr>
<td>Global regulatory cooperation</td>
<td>Manufacturers EOIs (Phase IIb/III &amp; approval by NRA/SRA in charge of oversight within 6 months &amp; compliance with criteria for assessment)</td>
<td>Establishment of assessment pathway according to NRA/SRA in charge of oversight</td>
<td>Approval granted by NRA/SRA in charge of oversight</td>
<td>Implementation of strategies for safety, quality &amp; effectiveness monitoring</td>
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<td>Establishment of strategies for expedited approval in participants &amp; post-listing monitoring</td>
<td>Discussions on rolling submission procedure</td>
<td>Establishment of Review Committee (NRA/SRA in charge of oversight &amp; regulators/reviewers from potential user participants)</td>
<td>Advisory committee convened (post-listing commitment)</td>
<td>Validity of listing based on new data generated</td>
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**Facilitated access to countries**

- Sharing of assessment/inspection reports/lot release with regional-designated country reps
- WHO-facilitated national approval process

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*Roadmap for WHO Assessment of vaccine x during the COVID-19 Public Health Emergency*
WHO’s regulatory alignment roadmap* is based on **collaborative principles & to be successful**...

- **Regional networks** must identify regional experts to take part in global assessment
- **Agreements** must be established with NRAs/SRAs in charge of oversight
- The **WHO reliance mechanism** must be adopted by participating countries
- **National regulatory agencies** must commit to sharing information & fast decision making

Estimated best case scenarios:

- First full EUL/PQ application submission – **Jan 2021**
- Timely EUL/PQ recommendation (contingent on parallel review) – **within days of approval by NRA / SRA in charge of oversight**
- Translation to in-country decisions or approval – **1 month post EUL/PQ**

* Roadmap for WHO Assessment of vaccine x during the COVID-19 Public Health Emergency
Next steps on WHO regulatory alignment activities for COVID-19 vaccines

- Continue implementation discussions with regional networks & reference NRAs
- Continue engagement & alignment with regulatory bodies (e.g. ICMRA, regional regulatory networks) incl. updates/webinars
- Publish (incl communication cascade) COVAX position paper on barcode/traceability and working position on labelling
- Clarify manufacturers and countries’ responsibilities on barcode/traceability/labelling
- Respond to issues raised to the COVAX Regulatory Advisory Group (WHO co-chairs)
- Continue support for planning of post-marketing / safety monitoring in countries
- Update on best practice principles for regulatory “agility”
Additional information EUL:

Procedure and Questions and Answers

https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/EUL_PQ_Vaccines/en/

Target product profile


Evaluation criteria and EOI. https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/resources/1_EOI-Covid-19_Vaccines.pdf?ua=1

Roadmap https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19

Contact: EUL@who.int
Backup
WHO’s ongoing COVAX regulatory work

• **Alignment ongoing** (Regulatory Advisory Group, ICMRA*, regional regulators)

• Biweekly regulatory updates, 15 regional update webinars

• **Documents published**
  - EUL procedure (Jan), Q&A (Jul)
  - Draft consideration criteria (Sep)
  - Expression of Interest (EoI) (EUL/PQ) (Oct)

• >10 dedicated company meetings hosted prior to EoI publication

• **Roadmap template** ([https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19](https://www.who.int/publications/m/item/roadmap-for-evaluation-of-astrazeneca-azd1222-vaccine-against-covid-19))

• **Safety preparedness manual**
  - PV Preparedness checklist, AESI definitions, active surveillance methods, guidance on RMPS, PSURs, data sharing platforms, reliance, work-sharing and risk communications

*ICMRA International Coalition of Medicines Regulatory Authorities*
## Features of PQ and EUL

<table>
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<th>Prequalification (PQ) 1987</th>
<th>Emergency Use Listing (EUL) 2015</th>
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<tbody>
<tr>
<td>• Review of extensive quality, safety and efficacy and PSPQ for international supply</td>
<td>• Risk benefit assessment of essential set of quality, safety and efficacy data for use during PHEs</td>
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<tr>
<td>• Assessment performed by WHO independent experts</td>
<td>• Rolling review of data</td>
</tr>
<tr>
<td>• Reliance on WHO Listed Authority (WLA) - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)</td>
<td>• Assessment performed by WHO independent experts in collaboration with National Regulatory Authorities (WLA)</td>
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<tr>
<td>• Pre-submission meetings encouraged</td>
<td>• Reliance on WLA - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)</td>
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<tr>
<td>• Post-PQ monitoring</td>
<td>• Pre-submission meetings encouraged</td>
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<tr>
<td>• Reassessment/requalification</td>
<td>• Post-deployment monitoring</td>
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<td>• Time limited recommendation</td>
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<td>• Development should continue for MA/PQ</td>
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Regulatory alignment, authorization and country processes
Context & need for global regulatory alignment

- **Rapid globalization** of supply chain of medical products & technologies (clinical trials, manufacturing, marketing, distribution)\(^1\)
- **Patchwork** of regulatory requirements & processes globally
- **Uneven global regulatory capacity** for new drug approval
- **Duplicated efforts** for a given product submitted to agencies in different countries\(^1\)
- **Increased time and cost** to bring new drugs to market\(^1\)
- **Barriers to assurance of drug efficacy/safety & efficient dev. of novel treatments**\(^2\)
- **COVID-19 context** calls for greater scale of cooperation (large number of vaccines under development and large number of countries to benefit from such vaccines)

Need for **multilateral strategic coordination of regulatory efforts**

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