Q&As developed by the COVAX Regulatory Advisory Group (RAG): Sep2020

Introduction:

The vaccine pillar, COVAX, of the ACT accelerator [https://www.who.int/initiatives/act-accelerator] has established a Regulatory Advisory Group (RAG) which is co-lead 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 supports vaccine developers on general matters related to vaccine development. Working group, 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.

These Q&As are intended to serve as a mean to make the wider community of Regulatory Authorities aware of questions and challenges vaccine developers are facing in development of COVID-19 vaccines.

The Q&As will be expanded as new questions are discussed at the RAG

The RAG applies the Chatham House rules, but divergent views will be reported as such without attribution.

Q&A : Post-approval changes

Background

- 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 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:
    - Challenges in scaling-up manufacturing to meet patient demand
    - Challenges in modifying control strategies to accommodate evolving product and process understanding
    - Challenges in demonstrating comparability because of limited batch history
    - 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)
    - 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 harmonisation 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 PQS. 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 of accepted globally.

Questions:

1. Can Reliance procedures, that may be agreed for MAA processes, also be applied to the post approval setting, with acceptance of an approval from a stringent Authority?

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

Answer:

A-Q1:

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 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 harmonisation can be achieved. There have been two projects – could look at principles suggested. There is also a WHO guideline for post-approval [https://www.who.int/biologicals/expert_committee/PAC_highlighted_20_Oct_2017.HK.IK.pdf?ua=1]. 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 [https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-party/quality-working-party-workshop-stakeholders-relation-prior-knowledge-its-use-regulatory-applications_en.pdf] provides some scientific elements and regulatory/procedural tools that is relevant to Process Validation and PACs.

A – Q2:
In principle, was agreed that based on ICH Q9 [https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf] could apply, but it was also pointed out that due to different legal requirements in countries, to obtain global recognition/reliance could be challenging.

Vaccine safety

Background:

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.

Questions:

- 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/PQ?

Answer:

The RAG recognized the importance of consistency of safety monitoring and of a standardised approach to post-marketing monitoring of the benefit and risk of COVID19 vaccines to facilitate exchange of emerging safety information. However, if 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.

Universal Label

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"
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 authorisation/licence 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 LMICs vs HICs as an example.

Question:

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

Answer:

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

- **Timing for response**
    - The increased pressure for the development of COVID-19 pandemic vaccines deserves significant acceleration, and this presents a challenge in terms of the provision of CMC information and their review by various Competent Authorities. Indeed, post approval changes such as shelf life extension, as well as process scale up and manufacturing sites addition are likely to occur to ensure vaccine large scale availability and supply sustainability.
    - This is especially true for stability data for which limited, or no stability data will be available at filling from the commercial scale batches. Yet expiry date for commercial batches will have to be defined as packaging/ labelling operations are to be anticipated to maintain the pace with vaccine market availability timelines. Therefore, this guidance on expiry date and stability requirements is required by 4Q2020.
- **Background**
    - 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 GFI 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.
    - The importance of 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 licence, 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

Questions:

- **Stability commitment submission:**

1. 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-authorisation as post approval commitments, as recommended in the EMA/FDA report?
2. 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?

• 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?

Answers:

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.

https://www.who.int/biologicals/areas/vaccines/ectc/en/

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