

Technical Brief: Regulation of COVID-19 Vaccines

Synopsis from the August to November 2020 COVAX RAG meetings

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Organization

Overview

The vaccine pillar, COVAX, of the [ACT accelerator](#) has established a Regulatory Advisory Group (RAG) which is co-led by WHO and CEPI. The RAG has members from Regulatory Agencies covering all WHO regions, including Argentina, Australia, Brazil, Canada, Europe (EMA & EDQM), Ghana, Japan, Singapore and USA.

COVAX also supports vaccine developers on general matters related to vaccine development. Working groups, so called SWAT teams, have been established for manufacturing, clinical development/operations and enabling sciences to support vaccine developers in solving product agnostic challenges in COVID-19 vaccine development. The SWAT teams have members from various stakeholders such as BMGF, WHO, GAVI and industry organizations (IFPMA and DCVMN).

The RAG was set up to give feedback on regulatory science questions of an agnostic nature raised by the COVAX SWAT teams in order to promote regulatory preparedness among COVID-19 vaccine developers. Feedback from the RAG is communicated back to the COVAX SWAT teams. It is also presented here, in the form of a Technical Brief, for the benefit of all COVID-19 vaccine developers and for the wider community of regulatory authorities.

The RAG applies the Chatham House rule, and divergent views are reported as such without attribution. However, for some subject matters, the RAG members have agreed that country specific recommendations/guidance may be reported/attributed.

The first Technical Brief was published by WHO and covered the August-October 2020 meetings. This Technical Brief replaces the previous publication by including information discussed in the November 2020 RAG meeting, where indicated as “update”.

For any questions, please contact COVAX-Reg@who.int.

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General

Coordinated feedback from Regulators

Requests to the RAG:

How can vaccine developers obtain a more coordinated feedback from regulatory authorities during the COVID-19 pandemic?

Feedback (provided in Aug-Oct 2020):

The RAG recognized that the COVID-19 pandemic situation is highly challenging and that there was a clear need for pragmatic and timely solutions to obtain coordinated responses from regulatory authorities. Thus, RAG members encouraged developers to simultaneously approach several agencies in parallel, e.g. four, including at least one stringent regulatory authority, in different geographic regions with the same data package and give permission to allow the agencies to exchange information and discuss a coordinated feedback.

Even if there were only a limited number of mutual recognition arrangements in place among regulatory agencies globally, it was considered that in the time of a pandemic coordinated advice given by several agencies would more easily be accepted by other regulatory agencies. There was however a note of caution. It is not certain that all approached regulators would necessarily agree.

Manufacturing, quality control, stability and labelling

Risk-based validation approaches

Background information provided by vaccine developers:

The unprecedented scale at which vaccines for COVID-19 must be manufactured has required many developers to use multiple Drug Substance (DS) (often 2 or more) and Drug Product (DP) (often 3 or more) sites nearly simultaneously. These sites are often located around the globe, representing manufacturing in many different countries and, often, in many different regions, highlighting the need for a common approach across different regulatory agencies and regional authorities. Additionally, some sites may have been recently renovated to accommodate new unit operations or elements of the manufacturing process for the newly introduced COVID-19 vaccine.

Process validation is an important element of ensuring control, both within a site and across sites. Given the need to perform process validation on processes and scales relevant to those that will be used for making vaccines for launch, process validation by necessity is one of the later steps in process development and can, in cases where clinical development has been accelerated, be rate-limiting for regulatory approval.

However, ICH Q9 provides for risk-based approaches to validation but different national regulatory authorities (NRAs) have developed their own requirements for the types of data required and timing

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for availability of said data. A common approach across all NRAs that recognizes appropriate risk-based approaches would help ensure fast and equitable access to vaccines.

Requests to the RAG:

Can all relevant NRAs recognize risk (based on [ICH Q9](#)) for defining the appropriate levels of validation for equipment, process and analytical methods at time of submission, applying thinking in terms of benefit to patient, allowing companies to manage aspects within their performance, quality and safety, or receiving data as post approval commitments, for example concurrent validation, with drug product validation being a post approval commitment as suggested in [recent FDA guidance documents](#)?

Feedback (provided in Aug-Oct 2020):

The RAG considered that, in principle, the tools outlined in [ICH Q9](#) could be applied. However, members were strongly of the opinion that a risk-based approach to process validation, where data usually submitted at the time of license application could be deferred and submitted post-licensure, should be decided on a product/process specific basis. Such a decision would depend on the previous experience the developer had with the platform and process, the data available to qualify the process with the proposed antigen, as well as the data to demonstrate that the process was under control. In addition, the history of compliance by the manufacturer in question would be a factor.

It was emphasized that shifting any part of process validation submission to post-licensure would need to be discussed and agreed with the regulators well before license submission. Manufacturers should also agree with regulatory authorities on the implementation plan for providing post-licensure data.

Where multiple site manufacture and scale up was necessary to ensure sufficient vaccine would be available for global markets, the RAG stressed that demonstration of comparability during development would help inform on the validation approach taken.

Vaccine developers are encouraged to consult [ICH Q5E](#). It was recognized that analytical methods for batch release are not validated early in development, but in the initial phase qualified methods could be considered acceptable together with qualified characterization tests.

Requests to the RAG:

De-coupling of drug substance (DS) and drug product (DP) validation: Can DP validation be conducted using DS lots manufactured prior to DS validation, for example DS lots manufactured under cGMP for clinical studies, if sufficient analytical data can be provided demonstrating the analytical relevance of earlier DS lots to the DP lots intended for validation?

Feedback (provided in Aug-Oct 2020):

The use of DS lots manufactured prior to validation of the DS process could be used to validate the DP process, provided analytical comparability is demonstrated between the pre-validation DS lots and the commercial lots. Again, the developers are encouraged to consult ICH Q5E. Overall, the RAG agreed that the issues of comparability of the same vaccine produced at different manufacturing sites, as well as scale up, were particularly challenging in the light of the Covid 19 pandemic and the urgent need for vaccine availability. Developers are thus strongly encouraged to seek scientific advice from regulators.

GMP inspections:

Background information provided by vaccine developers

Good manufacturing practice (GMP) inspections take significant time and human resources to

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include travel time and logistics; none of which at this point in the pandemic are in abundance for any one institution. In addition, travel restrictions are still in effect.

Requests to the RAG:

Could GMP inspections function under the recognition or reliance of prior GMP inspections executed by stringent regulatory authorities?

Feedback (provided in Aug-Oct 2020):

The short answer from several members of the RAG, is yes, GMP inspections could be facilitated by mutual recognition of GMP inspections done by a stringent regulatory authority. Of the RAG members that responded, they acknowledged the challenge of being able to perform an on-site inspection due to travel restrictions and the need to be flexible in these circumstances. One member stated that this would be done on a case-by-case basis and would be done when an application is filed; it would depend on several factors including quality, the relevance of the information that is available and whether travel is possible.

There are a number of mutual recognition relationships that already exist that can be leveraged. Another option is to rely on the GMP inspections performed by WHO PQ team or a PIC/S Regulatory Authority.

Requests to the RAG:

And/or could GMP inspections be performed as a virtual inspection- using remote technologies?

Feedback (provided in Aug-Oct 2020):

RAG members shared that they are utilizing additional tools to determine the need for onsite inspections, which could include a virtual/remote inspection, by:

- reviewing previous compliance history
- mutual recognition
- requesting records for review in advance
- exploring other remote/virtual strategies
- determining eligibility criteria to be inspected virtually could include:
 - o prior inspections by WHO PQ or a PIC/S Regulatory Authority
 - o good inspection history (at least 2 successful inspections ~ 5 years)

Additional information on GMP inspections during COVID-19:

EMA	Guidance on remote GCP inspections during the COVID19 pandemic
US FDA	Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers
Health Canada	Good Manufacturing Practices and COVID-19
HAS Singapore	Handling of Applications and Conduct of Inspections During COVID-19
TGA Australia	GMP approach to overseas manufacturers of medicines and biologicals during the COVID-19 pandemic

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Authority batch release testing of COVID-19 vaccines

Background provided by vaccine developers:

Currently several regulatory authorities have put in place emergency measures for National Control Laboratory (NCL) batch release of vaccines. For example, CBER '[Updated Instructions for Submitting Lot Release Samples and Protocols for CBER-regulated Products During the COVID-19 Pandemic](#)' and TGA '[Physical samples for batch release not required: a reminder for sponsors of biosimilars and biological medicines](#)' have momentarily suspended sample submission and subsequent batch testing since March 2020.

In consideration of the COVID-19 pandemic, it is asked that emergency measures be taken across the NCLs, to reduce risks of increasing batch release timelines, loss of stability period, and consuming additional resources at both the NCLs and manufacturers. Such reliance on batch releases could prevent vaccine shortages across the globe.

Requests to the RAG:

Is there a way to agree on a reduced set of NCL testing for COVID-19 vaccines and establish a mutual recognition of test results e.g., through a NCL network to minimize assay transfers, samples, reagents, etc. and allow focus to be on supply to patients based on manufacturers testing, GMP and controls?

Feedback (provided in Aug-Oct 2020):

As COVID-19 vaccines are being developed and manufactured under highly accelerated timelines, independent testing by NCLs is critical to make sure confidence in the quality and safety of these new vaccines are maintained. The independent control, including batch release testing, will be a key element to counter vaccine skepticism and contribute to good uptake of the first vaccines.

RAG members were, in principle, in favour of the idea of reliance and recognition with regard to authority batch release to avoid duplication of testing, although some countries, due to legal restrictions, are unable to share batch release data. It is important to note that the EU OCABR Network issues batch release certificates based on transparent criteria (available in the OCABR guidelines and in the procedures) which the manufacturers are free to share with NRAs/NCLs outside EU/EEA (see more on OCABR below).

If independent testing must be conducted, NRAs/NCLs should focus on a minimum set of harmonized critical testing parameters, related to identity, potency and where relevant/appropriate safety based on the product profile. The batch release tests should, to the extent possible, avoid in vivo methods, both due to time constraints and accuracy/robustness of the methods.

Ideally there would be a set of tests recognized globally for each vaccine. However, at present, neither a global mechanism for mutual recognition nor establishing harmonized batch release guidelines are available.

The WHO network of national regulatory authorities (NRAs) and NCLs responsible for testing and release of WHO-prequalified or EUL listed vaccines could potentially facilitate a higher degree of batch release recognition even if the network members have no legally binding obligation to recognize the release results from other network members. The network could also be a forum for discussing and agreeing on batch release guidelines for each vaccine. The network currently has members from over 40 countries but is open to new members subject to signing a confidentiality agreement. To leverage on the network's data/information sharing, it is a prerequisite that manufacturers agree that some information related to the quality control testing strategies for their vaccine is shared as well as the results of authority batch release.

Europe:

EDQM coordinates actively the Official Medicines Control Laboratories (OMCLs)/Official Control Authority Batch release (OCABR) network to ensure the continuity of the batch

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release of vaccines in Europe (through the OCABR process). The OCABR process is based on legally binding mutual recognition amongst the member states and prevents duplication of authority batch release of vaccines on the EU/EEA market and officially recognized partners (Switzerland and Israel).

Since the beginning of the pandemic situation, an emergency procedure has been put in place at the OCABR network level to ensure the batch release continuity of existing vaccines in case of capacity issues (e.g. absence of staff) in the OMCLs. Regarding COVID-19 vaccines, EDQM has also actively coordinated the OCABR Network to generate:

- A guidance document to facilitate timely transfer of the tests relevant for the batch release of the different vaccine candidates. The document provides a clarification that the transfer of the tests should be initiated as soon as shown to be fit for purpose to the selected OMCLs without waiting for the final validation of the analytical methods. This document has been distributed to the manufacturers and is available upon request: batchrelease@edqm.eu.
- A capability table to communicate to manufacturers the available testing capabilities of the different OMCLs for each category of COVID19 vaccine candidates. This will help manufacturers to orient their choice to select the appropriate OMCLs (particularly for manufacturers who are less experienced with the process). This document has been distributed to the manufacturers and is available upon request.
- Work is also ongoing within the OCABR network to identify relevant tests for OCABR based on current knowledge of manufacturers' quality control strategies and with a focus on potency and identity in order to develop appropriate OCABR guidelines for the first vaccines expected on the EU market.

Additional information:

EDQM	EDQM batch release for vaccines
OCABR	The EU batch release process (OCABR) is well structured and the OCABR certificate is already recognized in many countries outside Europe. For existing vaccines, a significant percentage of batches which are tested through the OCABR process are used outside the European market (An OCABR certificate is a pre-requisite in many countries outside Europe).

Update (November 2020): Use of reliance and recognition with regard to authority batch release testing

Background information provided by vaccine developers:

- 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.

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Additional background material:

WHO	“Good reliance practices in regulatory decision-making: high-level principles and recommendations” draft QAS/20.851 from Aug 2020; last accessed 27 Nov 2020
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Requests to the RAG:

Would all countries (NCLs) in the world agree on the release tests that are in alignment with local requirement? Could European OCABR certificates represent an appropriate reference?

Could all stakeholders (regulators, WHO, manufacturers) agree 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.)?

Feedback from the RAG (Nov 2020):

Constant efforts are being put forward to discuss these issues with multiple stakeholders, such as industry associations, OCABR network and advisory groups, 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.

Post-meeting update:

On 20 January 2021, WHO has published the [Operational Tool for efficient and effective lot release of SARS-CoV-2 \(Covid-19\) vaccines](#) describing how countries can rely on batch release performed by the responsible NRA/NCL designated by WHO.

Requests to the RAG:

Is there an agreed process to upload release certificates (or other information) in a WHO SharePoint?

In order to ensure appropriate confidence, could OMCLs directly upload the agreed upon information (provided concerned manufacturers written consent is given) into the WHO SharePoint which is accessible to all NCLs who adhere to the reliance/mutual recognition agreements?

Feedback from the RAG (Nov 2020):

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 and NRAs/NCLs. See also the above-mentioned WHO Operational tool for efficient lot release.

Some countries outside the European region are already relying on OCABR certificates, in some instances this certificate is a pre-requisite while sharing detailed test results is not current practice in the OCABR network. Although certificates are shared amongst the European countries based on mutual recognition, detailed results for every batch are not shared since it is not considered of added value. Also, sharing of detailed results for every batch would require prior agreements of each vaccine manufacturer. 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, as OMCLs' resources are limited, they would be better invested in the testing activities rather than the upload of the certificates into that database. 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 and testing will be refined if needed to remain fully aligned with regulatory approvals.

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Health Canada (HC):

Under its risk managed lot release program, HC would typically perform [lot release testing for new products](#), which would be focused on specific tests such as potency and safety. However, a different approach has been adopted under an [Interim Order \(IO\) framework](#) for platform technology-based vaccines manufactured in stringent regulatory jurisdictions. The factors considered with this approach included the extremely rapid product development, short timelines to implement appropriately qualified assays in the HC quality laboratories, as well as the urgency to provide doses of IO authorized vaccines to the market in the face of the pandemic.

The new policy (still considered “lot release” under the IO framework) utilized the submission review and assessment of the manufacturers’ own testing data against clinically related specifications, rather than performing lot-to-lot testing separately. HC considered that imposing agency-based lot-to-lot batch release in this situation, that would be comparable in reproducibility and quality to those of the manufacturers, could potentially be a barrier to the distribution of lots that were compliant with the approved specifications. Simultaneously, HC is to establishing qualified parallel testing for key stability indicating assays to monitor the consistency of manufacturing, assess the impact of changes in assays and assay standards over time, as well as prepare for full licensure applications.

As a risk mitigation strategy, HC requires manufactures to file Certificates of Analysis (CoA) for lots distributed in Canada, as well provide CoAs for all lots for the USA market produced from the same vaccine supply chain that serves Canada. Data from CoAs will be used to broadly monitor consistency of manufacturing.

Manufactures will also be required to provide regular lot disposition documentation for all drug substance and drug product lots manufactured for the Canadian and USA supply chain. This information is to include failed or aborted lots, with a brief description of issue(s) where this is relevant. Lot release letters will not be required prior to distribution, but this could be revisited if there are concerns. See an example of the [Quality Terms and Conditions for a recently approved vaccine](#).

This general approach will be applied under the time-limited IO approvals until products are considered for full licensure. If full licensure is approved, the lot release requirements will be reassessed.

Europe:

There is no reliance on countries outside of its jurisdiction unless a mutual recognition agreement exists, such as for example with Switzerland and Israel. Further to that, there is 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:

It plans 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 supports reliance on other authorities for batch release testing and highlighted their willingness to rely on OCABR testing.

Post-approval changes

Background provided by vaccine developers

- Implementation of significant numbers of post approval changes will be required for vaccines for COVID19, and to support maintenance of many global supply chains impacted by the need to manufacture sufficient capacity of COVID-19 medicines in order to enable supply on

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the scale required, to billions of patients.

- Accelerated, harmonized approaches to enable efficient introduction of changes are essential to COVID-19 patients. This highlights the need for a common approach across different regulatory agencies and regional authorities.
- Examples of post approval challenges will include:
 - o Challenges in scaling-up manufacturing to meet patient demand
 - o Challenges in modifying control strategies to accommodate evolving product and process understanding
 - o Challenges in demonstrating comparability because of limited batch history
 - o Challenges with the ongoing acceptability in the post-approval changes and inspections of novel approaches accepted in the original application (e.g. use of extensive modelling in establishing a shelf-life or retest period)
 - o Challenges in modifying or implementing approved Post-Approval Change Management Protocols (PACMPs) as a result of evolving process understanding
- While aware that most countries have national legal frameworks for handling changes, the possibility of reliance or recognition of approval from a stringent Authority would benefit global patients by removal of supply constraints and potential for vaccine shortages, which may occur under normal Post approval processes which can take 3-5 years to gain global approval. Companies may even opt to delay initial submission, so as to include supply chains if unsure of post approval procedures, with the consequence that this would delay access to vaccine for patients

Potential approaches to improve post approval harmonization will include:

- Data requirements and timings for post approval changes should be agreed early and efficiently through informal or formal scientific advice and globally, minimizing delay, repetition and inconsistency by leveraging reliance mechanisms. Such requirements should always be science and risk-based, taking into account considerations such as the control strategy and companies' approaches to ongoing process verification.
- Concepts such as 'established conditions' e.g. as described in ICH Q12 clearly defining areas to be covered by change controls and areas to be managed within a company performance, quality and safety. Also use of product lifecycle management plans should be considered for COVID-19 medicines
- The use of general/broader PACMPs for types of change e.g. supply changes, could be applied globally.
- Use of Emergency Change Management procedures, as proposed by EMA for supply related changes, should be explored for global application
- For stability and shelf life updating, use of (or greater use of) extrapolation and/or data modelling to predict stability under normal storage conditions more rapidly and to establish shelf-lives for product registration and for post approval changes
- Analytical methods and technologies will more likely change during late development and post approval and that a science and risk-based approach should be appropriate, for example in bridging/equivalence studies, with 'the same' interpretation accepted globally.

Requests to the RAG:

Can Reliance procedures, that may be agreed for marketing authorization application (MAA) processes, also be applied to the post approval setting, with acceptance of an approval from a stringent Authority?

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Feedback (provided in Aug-Oct 2020):

The RAG acknowledged that implementation of a significant number of post approval changes will be required for COVID-19 vaccines to support the maintenance of many global supply chains. Thus, an accelerated and harmonized approach across different regulatory authorities is needed. To achieve this upfront and proactive discussions are needed. So far limited discussion has occurred between regulators in international fora on post-approval change (PAC). Some RAG members acknowledged that this has not been sufficiently explored and regulators should come together to discuss this.

Some of the RAG members said that they would accept a risk-based approach regarding PACs and have a method of recognition based on decisions taken by other stringent regulatory authorities. It was also pointed out that to have comparability protocols in place would be needed to facilitate PAC approvals.

One concern was that changes to both manufacturing process and analytical methods would occur in parallel. This would make comparability very challenging to verify. It was therefore suggested that COVID-19 vaccine developers should aim at keeping a stable analytical strategy as a fundament to make comparability possible after changes to both manufacturing and analytical methods.

Unrelated to COVAX, WHO has been working with industry organizations like IFPMA and DCVMN to see if more harmonization can be achieved. There have been two projects – could look at principles suggested. There is also a WHO guideline for post-approval [‘WHO Guidelines on procedures and data requirements for changes to approved biotechnological products’](#). However, it was acknowledged that there is a need for PAC guidance specific to a PHEIC. A pilot PAC discussion under the leadership of WHO was suggested.

An EMA/FDA joint workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies) was convened in 2018. The aim of the workshop was to discuss between regulators and industry quality challenges and possible scientific and regulatory approaches which could be used to facilitate development and preparation of robust quality data packages, to enable timely access to medicines for patients whilst providing assurance that patient safety, efficacy and product quality are not compromised.

The meeting report [‘Meeting Report: Workshop with stakeholders on support to quality development in early access approaches’](#) provides describes some scientific elements and regulatory/procedural tools that is relevant to Process Validation and PACs.

Requests to the RAG:

Risk-based post approval approaches: Can all relevant NRAs recognize risk (based on ICH Q9), applying thinking in terms of benefit to patient, allowing companies to manage aspects of minor changes, within their performance, quality and safety (PQS)?

Feedback (provided in Aug-Oct 2020):

In principle, was agreed that based on ICH Q9 could apply, but it was also pointed out that due to different legal requirements in countries, to obtain global recognition/reliance could be challenging.

Update (November 2020): Reliance and CMC post-approval changes

Background provided by vaccine developers

- 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

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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 Authorization, 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 heterogeneous 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:
 - o 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).
 - o 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).
 - o 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 avoid delays in access to COVID-19 vaccines. 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.
- It is acknowledged that worldwide reliance is challenging, in particular with regards to review of local regulations in 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 populations waiting for a vaccine.

Background materials:

Dellepiane et al.	Alignment in post-approval changes (PACs) guidelines in emerging countries may increase timely access to vaccines: an illustrative assessment by manufacturers Vaccine (2020)
IFPMA	The complex journey of a vaccine – Part I; The manufacturing chain, regulatory requirements and vaccine availability (2014)
IFPMA	Considerations for effective regulatory reliance – an Industry perspective (Jun 2019)
NASEM	The need for increased reliance among regulators (2020)
Ramnarine et al.	Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry

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	One-Voice-of-Quality (1VO) Solutions PDA JPST (2020)
WHO	“Good reliance practices in regulatory decision-making: high-level principles and recommendations” draft QAS/20.851 from Aug 2020; last accessed 27 Nov 2020
WHO	Guidelines on procedures and data requirements for changes to approved biopharmaceutical products , WHO Technical Report Series, No. 1011, 2018

Requests to the RAG:

Can WHO's 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?

Would this include agreeing to a set short timing (for example 15 working days) for approval?

Feedback (November 2020):

The RAG, in principle, accept reliance procedures for post-approval changes. Short timelines for approval, for example 15 working days, would be difficult to achieve for complex PACs. However, RAG members expressed their willingness to discuss with vaccine manufacturers on a case-by-case basis and do their best to accelerate as much as possible.

Use of reliance and recognition as key enablers

Background provided by vaccine developers as of Nov 2020

- 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 adapted to meet the need to manage PACs efficiently for this pandemic situation.

Alignment on data requirements and timings for PACs:

Based on the principles of regulation, manufacturers assume that requirements are always science- and risk-based and take into considerations such as the control strategy and companies' approaches to ongoing process verification.

Requests to the RAG:

In this context, what are the views of RAG in developing upfront alignment, especially in a global emergency environment, using the reliance mechanisms to review and approval of PACs, as described in the WHO guidance on “Good reliance practices”?

Feedback (November 2020):

RAG was unable to provide consolidated feedback, but acknowledged that despite the existence of stringent regulatory authorities that can be relied on, a global perspective is still missing and WHO was encouraged to further advocate a reliance philosophy.

Use of global regulatory tools and science / risk-based approaches

Background provided by vaccine developers as of Nov 2020

- 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.

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Requests to the RAG:

Is there any plan to develop regulatory mechanisms (such as PACMPs) beyond ICH regions to facilitate the management of some PACs?

What are the views of RAG in using a science- and risk-based approach to assess PACs related to manufacturing and to support changes in analytical methods and technologies, as, for example, described in the article by Ramnarine et al.?

Feedback (November 2020)

Europe:

The legal and regulatory framework does not permit reliance on the review performed by other jurisdictions. The inverse mechanism is possible, i.e. its 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 the fact that data requirements and timelines 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. It was also recognized 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 Q2R2-Q14 concept paper).

Rapid changes using exceptional PACMPs is possible and guidance on this area is published on EMA's website.

Brazil:

Reliance procedure is already in place for marketing authorization (MA) and PACs ([OS n° 45/2018](#), in Portuguese). This procedure relies on the evaluation from EMA and/or FDA to allow for faster evaluation by the local NRA.

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 NRAs. The final benefit-risk assessment is done by the local NRA. Further, this procedure is regarded more efficient for CMC, provided that product approved by FDA and/or EMA is exactly the same as the one submitted locally (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.

Comparability to support manufacturing changes

Background information provided by vaccine developers:

- Development of manufacturing processes for COVID-19 vaccines is being executed within considerably reduced timelines, and with evolving knowledge on product, analytics and process, requiring potential deferral of activities (e.g., optimization/validation) after launch.
- Compared to other modalities, vaccines are diverse products, hence the level of risks /

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acceptance associated to the proposals may vary depending on the prior knowledge and degree of complexity and understanding of product and process, however, general scientific principles can be agreed across product types.

- In addition, clinical and post-launch supply will require use of multiple manufacturing sites and post-approval changes to support the administration of doses to billions of patients.
- The number of batches used in the clinic (Phase 1 and Phase 3) and the urgency with which these studies are being executed result in a limited historical dataset to establish statistically-based acceptance criteria which are typically applied for comparability assessment.
- While following a manufacturing change, the question arises as to whether the post-change product is comparable to the pre-change product, to ensure that the pre- and post-change products perform equivalently. In this context, building strong, quality risk-based comparability strategies is key to support fast access to vaccinees and sustainable lifecycle management.
- Comparability approaches and burdens of proof for comparability vary greatly from country to country, as do approval timings. This can create delays in getting vaccine to many markets quickly.
- Given the challenges associated with the COVID-19 emergency, comparability assessment may be on critical path. Cross-industry reflection and engagement of Regulatory Agencies is hence of high importance, as it may provide a structured set of options to be rapidly assessed for the individual platforms/products.

Potential approaches to demonstrate comparability of COVID-19 vaccines during development and lifecycle will include:

- The use of a risk-based analytical comparability assessment of manufacturing changes, for instance:
 - o evaluate a subset of Critical Quality Attributes that are impacted by the proposed changes and are known (e.g., via prior/platform knowledge) to possibly have impact on safety and/or efficacy at the levels exposed to the vaccinee (when administered at the desired dose).
 - o consider matrixed and bracketed approaches across DS and DP
 - o assess the need of additional characterization testing to reinforce comparability data
- The use of release, forced degradation and/or characterization data to demonstrate comparability, depending on the changes being made. In addition, the comparability strategy may vary depending on the nature of the change and supporting analytical and process evolution.
- Critical quality attributes for post-change lots could be compared to lots used in the pivotal study in which clinical efficacy has been demonstrated, thereby supporting comparability based on product quality with a link to the patient without a need to obtain further clinical exposure. Assessing manufacturing variability in clinical trials and appropriate dose selection (as per discussion at 2018 EMA/FDA early access workshop) would support definition of such patient-driven acceptance criteria for comparability.
- Where prior knowledge is limited and/or in the absence of statistically-based acceptance criteria, a “clinical development”-type approach to CMC comparability may be appropriate, aimed at demonstrating the preservation of critical quality attributes without the requirement of process consistency, given the limited manufacturing history in accelerated scenarios. This is in line with ICH Q5E, stating that “the goal of the comparability exercise is
- to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy.”
- The global use of general/broader PACMPs for routine changes (e.g. new reference standards/positive controls, new cell bank, new stock seed, changes to raw materials or

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excipients such as new suppliers, minor DS and DP manufacturing changes, manufacturing location or scale-up)

Approval of the original application with the comparability protocol can provide the applicant an agreed-upon plan to implement the change. Depending on the change, the applicant can provide control strategy, risk assessment, product knowledge to potentially reduce the reporting category for the CMC change.

Background materials:

EMA-US FDA Stakeholder workshop	Support to quality development in early access approaches, such as PRIME and Breakthrough Therapies
EFPIA White Paper	CMC development, manufacture and supply of pandemic COVID-19 therapies and vaccines (8 Jun 2020)
CBER's Draft Guidance	Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information Guidance for Industry

Requests to the RAG:

Would the Regulatory Advisory Group agree to the following?

- Apply risk-based analytical comparability assessments of the subset of critical quality attributes (CQAs) that may be impacted by the proposed changes.
- In cases where prior knowledge is limited, and when there is no statistical basis for acceptance criteria due to limited number of lots, use of approaches to comparability focused on product quality expectations.
 - A global single approach to comparability amongst nations, considering
 - early feedback from regulatory authorities on comparability approaches in advance of obtaining efficacy data from Phase 3 to help confirm requirements and ensure alignment on product specific approaches
 - global use of general/ broader PACMP for routine changes/introduction of multiple manufacturing process changes, including introduction of reliance mechanisms

Feedback from the RAG (provided Aug-Oct 2020)

The Developers would need to focus on CQAs known to affect safety and efficacy and these CQAs should be well defined and supported. It is uncertain if there could be a single global approach, but the elements proposed to establish comparability seem reasonable and in line with [ICH Q5E](#). Moreover, the RAG supported the risk-based approach.

The only caveat is that comparability should also consider the specifics of each case. It is therefore difficult for the RAG to say in every scenario whether regulators will be able to transpose the proposed strategy to all vaccines.

It is noted that many of the developers are manufacturing vaccine at risk and the impression is, based on what has been communicated to regulators, that a substantial amount of manufacturing data is being generated. Hence, RAG members were of the opinion that there will be sufficient manufacturing information available, which would make a risk-based approach comparability feasible. That said, it should be adequately demonstrated that lots included in a comparability exercise are reflective of lots used in clinical trials and material to be used at commercial scale. COVID-19 vaccine developers are strongly encouraged to get early feedback from regulators on their comparability approach.

Forced degradation studies are an excellent way to assess relative stability pre- and post-manufacturing change, provided the stability indicating potential of the assays is well defined. While harsh degradation conditions (e.g., oxidative and temperatures > 50°C) are reasonable initial conditions to evaluate, more appropriate conditions reflective of typical temperature

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excursions (e.g., $\leq 37^{\circ}\text{C}$) will be more biologically relevant for the evaluation of the product, assuming the stability indicating potential of the assays has already been demonstrated appropriately. It was acknowledged that there may be situations where the antigen is highly stable, but that needs to be shown with multiple orthogonal methods to provide convincing data to demonstrate such stability.

While preclinical and clinical data is important in the evaluation of stability indicating quality attributes, the high degree of variability associated with *in vivo* assays could make comparability challenging. Thus, RAG stressed that appropriately designed *in vitro* stability indicating assays can be more sensitive, robust and reproducible and are therefore preferred for quality control purposes.

RAG members stressed that there is a need for very strong analytical packages and that the analytical package must be focused on the proposed changes in the manufacturing process. Moreover, it will be important to include stability data and characterization tests in the analytical package. If analytical methods are changed during the development of the product, then comparability of the old and new method must be well characterized or the assessments could prove difficult. As far as possible, the analytical methods should not be modified significantly all along the clinical development phases in order to have a solid baseline for the comparability exercises.

It was pointed out that in addition to the routine release tests used in a comparability exercise, developers should consider additional characterization tests to support comparability over the life-cycle of the vaccine. This is particularly important during the clinical development phase, up to the registration to be sure that comparability of commercial lots can be linked to batches that have been found to be safe and efficacious in clinical trials.

Clinically relevant product specification considerations

Since Phase 3 trials are generally used to demonstrate clinical consistency, there is a tendency to use lots that are relatively consistent in terms of quality attributes. This tends to lead to the establishment of narrow specification ranges, since the specifications should be linked to the clinical lots. The tighter the quality specifications are, the more likely batch rejections will be for potentially useful clinical lots. Hence, it is recommended that during early clinical development, sponsors should aim at established clinically meaningful ranges for specific CQAs. This would typically occur during phase 2a dose-finding studies to support CQAs such as potency. When correlates of protection are not defined, as is the case with COVID-19, the alternative is to perform a broader set of immunological assays (e.g. neutralizing antibody titres, CMI, cytokine profile etc.) potentially on a smaller subset of subjects. Such studies should be developed in coordination with regulatory authorities.

Universal Label

Background provided by vaccine developers:

Due to the urgent need of access to COVID-19 vaccine post-approval, the fact that doses intended for commercial use are manufactured at risk and the need for flexible allocation of doses, label items will be in a dynamic state at the time when the vial label needs to be finalized. It is critical that this topic is raised now in order for developers to have production ready labels when needed.

We are proposing a universal vial label intended for both the outer and immediate packaging for all COVID-19 vaccines used in combination with QR code (see separate question) to contain up to date information that is typically required on a traditional vial label.

This universal label should consist of one language; however, one may consider a second and even a third language. We proposed that this label be utilized without further review and approval by a country/region and contain the following:

- 1) Statement for "For Pandemic Use Only"

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- 2) Invented name
- 3) Common name (e.g. Covid-19 vaccine, DNA plasmid)
- 4) Route of administration
- 5) Dose/concentration
- 6) Lot number
- 7) Name marketing authorization/license holder
- 8) Storage information
- 9) Manufacture Date (Expiry date on QR code)

The statement: “For Pandemic Use Only” shall be used to inform officials in countries and regions that the product does not need to be detained for further review and approval for use in that country or region. This suggestion is based on the experience with distributing Merck’s Ebola vaccine. That is not to say that all vaccines can be used in all countries and regions. There will still be the requirement vaccines need to adhere to the distribution that are destined for use in low- and middle-income countries (LMICs) vs high-income countries as an example.

Requests to the RAG:

Would you support the use of a universal label in your country or region?

Feedback (provided Aug-Oct 2020):

The RAG agreed, in principle, that having a universal (standard) label would be advantageous in this pandemic setting; however, there was not clear alignment on the proposal. While some members supported parts of the proposal others thought certain elements such as a single language to be problematic. There seemed to be some support for in the inclusion of the manufacturing date instead of the expiry date. Individual developers need to begin to approach their relevant regulatory authorities to begin this dialogue to explore the feasibility on any proposed exemptions such as the most critical:

- Use of 1-2 languages
- Date of manufacture
- QR codes if one can use them
- Inclusion of an abbreviated patient information leaflet - not 1:1 but maybe for one per shipping carton for then a public health authority and/or healthcare provider to reproduce on site.

Shelf life/ Expiry Date

Background provided by vaccine developers:

- Stability is frequently on the critical path for drug substance and drug product development and medicine supply. Additionally, the rigid application of ICH Q5C indications, like the core stability data package exemplification and requirements for real time data, is not compatible with the accelerated vaccine development and industrial plan needed for urgent global supply of COVID vaccines. In these circumstances, it is more logical that benefit vs scientific risk-based thinking is applied. In cases of incomplete data sets, making use of prior knowledge and accelerated stability studies to base their claims on shelf life will be critical for Applicants.
- It is acknowledged that post marketing commitments to provide full shelf life data may be acceptable with appropriate justification (FDA Guidance for industry on Development and Licensure of Vaccines to Prevent COVID-19). Yet, it is not clear to what extent the vaccine manufacturer will be able to leverage prior knowledge and scientific/risk-based approaches to fix the vaccine expiry date for the initial licensure and to defer as post approval commitments the submission of confirmatory stability data generated on commercial batches.

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- The importance of vaccine vial monitor (VVM) as a visual signal in standard use and during campaigns has been reminded by WHO. However, it is acknowledged there is only one supplier of VVM tags and the need to supply billions of tags would be a bottle neck.

Supportive stability data for licensure: Do NRAs concur with a scientific risk-based approach to determine the proposed vaccine shelf life in the absence of real time stability data on the commercial batches:

- Using modelling and/or extrapolation/platform data. This approach is specific to the type of vaccine and product. Therefore, it would be agreed upfront with the reference country through official consultation. The consultation outcome would then be shared and applied by reliance by other NRAs.
- Using stability data generated on clinical, small scale, or engineering batches in place of commercial batches in the initial license, as was indicated in the EMA/FDA report on early access quality approaches
- Allowing data generation under normal conditions on the final process/final scale to become confirmatory rather than pivotal

Requests to the RAG:

Stability commitment submission:

Do NRAs concur with the submission of stability protocols on the final process/final scale in the initial licensure and that data collection is carried out post-authorization as post approval commitments, as recommended in the EMA/FDA report?

Do NRAs concur that annual stability protocols would be enough to support the addition of manufacturing sites if ICH stability studies are already in place to support the final process/final scale batches shelf life, and analytical comparability can be demonstrated?

Feedback (provided Aug-Oct 2020):

The RAG agreed in principle that flexibilities are required here given that there will not be the required amount of data generated to know the expiry of the vaccine. EMA took a flexible approach in 2009 for the H1N1 pandemic. There was mention of using the [WHO guidance for Extended Controlled Temperature Conditions](#) (ECTC) which outlines the use of stability protocols. Generating stability data from small scale engineering runs for the initial licensure and then working towards the final stability post licensure with the necessary comparability was another approach. Individual developers will need to submit their detailed plan to the appropriate regulatory authority based on their vaccine platform.

Requests to the RAG:

Vaccine vial monitor (VVM) labelling temporary exemption: Given the rapid development cycle required, the fact that commercial stability data is not likely to be available, and the manufacture of VVM labels is limited, would WHO concur with a temporary exemption for VVM labelling at time of WHO PQ?

Feedback (provided Aug-Oct 2020):

Regarding the VVM labels, while WHO in principle supports this exemption, developers are encouraged to discussion directly with the WHO PQ Team.

Update (November 2020): Labelling, carton and insert requirements

Background provided by vaccine developers as of Nov 2020

- Two imperatives are regarded as key during COVID-19 pandemic situation:

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- o Speed of introduction of new vaccines
- o Flexibility of world vaccine supply (i.e. any vial could go anywhere at any time)
- The current regulatory environment is not able to accommodate the above demands. Requirements for labels, carton, insert differ from country to country; each of these components 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).

Background materials:

WHO	Bar-codes, QR codes and Vaccine Vial Monitors in the context of COVID-19 vaccines (Working version 2.1, 30 Oct 2020), last accessed 27 Nov 2020
WHO	Model packaging for carton and label for vials for Covid 19 vaccines (working version, 04 Nov 2020), last accessed 27 Nov 2020
GS1 standards	https://www.gs1.org/industries/healthcare/standards

Primary Package: Label

Background provided by vaccine developers as of Nov 2020:

- Vaccine label is different from country to country (i.e. local language, unique numbering format, etc.), often with 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.

Requests to the RAG:

To avoid segregation of material upon market-specific labels, would RAG foresee the use of a generic, single language label for all markets globally using readable formats with an optional use of barcode in the label (in addition)?

If this is feasible, training materials can be made available well in advance to ensure correct label readings.

See [Feedback \(November 2020\)](#)

Primary Package: Expiry date

Background provided by vaccine developers as of Nov 2020:

- 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.

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Currently the information to be provided in the label includes lot number, manufacture date, place to consult expiry date (a website pointing to a site with expiry date per lot where expiry date which is maintained by the vaccine developer and updated in real time, all of which to be on human readable format while the use of barcode is optional.

Requests to the RAG:

What are the views of RAG to use an approach which allows transitioning towards a more conventional expiry date format on a product-by-product basis?

If acceptable, 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. Vaccine developers propose this would be the responsibility of the immunization programme.

See [Feedback \(November 2020\)](#)

Primary Package: Vaccine Vial Monitor (VVM)

Background provided by vaccine developers as of Nov 2020

- VVMs are used for UNICEF-distributed vaccines and 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.

Requests to the RAG:

To mitigate any delay and distribution bottleneck, would RAG consider 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 could be envisaged.

Note from vaccine developers: 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.”

Feedback (November 2020)

The RAG advised that this question should be addressed through discussions with WHO.

Secondary Package: Carton

Background provided by vaccine developers as of Nov 2020:

- Vaccine label is different from country to country (i.e. local language, unique numbering format, etc.), often with 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.

Requests to the RAG:

Would RAG accept the use of a generic, single language carton for all markets globally with lot-specific information in human readable format and GS1 barcode format, including a link (human readable and digital formats) pointing to a site in which expiry date can be consulted?

As 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 proposed generic, single language

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carton will support this activity and training materials can be made available well in advance to ensure correct carton readings.

See [Feedback \(November 2020\)](#)

Secondary Package: Serialization number

Background provided by vaccine developers as of Nov 2020

- Serialization provides a means to avoid products being illegally diverted and a unique serial number is given to each carton to create a unique identity of each carton. However, 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.
- 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.

Requests to the RAG:

Would RAG agree to use unique serialization numbers where/when possible immediately? If not doable, would RAG accept a waiver during the first 9 months after market approval with intention to implement 12 months after approval?

Note from vaccine developers: this proposal is NOT aligned with the WHO 30 October draft guidance on “Barcodes, Labeling and Serialization”.

Feedback (November 2020)

The EMA supports having serialization and mentions that companies recognize this is important to address falsified medicines.

No other views were expressed.

Secondary Package: QR code on carton

Background provided by vaccine developers as of Nov 2020

- Package leaflet can be separated from carton in the field.

Requests to the RAG:

Would RAG consider using a separate leaflet from carton by using a QR code printed on the carton?

If acceptable, 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. In addition, the use of QR codes allows for quicker update of latest approved information.

See [Feedback \(November 2020\)](#)

Inserts: Electronic insert

Background provided by vaccine developers as of Nov 2020

- 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

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activities.

Requests to the RAG:

What is the view of RAG on generic and simplified insert supplied with each carton, which has basic information in a standard set of languages?

Such simplified insert will allow containing a QR code that leads to the full insert in the desired language (following approved insert in the country chosen).

Alternative approach to electronic insert would be countries to be responsible for printing the insert from the website and distributing it to practitioners who would be administering the vaccine.

Note from vaccine developers: this proposal is not aligned with the WHO 30 October draft guidance on “Barcodes, Labelling and Serialization”. (Nov 2020)

Feedback (November 2020)

Due to differences in the legal frameworks, the RAG agreed to reference different positions expressed by the region or a country.

EMA:

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 to get access to information via this tool.

EMA supports having serialization and mentions that companies recognise this is important to falsified medicines.

[EMA Questions and answers on labelling flexibilities for COVID19 vaccines Quality Review of Documents \(QRD\) group](#) (16 Dec 2020)

FDA:

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) like procedures. However, it was stressed that these same flexibilities cannot be sought for licensed products.

Health Canada:

Interim Orders deploy a similar level of flexibility for initial access to COVID-19 vaccines. Such a legal mechanism allows flexibility to accommodate the proposals brought to the RAG (manufacturing date instead of expiry date, QR codes, etc). The requirement for both official languages (French and English) is considered key, however this can be accommodated via electronic formats.

Note:

LMICs may not have the technologies required to access information from technology of QR codes. For some even under EUA legislation does not allow absence of expiry dates due to extreme temp/humidity conditions and logistic requirements.

Labelling issues should be discussed with the National Immunization Programs since they understand better the particularities of each country, in particular the element related to access to technology in remote areas.

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

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agree risk minimization strategies with the National Immunization Programs prior to marketing authorization and vaccine distribution.

WHO/CEPI was encouraged to develop a symbolic language that could be used in future pandemic situations to overcome language-related challenges.

WHO would update its working position on barcodes as needed.

Clinical

Vaccine safety

Background information provided by vaccine developers:

Some vaccine developers have little to no prior licensure experience and need assistance in creating and implementing a risk management plan (RMP) for their vaccine.

To facilitate that all vaccines are monitored according to similar standards, the Vaccine Safety Working Group (VSWG) within the Clinical SWAT aims to develop a “core” pandemic COVID-19 risk management plan. This will provide minimal generic requirements with an option for regulators to add vaccine-specific requirements. A similar approach was previously demonstrated with the development of a core pandemic influenza vaccine RMP with EMA. Close partnership with WHO/PQT as well as a stringent regulatory authority will be needed to ensure regulatory adoption as well as WHO endorsement.

Requests to the RAG:

What level of engagement / collaboration with WHO is possible on this topic?

Should COVAX propose the development of a COVID-19 core pandemic RMP to Stringent Regulatory Authorities or should this proposal be routed via WHO prequalification (PQ)?

Feedback (provided Aug-Oct 2020):

The RAG recognized the importance of consistency of safety monitoring and of a standardized approach to post-marketing monitoring of the benefit and risk of COVID19 vaccines to facilitate exchange of emerging safety information. However, it was noted that the EMA, whilst acknowledging its usefulness in the 2009 influenza pandemic, has decided not to utilize the core pandemic RMP concept for COVID-19 vaccines due to the significant differences between vaccine platforms and the many vaccines under development. The RAG considered that a generic RMP at the level of vaccine platforms might be workable and suggested that a draft be prepared by the Vaccine Safety Working Group of the Clinical SWAT for further consideration by the RAG.

The use of Burden of disease as end-point for efficacy

Background information provided by vaccine developers:

The consensus for the primary efficacy objective in pivotal Phase 3 vaccine efficacy (VE) trials has been clinically symptomatic COVID-19 rather than asymptomatic SARS-CoV-2 infection. However, there is no consensus on the appropriate case definition for the primary endpoint which is reflected by the various case definitions outlined in the publicly available VE trial protocols of various developers.

It is likely that COVID-19 vaccines, like other respiratory and mucosal virus vaccines, are most effective in preventing severe disease rather than mild disease or asymptomatic infection. The vaccines will prevent disease progression and severity may shift from severe to mild (vaccine-mediated attenuated disease (VAD)) among COVID-19 cases of vaccine recipients. If a vaccine acted in this way, unknown to the investigators, then, in a clinical vaccine efficacy (VE) trial with a primary endpoint of ‘COVID-19 / any severity’, mild COVID-19 occurring in vaccine recipients

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would be counted as vaccine failure (endpoint case) rather than as successful prevention of disease progression (VAD). This may be a concern when assessing 'COVID-19/any severity' as a primary efficacy endpoint.

The epidemiology of COVID-19 shows that the incidence of mild disease far exceeds severe. This makes the convincing demonstration of VE against severe disease challenging and requiring a trial size much larger than the already large size trials based on any symptomatic disease endpoint. Therefore, in these trials, severe COVID-19 is being included as a key secondary endpoint.

The analyses such as testing hypotheses or deriving confidence intervals uses the classical approach gives a score of 0 to a non-case and a score of 1 to a case. The BoD expands this approach further. It gives an integer score such as 0, 1, 2 and so on, with increasing score signifying increased severity. For example, in a VE trial of COVID-19 vaccine, a score of 0, 1, 2, 3 or 4 is given to asymptomatic infection, mild disease, moderate disease, severe disease and death, respectively. The score for each group is then, as in the classical case, the sum of the scores of the individuals. The difference in scores can be tested to calculate vaccine efficacy and a confidence interval for VE. The extension of the statistic from 0 and 1 to several positive integers makes the statistical distributions somewhat different, but not unusual.

BoD or Burden of Illness (BoI) endpoint has previously been accepted for regulatory approval of Zostavax.

The design of pivotal Phase 3 COVID-19 VE trials may benefit from including BoD as follows:

- dual primary endpoint (alongside 'COVID-19/ any severity') or
- triple primary endpoint (alongside 'COVID-19/any severity' and 'COVID-19/moderate to severe') or
- key secondary endpoint (e.g. with 'COVID-19/any severity' and 'COVID-19/moderate to severe' as dual primary endpoint)

It is unclear whether or not Phase 3 VE trials will meet the requested minimum 50% VE target (with lower bound confidence interval of >30%) against 'COVID-19/any severity' if the main effect of the vaccine is prevent severe disease with relatively lower effect on mild disease . On the other hand, Phase 3 VE trials are unlikely to be sufficiently powered to demonstrate VE against severe COVID-19 based on the targeted 150-160 confirmed cases of symptomatic disease.

A BoD endpoint seems to be an appropriate approach to assess VE against progression to severe disease and de-risk a situation in which inappropriately defined primary endpoints do not reflect an important aspect of the potential protective efficacy of COVID-19 vaccine leading to Phase 3 trial failure.

Nevertheless, pivotal Phase 3 VE trials should assess other aspects including severe COVID-19 as well as infection and transmission as additional (e.g. secondary endpoints).

Background materials

- [Clinical Endpoints for evaluating efficacy in COVID-19 Vaccine Trials](#). Mehrotra D. et al, Ann Intern Med. 2020 Oct 22 : M20-6169. [10.7326/M20-6169](https://doi.org/10.7326/M20-6169)
- Zostavax: [EPAR scientific discussion](#)
- Callegaro A, Curran D, Matthews S. [Burden-of-illness vaccine efficacy](#). Pharmaceutical Statistics 2020; 19: 636-645. <https://doi.org/10.1002/pst.2020>

Technical Brief: Regulation of COVID-19 Vaccines

Requests to the RAG:

- 1) Would a BoD endpoint be acceptable as a single, dual or triple primary endpoint in Phase 3 trials to establish VE against COVID-19? (Aug-Oct 2020)

Rationale: BoD endpoints should be acceptable as separate endpoints in addition to endpoints assessing COVID-19 illness of pre-defined specific severity. This would de-risk pivotal Phase 3 VE trials in case other endpoints do not meet pre-specified criteria because of low VE (COVID-19 of any severity with mostly mild cases) or because of insufficient number of cases (e.g. severe COVID-19, hospitalization, death).

- 2) If a BoD endpoint was to be an acceptable primary endpoint, what would be the requested success criteria for a BoD endpoint? (Aug-Oct 2020)

Rationale: The success criteria for VE as recommended by FDA as well as draft WHO Prequalification/Emergency use listing (EUL) guidelines is a point estimate that is $\geq 50\%$ with a lower bound confidence interval of $>30\%$.

Feedback (provided Aug-Oct 2020):

The RAG fully understands the rationale behind this question, i.e. vaccines may show better efficacy in preventing severe disease than mild disease. This is at least what is known for other respiratory viruses. It was therefore recognized that there is risk that an all-comer study using “any severity” as the primary endpoint could fail but, that the secondary end point of “severe disease” could be statistically significant. To accept this approach would take some more discussion as it is not straight forward. One challenge would be how to transform the outcome into a meaningful indication.

RAG members had diverging viewpoints. Some were open to discuss the possibility of using two primary end-points: “any severity” and “severe disease spectrum”. This can be tackled methodologically and statistically in ways that are acceptable to regulators. However, it is a prerequisite to have a good definition of what is meant by “moderate” and “severe disease”. There are concerns that definitions currently used in some studies are not acceptable. COVID-19 vaccine developers should make an attempt to have homogeneous definitions of moderate and severe disease. A simple way would be to just follow what WHO has published in terms of [clinical management of patients with COVID-19](#).

Other opinions were that a BoD endpoint which evaluates severity adjusted vaccine efficacy, could provide useful data on the target population who might benefit most from the vaccination. However, as it is based on a scoring system instead of a binary outcome of “yes” or “no” to the presence of symptomatic disease, it could potentially bias the results in favour of the vaccine (i.e. inflate the vaccine efficacy) in the scenario where the vaccine only attenuates the disease, but does not actually reduce the overall incidence of the disease. Therefore, the preference was for the primary efficacy endpoint to focus on a reduction in the incidence of symptomatic disease, which would provide an unbiased estimation of the true vaccine efficacy. However, BoD could be considered as a key secondary endpoint, in addition to the existing conventional secondary endpoints that already measure severe disease.

Some RAG members were concerned that adequate data collection for a BoD endpoint could be challenging in large studies.