

Q&As developed by the COVAX Regulatory Advisory Group (RAG):

1. Labelling, carton and insert requirements.

Background

- Two imperatives are regarded as key during COVID-19 pandemic situation:
 - Speed of introduction of new vaccines
 - Flexibility of world vaccine supply (i.e. any vial could go anywhere at any time)
- The current regulatory environment is not conceived able to accommodate to the imperatives above. Requirements for labels, carton, insert differ from country to country; these contents need to be approved prior to vaccine distribution to markets and their printing and implementation cause delay.
- WHO has published a draft paper addressing these items (see reference material nr 1 under the “Background materials” section).
- IFPMA packaging experts work on “What would have to be true to get maximum speed and flexibility of COVID-19 vaccine supply” concluded the key to meet the above mentioned imperatives is to avoid any country-specific requirements (label, carton, insert).

The following situations and proposals (based on WHO draft paper) were put forward to the RAG for discussion and alignment:

Primary Package: The Label, Expiry Date and Vaccine Vial Monitor

Label:

Situation	Vaccine label is different from country to country (i.e. local language, unique numbering format, etc.).
	Existence of country-specific inventories (segregation of vaccine material upon country).
	Labels are to be approved by country. Market introduction is slowed down due to printing, labelling, and packaging activities.
Proposal(s)	The use of a generic, single language label for all markets globally using readable formats. This avoids segregation of material upon market-specific labels.
	The use of barcode in the label (in addition) is optional.
	Training materials can be made available well in advance to ensure correct label readings.

Expiry date:

Situation	Shelf-lives (SL) being approved in initial filings are not expected to be very long due to limited availability of product-specific stability data.
	SL will need to be modified/extended during the 6-12 months after approval and upon collection of real-time stability data.
	Printing expiry dates on the label can only happen after approval, which would limit the period of usage for the vaccine within the approved SL. This could also lead to premature disposal of vaccine and significant wastage.
Proposal(s)	Information to provide in the label is: lot number; manufacture date; place to consult expiry date (a website pointing to a site with expiry date per lot).

	Expiry date would be maintained by the vaccine developer and updated in real time.
	Information to be on human readable format while the use of barcode is optional.
	The proposed approach would be transitioned towards a more conventional expiry date format on a product-by-product basis.
	Placing a sticker onto the carton with the expiry date at the last point where internet availability is certain could be envisaged, in case of risk for no internet access at point of vaccine use. This would be the responsibility of the market.

Vaccine Vial Monitor (VVM):

Situation	VVMs are used for UNICEF-distributed vaccines.
	Vaccine manufacturers select a VVM type based on corresponding stability studies. This kind of dedicated studies may not be available for initial filings/approvals due to resources and time constraints (unprecedented vaccine development speed).
	Distribution of vaccines could be restricted if VVM is required.
Proposal(s)	Optional use of VVM for the first 18 months after initial market approval (i.e. “grace period”). After the 18-month grace period either use of VVM or proper justification for non-use. <i>Note: this proposal is not aligned with the WHO 30 October draft guidance on Barcodes, Labeling and Serialization; that guidance lists the “Use of Vaccine Vial Monitors (VVMs) as a preferred product characteristic.”.</i>

Secondary Package: Cartons, Serialization numbers and QR codes

Carton:

Situation	Vaccine label is different from country to country (i.e. local language, unique numbering format, etc).
	Existence of country-specific inventories (segregation of vaccine material upon country).
	Cartons are to be approved by country. Market introduction is slowed down due to printing, labelling, and packaging activities.
Proposal(s)	The use of a generic, single language carton for all markets globally. Lot-specific information will be in human readable format and GS1 barcode format. Link to be included (human readable and digital formats) pointing to a site in which expiry date can be consulted.
	UNICEF, the World Bank and GAVI are developing a global repository to harmonize uptake and systems in low- and middle-income countries. The use of a generic, single language carton supports this activity.
	Training materials can be made available well in advance to ensure correct carton readings.

Serialization number:

Situation	Serialization provides with a means to avoid products being illegally diverted. A unique serial number is given to each carton to create a unique identity of each carton.
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	<p>Serialization exists today for vaccines in only 17 market areas, with each market area having a different and unique serialization system. Products with serialization codes for one market cannot be read in another market. Thus, the world has 17 unique market systems, and the rest of the world has no such systems.</p> <p>Taking the approach of attempting serialization while undergoing the largest inoculation campaign in human history would put installing a global system on critical path to distribution.</p>
Proposal(s)	<p>Use of unique serialization numbers where/when possible immediately. If not doable, a waiver could be accepted during the first 9 months after market approval with intention to implement 12 months after approval.</p> <p><i>Note: this proposal is NOT aligned with the WHO 30 October draft guidance on “Barcodes, Labeling and Serialization”.</i></p>

QR code on carton:

Situation	Package leaflet can be separated from carton in the field.
Proposal(s)	<p>Separate leaflet from carton by using a QR code printed on the carton. The QR code would have a multi-language (6 UN languages) caption to prompt the user to a website where the user could choose the insert for that country.</p> <p>Use of QR codes allows for quicker update of latest approved information.</p>

Inserts

Electronic insert:

Situation	Insert is different from country to country (same situation as for label and carton).
	Existence of country-specific inventories (segregation of vaccine material upon country).
	Inserts are to be approved by country. Market introduction is slowed down due to printing activities.
Proposal(s)	<p>Generic and simplified insert supplied with each carton, which has basic information in a standard set of languages. It contains also a QR code that leads to the full insert in the desired language (following approved insert in the country chosen).</p> <p>Alternative approach to electronic insert: countries to be responsible for printing the insert from the website and distributing it to practitioners who would be administering the vaccine.</p> <p><i>Note: this proposal is not aligned with the WHO 30 October draft guidance on “Barcodes, Labelling and Serialization”.</i></p>

Background materials:

1. WHO draft paper on “Bar-codes, QR codes and Vaccine Vial Monitors in the context of COVID-19 vaccines” (WHO Draft from 30 October 2020; Working Version 2.1; last accessed 27 November 2020).

<https://www.who.int/publications/m/item/bar-codes-qr-codes-and-vaccine-vial-monitors-in-the-context-of-covid-19-vaccines>

2. WHO working position on “Model packaging for COVID-19 vaccines – WHO working position” (WHO working position from 4 November 2020; last accessed 27 November 2020)
<https://www.who.int/teams/regulation-prequalification/eu/covid-19/covid-19-model-packaging>

3. GS1 Standards

<https://www.gs1.org/industries/healthcare/standards>

Questions:

Considering the above-mentioned background, does the RAG agree that the following approaches for COVID-19 vaccines will satisfy vaccine user needs while meeting regulatory intent, and that risks outlined can be well-mitigated, again meeting regulatory intent?

RAG Answers

Different positions emerged within the RAG depending on the region, primarily due to differences in the legal frameworks in place in these regions. The positions are reflected here under.

In EU it was acknowledged that the use of generic labels for harmonisation purposes is easier to agree for small vials as compared to cartons. This is due to the different legal requirements at the national level (the so called “blue box”). It was mentioned that printed leaflets are still required. Further it is understood that QR codes represent the best option currently available for the provision of expiry dates while vaccine manufacturers are producing at risk and assignment of expiry dates prior to approval is not possible. In view of this, the QR code is an appropriate option for initial vaccine access. After authorization, this may not be the way forward since there are difficulties for some people to get access to information via this tool.

EMA supports having serialization and mentions that companies recognise this is important to counterfeit medicines. EMA has recently published a Q&A document about labelling (see https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf).

In other regions, such as the US, it was noted that implementation of the proposals as brought to the RAG (use of QR codes on carton, avoidance of expiry date on vial labels/cartons, electronic package inserts), are possible in case of COVID-19 vaccines made available under Emergency Use Authorization (EUA). However, it was stressed that these same flexibilities cannot be sought for licensed products.

A similar level of flexibility was noted by another region (Canada) in which Interim Orders are deployed for initial access to COVID-19 vaccines. Such a legal mechanism allows flexibility to accommodate to the proposals brought to the RAG (manufacturing date instead of expiry date, QR codes, etc). The requirement for local language is considered key, however it can be accommodated via electronic formats. With respect to VVMs, Canada does not see the regulatory benefit in those and considers instead more relevant to conduct stability assessments under appropriate statistical methodologies.

A different region (Brazil) mentioned the importance to discuss with the National Immunisation Programs since they understand better the particularities of each country, in particular the element related to access to technology in remote areas. It was also highlighted that in certain regions it will be important to define how the cold chain is to be monitored during vaccine distribution if there is no VVM used. Therefore, it was regarded as key to discuss and agree risk minimisation strategies with the National Immunisation Programs prior to marketing authorisation and vaccine distribution.

Lastly, one RAG member encouraged WHO/CEPI to develop a symbolic language that could be used in future pandemic situations to overcome language-related challenges.

WHO closed this topic mentioning a final guidance document will be prepared.

2. Reliance proposal for CMC Post approval Changes to maintain vaccine supply to Global patients.

Background

- Definition of Reliance (WHO Working document QAS/20.851 June 2020): The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others
- Due to the accelerated development of COVID-19 vaccines, it is anticipated that a lot of CMC information will have to be submitted post-approval to complement the initial Marketing Authorisation, and that a significant number of post-approval changes (PACs) will be needed to reflect the maintenance and optimization of the manufacturing process, plus the timely addition of manufacturing and testing capacity.
- There is a high risk that COVID-19 vaccines experience shortages or discontinuities in supply as a result of difficulties in meeting standard regulatory lifecycle management expectations. This could even be exacerbated if heterogenous regulatory requirements from Health Authorities worldwide result in differences between countries in the approved manufacturing process (e.g. duration of a manufacturing step) or control strategy of the vaccine.
- Three key challenges have been identified once COVID-19 vaccines will be in post approval/life-cycle space:
 - Massive increase in volumes of PACs as compared to “conventional” vaccines: A high number of PACs are expected already shortly after approval for a high number of market approvals (approval likely in more than 100 countries within a few months’ timeframe).
 - Lengthy global approval time (a given change can take up to 4 years or more to be approved worldwide, reference is made to document number 1 under section the “Background materials” section).
 - Lack of global alignment will prevent sustainable global supply of COVID-19 vaccines for patients (i.e. country-dependent regulatory processes; different requirements, review and approval timelines; numerous countries in the world require approval of the PAC in a reference country (usually the country of origin where the vaccine is manufactured; added complexity where multiple supply chains for COVID vaccine) before starting their own review; time for implementation of the change, etc.).

Accelerated, reliance-type approaches to enable efficient global introduction of changes are essential to COVID-19 patients. Making use of the many reliance or recognition processes that already exist world-wide may be possible, including countries such as: Australia, Egypt, Jordan, Saudi Arabia, South Africa, and at least 14 countries in the LATAM region (e.g. Brazil, Mexico, Argentina, Peru), as well as ACSS and EAEU recognition pathways.

In view of the above, the following situations and proposals were put forward to the RAG for discussion and alignment in the context of reliance mechanisms for COVID-19 PACs:

Use of reliance and recognition as key enablers

Situation	Lack of alignment on data requirements and timings for PACs can lead to repetitions and inconsistencies resulting in delays and vaccines shortages.
	A number of reliance processes are already in existence globally, which could be applied directly or adapting to meet the need to manage PACs efficiently for this pandemic situation.
Proposal(s)	Alignment on data requirements and timings for PACs.
	Requirements should always be science- and risk-based, taking into account considerations such as the control strategy and companies' approaches to ongoing process verification.
	Upfront alignment would facilitate reliance mechanisms, as fostered by WHO for the review and approval of PACs (reference is made to document number 4 under the "Background materials" section). This is even more essential in the context of a global emergency.

Use of global regulatory tools

Situation	Regulatory tools such as PACMPs are already implemented in some regulations (including the WHO guideline on post-approval changes for vaccines; reference is made to document number 5 under the "Background materials" section). However, one of the current limitations for the use of PACMPs is the fact that this mechanism does not exist in the vast majority of countries.
Proposal	Develop regulatory mechanisms (such as PACMPs) beyond ICH regions to facilitate the management of some PACs.

Use of science- and risk-based approaches

Proposal	A science- and risk-based approach could be used to assess PACs related to manufacturing and to support changes in analytical methods and technologies, for example in bridging/equivalence studies, with "the same" interpretation accepted globally, grounded on performance expectations for the test, considering the test purposes (reference is made to document number 7 under the "Background materials" section).
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Background materials:

1. The complex journey of a vaccine – Part I; The manufacturing chain, regulatory requirements and vaccine availability; IFPMA; 2014.
2. PDA conference on Vaccines / Malaga-Spain / Vaccine life cycle management complexity / A Deavin & T Gastineau, 2018.
3. Alignment in post-approval changes (PACs) guidelines in emerging countries may increase timely access to vaccines: an illustrative assessment by manufacturers. N Dellepiane et al. Vaccine: X 6 (2020)100075.
4. WHO working document on "Good reliance practices in regulatory decision-making: high-level principles and recommendations" (draft QAS/20.851 from June 2020; last accessed 27 November 2020).

https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_good_reliance_practices.pdf?ua=1#page=2

5. WHO “Guidelines on procedures and data requirements for changes to approved biotechnological products” (Expert Committee on Biological Standardization, Geneva 17-20 October 2017; last accessed 27 November 2020).

https://www.who.int/biologicals/expert_committee/PAC_highlighted_20_Oct_2017.HK.IK.pdf?ua=1

6. NASEM report on reliance, “Considerations for effective regulatory reliance – an Industry perspective” (IFPMA, 2019)

<https://doi.org/10.17226/25594>

7. PDA, “Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry One-Voice-of-Quality (1VQ) Solutions” 2020:

<https://journal.pda.org/content/early/2020/05/28/pdajpst.2020.011734>

Questions:

It is acknowledged that worldwide reliance brings a high challenge, in particular with regards to review of local regulations in a such a short period of time. In spite of these challenges, developing reliance mechanisms, by global leveraging the WHO draft principles and recommendations on Good Reliance Practices (reference is made to document number 4 under the “Background materials” section) is likely a more efficient way to streamline the overall process of PACs approval, make best use of resources, prevent vaccine shortages and, most importantly, meet the needs of global patients waiting for a vaccine.

For COVID-19 vaccines:

- Can existing and “new” reliance procedures also be applied to the CMC post-approval setting, predicated on the acceptance of an approval from a stringent Authority?
- This includes agreeing to a set short timing (for example 15 working days) for approval. The WHO proposals help in defining how this might work in an emergency situation such as the current COVID-19 crisis (reference is made to document 4 under the “Background materials” section).

RAG Answers

In Europe the legal and regulatory framework does not permit to rely on the review performed by other jurisdictions. The inverse mechanism is possible, i.e. European review can facilitate the review in other regions. It was noted that the European framework has been shown to be helpful in moving forward the PACMP mechanism, which is now firmly established in this region. In the scope of the current pandemic further flexibilities on how to put PACMS in initial filings are to be expected for vaccine developers thereby allowing the subsequent filing of post approval changes via downgraded variations. Despite it is considered that data requirements and timings are clearly defined in the current framework, European regulators are prepared to accelerate the published timelines on a need basis and to explore widening the scope of the existing PACMPs. It was pointed out that even if ICH Q12 is not fully implemented in Europe yet, its elements can be supportive to foster accelerated approval (ICH Q12: <https://www.ema.europa.eu/en/ich-q12-technical-regulatory-considerations->

[pharmaceutical-product-lifecycle-management](#)). It was also recognised that a high number of PACs will take place. Utilization of upcoming ICH Q14 principles for a risk-based approach for analytical methods is not foreseen for this pandemic yet (ICH Q14 concept paper: [Q2R2-Q14 EWG Concept Paper.pdf](#)). Rapid changes using exceptional PACMPs is possible and guidance on this area is published on EMA's website.

One region (Brazil) described a reliance procedure already in place in their jurisdiction for marketing authorization (MA) and PACs. This procedure relies on the evaluation from EMA and/or FDA to allow for faster evaluation by the local Health Authority (HA). Companies wishing to apply for this procedure should present the whole documentation package as required by the Brazilian regulatory framework together with the full assessment reports issued by either of the mentioned HAs. It was highlighted that the final benefit-risk assessment is done by the local Brazilian HA. Further, it was mentioned that this procedure is regarded more efficient for CMC, provided the product approved by FDA and/or EMA is exactly the same as the one submitted to Brazil (i.e. same manufacturing sites, same specifications). Some differences can be accepted, for example for storage conditions and in-use stability conditions due to differences in climatic zones. The reliance process speeds up the local evaluation and decision-making process. The applicant is requested to keep full transparency and provide all information regarding previous discussions with EMA and/or FDA.

With regards to the proposed short timings for approval (example of 15 working days), both the European and USA regions indicated it would be difficult to achieve such a timeline for complex PACs (i.e. in Europe type II variations). However, both HAs expressed their willingness to discuss with vaccine manufacturers on a case-by-case basis and do their best to accelerate as much as possible.

In conclusion, it was recognised that, despite the existence of stringent regulatory authorities that can be relied on, a global perspective is still missing. WHO was called upon to advocate a reliance philosophy. Last, it was regarded necessary that relying NRAs commit to finalising approval within acceptable timelines.

3. Testing and batch release

Background

- Challenges regarding the batch release testing of COVID-19 vaccines had been previously brought for discussion to the RAG (reference is made to document number 2 under the "Background materials" section).
 - A request to apply emergency measures across National Control Laboratories (NCLs) had been raised, to reduce risks of increasing batch release timelines, loss of stability period, and consuming additional resources at both the NCLs and manufacturers.
 - Reliance on batch releases had been identified as key mechanism to prevent vaccine shortages across the globe.

During the RAG November meeting, additional points about batch release testing were presented to the RAG for consideration, as follows:

Use of reliance and recognition of batch release authorities as reference

Situation	Few quantities of vaccine samples and few reagents are expected to be available to enable test transfers to all NCLs who would request for a local testing, in addition to the testing performed by a reference control laboratory (i.e. OMCL in the EU).
	The initial shelf lives of COVID-19 vaccines will be limited due to limited data on stability at time of initial regulatory approvals. Any extended time required to

	execute additional local batch testing would inevitably result in a reduction of the residual shelf life remaining for the vaccine, leading to a situation where inappropriate shelf-life time is available at the end-user level. This would result in the loss of compliant vaccine doses which would not be able to be used for vaccination.
	Transferring test methods to multiple NCLs within the same and very tight timeframe will unlikely be possible from a technical and limited expert resources point of view at manufacturers level.
Proposal(s)	Agreement to reach between all countries (NCLs) in the world on the release tests so that they align with local requirements. European OCABR certificates could represent an appropriate reference.
	Agreement to reach between all stakeholders (regulators, WHO, manufacturers) on the type of document(s) which would be necessary and sufficient for the batch release in the importing countries (release certificate only, detailed test results, etc).
	Agreement to reach on the process to upload release certificates (or other information) in a WHO SharePoint. In order to ensure appropriate confidence, OMCLs could directly upload the agreed upon information (provided concerned manufacturers written consent is given) into the WHO SharePoint, which access would be available to all NCLs who adhere to the reliance/mutual recognition agreements.

Background materials:

1. WHO working document on “Good reliance practices in regulatory decision-making: high-level principles and recommendations” (draft QAS/20.851 from June 2020; last accessed 27 November 2020).

https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_good_reliance_practices.pdf?ua=1#page=2

2. Frequently asked questions on regulation of COVID-19 vaccines. Q&As developed by the COVAX Regulatory Advisory Group (RAG) 22 October 2020; last accessed 27 November 2020.

<https://www.who.int/publications/m/item/frequently-asked-questions-on-regulation-of-covid-19-vaccines>

Questions:

This topic was brought to the RAG for update purposes only, with no additional questions being raised. A set of proposals were brought to the RAG for discussion (see Background section above).

RAG Answers/Discussions

Some RAG members reiterated the constant efforts put forward to discuss with multiple stakeholders such as industry associations, OCABR network and advisory group, vaccine manufacturers association. It was acknowledged that having one single agreement for all countries worldwide aligned with local release testing requirements remains difficult at this stage.

A mechanism based on mutual recognition would need to be built far in advance and this is not foreseen as an option in the current timeframe and global situation. Instead, the RAG was generally

in agreement that reliance is the most feasible process that can be considered since this is already reflected in the current practice, as applied by many vaccine manufacturers.

It was mentioned that some countries outside the European region are already relying on OCABR certificates, in some instances this certificate is a pre-requisite. With regards to sharing detailed test results, it was highlighted that this is not current practice in the OCABR network. Certificates are shared amongst the European countries based on mutual recognition, however, detailed results for every batch are not shared since it is not considered of added value. Also, this would require prior agreements from vaccine manufacturers accepting that sharing of data.

Equally, vaccine manufacturers can decide to share the certificates with Regulatory Authorities outside the European Union (EU). Due to this, the proposal to have a WHO database in which certificates could be uploaded was not considered essential. In addition, it was commented that OMCLs' resources are limited, and that they would be better invested in the testing activities rather than the upload of the certificates into that database. It was pointed out that tests for the first vaccines coming into the EU market have already been defined based on discussions held directly with vaccine manufacturers. OCABR guidelines for these vaccines have been recently published (<https://www.edqm.eu/en/ocabr-activities-related-covid-19-vaccines>) and testing will be refined if needed to remain fully aligned with regulatory approvals.

Canada commented that although batch release testing would be done for new products in a normal situation (focusing on some tests like potency and safety), a different approach is being adopted under the Interim Order (IO) framework, given the extremely rapid development times in implementation of tests. The new policy (still to be called "lot release"), will focus on the review and assessment of the manufacturers' own testing data rather than doing batch-to-batch testing separately. The Canadian region considered it is not realistic in this situation to have Agencies (external to manufacturers) establish reliable assays that would be comparable in reproducibility and quality to those of the manufacturers and that it could even result in a barrier to distribution of perfectly valid lots. The Canadian Agency plans to establish parallel testing with a different scope, i.e. assessment of assays robustness. It was pointed out that Canada will require Certificates of Analysis (CoA) to be filed as well as a lot disposition document to report on the number of lots being manufactured, aborted, failed in testing etc. This approach will be applied until products move into full licensure, at which time a more routine testing approach will be adopted. Canada mentioned that OMCL certificates would be acknowledged though not required.

In Europe, it was commented there is no reliance on countries outside the European Economic Area (EEA), unless a mutual recognition agreement exists, such as for example with Switzerland and Israel. Further to that, it was highlighted that there exists a high level of confidence in the EDQM and OMCL Network to deliver batch release testing in the usual manner and without delays. Batch release testing was considered of key importance to build public confidence in these vaccines.

Japan commented on their plan to conduct a minimum number of tests and to rely on testing performed by other countries. This was considered acceptable for Covid-19 vaccines.

Singapore fully supported reliance on other authorities for batch release testing and highlighted their willingness to rely on OCABR testing.