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, UK 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.

Information discussed in the RAG meetings from August 2020 to February 2021 is summarized and published in the Technical Brief issued on 14th April 2021. May 2021 issue of the Technical Brief includes only the information discussed in the 15 April 2021 RAG meeting.

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

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Manufacturing, quality control, stability and labelling

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. 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.

Requests to the RAG:

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?

c) 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

- 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.

**Request to RAG:**

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 proposes 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**

- Notification of a change on an annual basis could be acceptable though it would very much depend on 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**

**Clinical studies in children aged 5 to 11 years old**

The US 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 FDA has initiated discussions with vaccine manufacturers that already have an Emergency Use Authorization (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 y.o.), for the 5-11 y.o. 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 y.o. However, there is currently a discussion about vaccination of children (5-11 y.o.) 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 y.o. 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.

Evaluation of vaccines addressing SARS-CoV-2 variants
CMC requirements

Request to the RAG
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:
• 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.

Requests to RAG:

a) 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?

b) 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:

- 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.

Request to RAG:

a) 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)?

b) 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:

- 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.

Request to RAG:

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:

- 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.