Regulatory alignment and authorization of vaccines under EUL/PQ

Developing Countries Vaccine Manufacturers' Network

21st Annual General meeting

"Vaccines, a healthy future"

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Department of Regulation and Prequalification (RPQ)

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World Health Organization

Goal & objectives

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

- 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

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Development criteria	Submission requirements	Assessment process	In-country approval for use & post-approval monitoring

Efficacy

Safety

Quality

Programmatic suitability

WHO EUL/PQ evaluation

NRA/SRA independent assessment

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

✓Completed • Ongoing ☐Details on following slides

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

- **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

☐ Detailed in following slide

Labelling • Goes beyond regulatory processes; national exemptions from legal requirements will be needed	›	**Progress on regulatory agreement on single label (model)** – finalizing WHO/PQ & EU alignment; WHO DG letter to countries?
Bar codes on **secondary packaging** (i.e. carton) to support traceability	›	**Preferred characteristic** by UNICEF[1]
Bar codes on **primary packaging** (i.e. vials) to support traceability and monitoring	›	**Optional** but not as a replacement for other printed label information
QR codes *in lieu* of statutory labelling information printed on the **vial and/or inserts**	›	**Not acceptable**
QR codes *in addition* to statutory labelling information printed on the **vial and/or inserts**	›	**Acceptable**
Translated inserts	›	**Expected**

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

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Risks	Solution space
Specific legal exemption required for acceptance of a single labelling model (& language) in many countries	**Letter from WHO DG/COVAX – part of T&C?**
Lack of local language versions posing potential risks to HCPs and subjects	**Compensation by training** – responsibilities need to be defined
Undefined information behind QR codes (when QR codes are proposed)	**Clear definition and mechanism** of what can be updated via the QR codes – e.g. expiry date, indications, take over printing of translated leaflets
Vulnerability to misuse and product diversion (grey and black market)	**Printing** expiry date on vials & **time-limiting** those without expiry date
Lack of **manufacturers understanding of requirements on inserts translation**	**Communication** to manufacturers
Vaccine Vial Monitors not possible	**Manufacturer and country obligations** to be clearly communicated

Illustration: WHO COVID-19 generic vial label & vaccine carton

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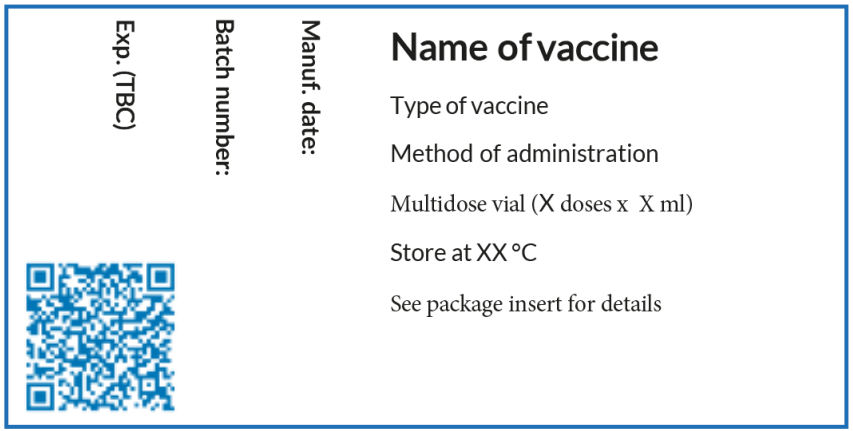
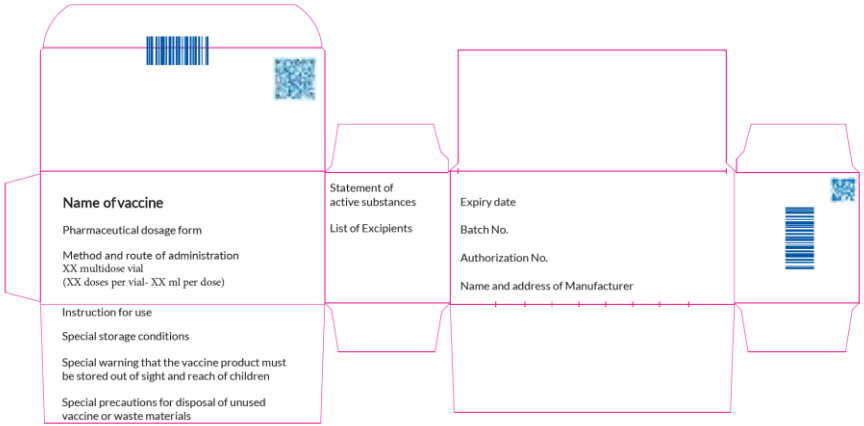
Generic vial label



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)

Areas of COVID-19 specific guidance

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
- Follow-up in clinical trials
- Requirement for a risk management plan
- Specific data:
  - Clinical efficacy data
  - Immunogenicity data
  - Duration of protection
  - Indirect effect
  - Target populations
  - Safety data
  - Benefit risk assessment report

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

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**

Source: https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf

WHO regulatory alignment roadmap for COVID-19 vaccines: overview of recognized pathways, and summary of related alignment activities

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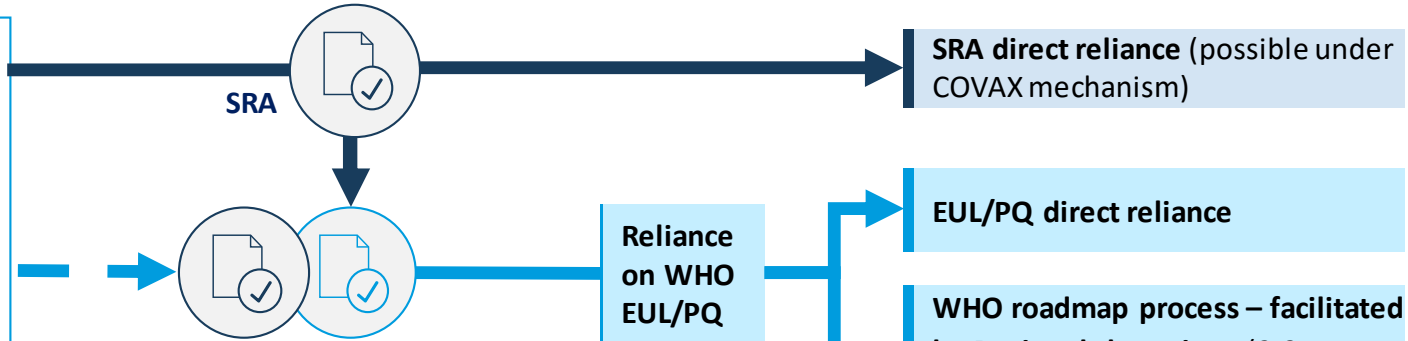
Submission requirements	Assessment process	In-country approval for use & post-listing monitoring

Data in dossier:
- Efficacy
- Safety
- Quality

Inspection data (GMP, GCP, GLP, GVP)

Lot release data

Etc...



- **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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1. Preliminary activities	2. Launching of EOIs	3. Submissions & assessment	4. Recommendation for listing	5. Post-listing monitoring
• **Global regulatory cooperation** • Establishment of **strategies for expedited approval** in participants & post-listing monitoring	• **Manufacturers EOIs** (Phase IIb/III & approval by NRA/SRA in charge of oversight within 6 months & compliance with criteria for assessment) • Discussions on **rolling submission** procedure	• Establishment of **assessment pathway** according to NRA/SRA in charge of oversight • Establishment of **Review Committee** (NRA/SRA in charge of oversight & regulators /reviewers from potential user participants)	• **Approval** granted by NRA/SRA in charge of oversight • **Advisory committee** convened (post-listing commitment) • **WHO EUL/ PQ recommendation** with conditions	• Implementation of **strategies for safety, quality & effectiveness monitoring** • **Validity of listing** based on new data generated • Possible **conversion of EUL to PQ**

COVAX | EUL/PQ | NRA reliance on EUL/PQ

Facilitated access to countries

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

* *Roadmap for WHO Assessment of* vaccine x *during the COVID-19 Public Health Emergency*

Setting expectations…

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* vaccinex *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

https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true

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

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WHO/Otto B.

WORKING TOGETHER

Department of Regulation and Prequalification, WHO

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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
- **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

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Prequalification (PQ) 1987

- Review of extensive quality, safety and efficacy and PSPQ for international supply
- Assessment performed by WHO independent experts
- Reliance on WHO Listed Authority (WLA) - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings encouraged
- Post-PQ monitoring
- Reassessment/requalification

Emergency Use Listing (EUL) 2015

- **Risk benefit assessment of essential set of quality, safety and efficacy data for use during PHEs**
- **Rolling review of data**
- Assessment performed by WHO independent experts in collaboration with National Regulatory Authorities (WLA)
- Reliance on WLA - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings encouraged
- **Post- deployment monitoring**
- **Time limited recommendation**
- **Development should continue for MA/PQ**

Regulatory alignment, authorization and country processes

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1 Context & need for global **regulatory alignment**

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- **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**

1 "International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary." Forum on Drug Discovery, Development, and Translation. V. Weisfeld and T.A. Lustig, Eds. National Academies Press (US), Washington (DC). 24 Oct. 2013. Web.
2 Zerhouni, Elias and Margaret Hamburg. "The need for global regulatory harmonization: A public health imperative," Science Translational Medicine. 8:338 (2016).