

Q&As developed by the COVAX Regulatory Advisory Group (RAG): Apr2021

Industry consortium (manufacturing SWAT): SARS-CoV-2 Variants

Pre-read material had been distributed from the Manufacturing SWAT Team to the RAG to address CMC questions about regulatory requirements for vaccines against SARS-CoV-2 variants. Assumptions to base these variants on the parent vaccines had been made and described in the pre-read material.

Four questions were brought to the RAG:

Background

The emergence of variants to the initial COVID-19 “parent” strain poses a significant threat to public health. Genetic sequencing data suggest that variants now make up a substantial portion of the population in a number of countries (5, 6). These variants, in the lab and in the clinic, decrease to varying degrees, the effectiveness of vaccines developed against the parent strain (7). As of April 2021, at least one company has entered the clinic with a variant vaccine that is being tested both as a second, booster dose after an initial single dose of the parent strain vaccine and as a multi-valent vaccine. As noted above, some regulatory positions have been issued by FDA (2) EMA (3, 8, 9), MHRA (4) and WHO (10), but questions remain for countries outside those with specific guidances with respect to variant vaccine CMC data expectations, regulatory authorization and regulatory maintenance.

Challenges

The experiences from managing seasonal influenza can provide important knowledge and be leveraged to inform the addressing of COVID-19 vaccine strain changes. Based on this experience, key elements of managing COVID-19 variants should include: 1) Establishment of a strain surveillance network (capable of sequencing and neutralization experiments and global standard assays for each new variant) while maintaining the current, effective influenza monitoring network (11, 12) and 2) establishment of exceptions to the Nagoya Protocol for COVID-19-related strains and sequences. While these elements are not in the regulatory domain *per se*, all are critical to managing the COVID-19 parent strain and variants, and are thus noted here for context.

Experience also suggests that fast track regulatory pathways, pathways that are clear and have highly accelerated authorization schedules, are critical enablers of the timely prevention of seasonal influenza strains; however, the lack of globally harmonized regulatory pathways for seasonal influenza makes the process of getting vaccines against new strains to market unnecessarily complex, slow and burdensome. For COVID-19, some regulators have worked in heroic fashion to provide scientific advice, regulatory guidance and high priorities for vaccine authorizations to meet the needs of the pandemic. Although these efforts are greatly appreciated, having fast-track *globally-converged* regulatory mechanisms (based on reliance or mutual recognition) that can allow multiple countries to address COVID-19 variants on unprecedented timelines using the same application remains the ideal.

In addition to those challenges learned from the seasonal influenza experience, the following potential issues need to be considered in the current COVID-19 context and evolving regulatory landscape:

- Where the “parent” vaccine has already been authorized, it will be essential to adopt risk-based approaches where limited CMC data would be submitted in support of the initial authorization of the “variant” vaccine and additional data submitted as post-authorization commitments.
- As anticipated, a significant number of post-authorization changes have been required and need to be managed after the initial authorization of “parent” COVID-19 vaccines. In the event of the concomitant use of a “variant” vaccine with the “parent” vaccine, the management of post-authorization changes between the “parent” and “variant” vaccines could become unnecessarily complex and impact market availability. Given the assumption that the “variant” vaccine is based on the “parent” vaccine platform with no significant process changes, the approved post-authorization changes of the “parent” vaccine should be attributed to the “variant” vaccine in such a way that there are no resulting additional limitations to the supply of the “variant” vaccine.
- In addition to mono-valent vaccines, multi-valent vaccine formats should be anticipated. Developing such formulations will present the need to run additional studies such as demonstrating the absence of interferences within the multi-valent formulations which may jeopardize the quality, safety and efficacy of the vaccine. The associated regulatory process for multi-valent vaccines (where variant antigens are based on the parent antigen platform) should limit as much as possible the additional timing required for regulatory authorization.

Question 1: convergent/reliance regulatory pathways

Question 2: a) PPQ and b) shelf-life for monovalent variant vaccines

Question 3: a) PACs and b) manufacturing sites, for variant and parent vaccines

Question 4: PPQ for multivalent vaccines

Q1: Leveraging the first “positions” issued in this area by EMA, FDA, ACCESS, and WHO, would it be possible for Regulators to develop a global convergent/reliance pathway for variant vaccines based on approval processes for the parent strain?

Feedback to Q1:

- It was acknowledged that having a single global regulatory position/guideline remains challenging, due to differences in regional legal frameworks to which regulatory agencies are bound.
- However, it was noted that current guidelines are not differing in essence for most of their content.
- The level of knowledge available to issue these guidelines remains limited, as compared to other pathogens, diseases or types of products.
- Efforts are being deployed to obtain as much alignment as possible at global forums such as ICMRA.
- Best practices as applied over the past months - primarily from work sharing - have already demonstrated a good level of convergence.
- An authorized vaccine was cited as a case example to demonstrate the uniformity and speed in regulatory processes and reviews followed by different regions. The same could be expected for variants vaccines.

- One specific region expressed its alignment towards convergence, having already a regulatory procedure in place to rely on SRA (specifically for CMC PACs).
- It was recognized that vaccine developers are evaluating points that may differ amongst various guidelines to identify topics that would necessitate further discussion with agencies.
- The RAG would welcome discussions on particular items that can initially appear to be divergent in the various guidelines and that could be further discussed within global forums to explore if further alignment can be achieved.
- In addition, RAG members remain open to continue the dialogue with developers knowing that current guidelines represent a starting point and that each product is to be handled case-by-case.

Q2:

- If PPQ has been successfully completed for the “parent” vaccine, and one batch of variant vaccine (covering drug product and drug substance) has been completed at intended scale that passes specifications established by the developer, could PPQ completion for the variant vaccine be submitted as a post-authorization commitment, upon appropriate justification?**
- If analytical comparability is shown between the “parent” vaccine and the variant vaccine (i.e., new antigen(s) which, despite the slightly different molecular structure, have a comparable stability behavior as the parent in accelerated conditions), could the “variant” vaccine receive shelf-life equivalent to the “parent” vaccine with a commitment to gather real-time stability post initial authorization, upon appropriate justification? This is currently only provided for in EMA, MHRA guidances. Additionally, could the use of modeling be encouraged to support stability while real-time data is obtained, if applicable?**

Feedback to Q2:

- If these areas have been investigated appropriately for the “parent” vaccine and have been proven successful, then it is possible to extrapolate to monovalent variant vaccines as well. As an example, the requirement to complete PPQ for the variant could be deferred to a later time point, provided consistency in manufacturing could be demonstrated based on other elements.
- One specific region commented that shelf-life establishment of a variant vaccine could be based on tools such as forced degradation studies at appropriate temperatures, comparing profiles of the two materials and demonstrating no significant differences. Accumulating real-time data should confirm the shelf- life established with such tools.

Q3:

- When post-approval changes for the parent vaccine are approved, and having essential laboratory data showing no impact on variant analytical comparability, could these post approval changes automatically apply to the variant vaccine (Do & Tell)?**
- When a new manufacturing site is approved for one authorized strain, could it also be automatically approved for another authorized strain(s) (Do & Tell)?**

Feedback to Q3:

- One region noted that variant vaccines will be part of the same marketing authorization which leaves room for the company to decide whether changes should apply to the parent, to the variant or to both vaccines. Justification for leveraging studies from the parent vaccine to be applied to the variant vaccine could be acceptable, provided the justification is adequate. Changes will need to follow the applicable regulatory framework.
- Legislation is currently under revision in that region to enable having multiple scenarios for the same marketing authorization (via variation procedure): parent vaccine either being replaced or in co-existence with a variant vaccine or with a multivalent vaccine. Products would have a different product name qualifier (invented name) to distinguish them, while potential differences in indications would be covered in the respective product information (PI). It was noted that a similar concept already exists for veterinary vaccines.
- WHO informed the RAG that the International Nonproprietary Name Committee is meeting the week of 19 April to discuss a nomenclature scheme that assigns INNs to the variant vaccines, either with a suffix or a prefix to the name assigned to the parent vaccine.

Q4: For multi-valent formulations combining parent and variant strain(s), if PPQ has been successfully completed for the “parent” vaccine, and one batch of variant(s) DS has been completed at intended scale that passes specifications established by the developer, could PPQ completion for the variant(s) DS be submitted as a post-authorization commitment, upon appropriate justification?

Feedback to Q4:

- The RAG commented the proposed approach could be acceptable if sufficient data would already be available for the parent vaccine and appropriate justification would be provided to defer DS PPQ to post-approval.
- It was noted, though, that such acceptance cannot be generalized across products and/or manufacturers. It would very much depend on the level of experience of the vaccine manufacturer. Therefore, allowances would need to be tailored for each company, according to their product and manufacturing facility history.

Other points were raised with regards to multivalent vaccines:

- As platform knowledge evolves for certain technologies such as mRNA, further flexibilities might be possible, but it is too early to conclude on this today.
- Multivalent vaccines may potentially pose more challenges as compared to monovalent vaccines. Specifically, it was mentioned that immunogenicity studies evaluating the dosing of each of the valents would likely be needed.

Post Approval Changes (PACs): component/material supply issues

The Manufacturing SWAT team brought an item related to the current supply chain crisis (i.e. components and raw materials shortages) and how this is foreseen to heavily impact management of PACs. Pre-reads had been distributed. Acceleration of PACs review and approval processes, alignment for regulatory requirements and reliance are proposed mechanisms to alleviate the situation. An IFMPA/COVAX taskforce has been set up to identify solutions.

Three questions were brought to the RAG:

Question 1: a) recognition or reliance for PACs approval and b) alignment on data requirements

Question 2: expedited review of PACs

Question 3: use of Product Quality System for PACs

Q1:

- a) Does the RAG agree to engage in urgent discussions with all world-wide National regulatory agencies in order to encourage regulatory recognition and reliance mechanisms with a target of 2-5 working days for reviewing and approving PACs which are limiting factors to timely supply is achieved?
- b) Does the RAG agree to lead discussions for defining alignment on data requirements for selected PACs?

Q2: In those countries where approvals based on recognition or reliance mechanisms are not possible, does the RAG agree to engage in urgent discussions with all world-wide regulatory agencies in order to encourage an expedited review and approval of PACs within 2-5 working days for PACs which are limiting factors to timely supply, such as material shortages?

Feedback to Q1 and Q2:

- A reliance mechanism is not foreseen in the legal framework of certain regions and can therefore not be applied. However, these regions are willing to consider decisions made by other jurisdictions for PACs as an informative tool that could expedite their own review and approval process.
- Guidelines and regulations are already available to assess the categorization of changes and which data requirements to fulfil.
- Some authorities are already reviewing PACs within the 2 to 5-day time window given the ongoing emergency situation. In addition, official mechanisms to accelerate implementation of changes have been put in place in some regions. For example, the use of an exceptional change management protocol (ECMP) in the EU allows for rapid change implementation with a variation submission at a later time point.
- Other regions expressed their ability to adopt reliance based on approval by stringent national regulatory authorities (NRA), since this mechanism is already foreseen in their jurisdictions. Full documentation as provided by stringent NRA is part of the submission process.
- A comment was noted to promote more work-sharing and communication between worldwide regulatory agencies. An ideal scenario was presented for pandemic situations in which all agencies worldwide would receive the same application dossier. It was noted that this ideal situation would enable more rapid approval and access to vaccines. Specific local requirements would need to be put aside to make this happen.
- WHO implementation workshops for marketing application implementation guidelines (conducted between 2018 and 2021) were highlighted to have proven useful and efficient in the COVID-19 pandemic since many countries' approvals/EUAs were based on WHO EUL and dealt with in an expedited way (i.e. within 30 days). The same pathway (reliance on WHO EUL lifecycle) would be expected for management of PACs.
- WHO commented that some countries having granted EUA did not receive applications directly from the vaccine manufacturers but relied directly on documentation submitted to WHO PQ in the context of EUL. Some other countries (approximately 30) did not issue EUA and imported directly the product. For those, no regulatory pathway is established for PACs.

- A higher level of transparency was mentioned to be helpful for the industry to identify which countries rely on either WHO EUL or SNRA approvals and which ones would be performing an expedited review. In the current supply shortage situation, this knowledge would facilitate better submission planning and, as a consequence, a more rapid approval of PACs.
- The need to map which countries still need to develop regulations that would enable reliance or expedited processes was commented.

Q3:

- a) For changes to be reported as notifications to regulatory authorities, could companies be allowed to manage these within their Product Quality System using a risk-based assessment, demonstrating acceptability of the change to the vaccine, and if requested report them on an agreed timeline, e.g., annual basis, instead of reporting according to current requirements?**
- b) PDA One-Voice-of-Quality group paper is cross-referenced as an example, which proposed to use a decision tree and asks that ICH Q9/Q10/ Q12 principles are utilized. It applies a risk-based approach when assessing each change and enables to determine the reporting category. By applying those principles and methodology, it is expected that more changes are managed within the PQS system of the company and available for review during inspection. Would these approaches be acceptable to the RAG?**

Feedback to Q3:

- Notification of a change on an annual basis could be acceptable though it would very much depend on the the type of change. Therefore, a case-by-case approach is clearly needed for this situation.
- Current existing guidelines should support the assessment of changes and the requirements for reporting vs. being managed as part of the product quality system, based on risk assessments.
- It was reminded that all parts of ICH Q12 are not fully implemented yet in all regions.

Clinical studies in children aged 5 to 11 years old

FDA brought to the RAG an item about clinical studies in the paediatric population and the amount of safety data deemed acceptable. It was intended to raise awareness within the RAG and to be able to share views in upcoming RAG meetings.

Following points were shared for consideration:

The agency has initiated discussions with vaccine manufacturers that already have an EUA in place with regards to clinical studies in the paediatric population. While demonstration of effectiveness is acceptable based on immunogenicity studies for adolescents (12-17 yo), for the 5-11 yo age group direct efficacy data needs to be generated. The amount of safety data to be required is still under discussion. In particular for US licensure purposes, a 6-month safety follow up is expected for children aged less than 12 years old. However, there is currently a discussion about vaccination of children (5-11 years old) and adolescents under EUA due to rising COVID-19 cases in the US. Safety assessments in adolescents is likely to be accepted based on 1-month safety follow up as a minimum, with a subset of subjects being

followed for up to 2 months. Discussions are to take place on the acceptable level of safety data required for the 5-11 years old population and should they be vaccinated under EUA. It was mentioned that this will be taken to an upcoming VRBPAC meeting in June.

The RAG recognized the importance of this topic and remained open to further discuss and exchange during future RAG meetings.

<i>Documents shared during the meeting</i>	
Document title	Web link
Draft WHO good reliance practices in regulatory decision-making: high level principles and recommendations, 2020.	<u>QAS20_851_good_reliance_practices.pdf (who.int)</u>
WHO guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries.	<u>WHO_TRS_1004_web_Annex_7.pdf</u>
Guidelines on procedures and data requirements for changes to approved vaccines.	<u>Annex4_Guidelines_changes_to_approved_vaccines_eng.pdf (who.int)</u>
WHO Workshop on Implementation of Guidelines for procedures and data requirements for changes to approved vaccines.	<u>FINAL_Report_WHO_Workshop_on_Implementation_of_Guidelines_for_PAC.pdf</u>