Q&As developed by the COVAX Regulatory Advisory Group: Aug2020

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 through its SWAT teams for manufacturing, clinical development/operations and & enabling sciences. 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.

General

Coordinated feedback from Regulators

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

A: 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 agreements 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

Risk-based validation approaches

Background:

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 NRAs have developed their own requirements for the types of data required and timing 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.

Q: Can all relevant NRAs recognise risk (based on ICH Q9 [https://database.ich.org/sites/default/files/Q9%20Guideline.pdf]) 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 PQS, 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 [https://www.fda.gov/media/139638/download]?

A: The RAG considered that in principle the tools outlined in ICH Q9 [https://database.ich.org/sites/default/files/Q9%20Guideline.pdf] 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 [https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf]. It was recognised 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 characterisation tests.

Q: 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?

A: The use of Drug Substance lots manufactured prior to validation of the Drug Substance process could be used to validate the Drug Product process, provided analytical comparability is demonstrated between the pre-validation Drug substance lots and the commercial lots. Again, the developers are encouraged to consult ICH Q5E [https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf]. 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

GMP inspections take significant time and human resources to 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.

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

A: 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.

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

A: 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:
    - prior inspections by WHO PQ or a PIC/S Regulatory Authority
    - good inspection history (at least 2 successful inspections ~ 5 years)

Additional information from some Regulatory Authorities on GMP inspections during COVID-19:

EMA: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-remote-gcp-inspections-during-covid-19-pandemic_en.pdf

FDA: https://www.fda.gov/media/141312/download

HC: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices.html

Singapore: https://www.hsa.gov.sg/therapeutic-products/dealers-licence/handling-of-applications-and-conduct-of-inspections-during-covid-19

TGA: https://www.tga.gov.au/gmp-approach-overseas-manufacturers-medicines-and-biologicals-during-covid-19-pandemic

Authority Batch release testing of COVID-19 vaccines

Background:

Currently several regulatory authorities have put in place emergency measures for National Control Laboratory (NCL) batch release of vaccines. For example, CBER [https://www.fda.gov/vaccines-blood-biologics/lot-release/updated-instructions-submitting-lot-release-samples-and-protocols-cber-regulated-products-during], and TGA [https://www.tga.gov.au/physical-samples-batch-release-not-required-reminder-sponsors-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.

Q: 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?

A: Several RAG members pointed out the need for independent testing by National Control Laboratories (NCLs) due to the fact that COVID-19 vaccines are being developed and manufactured under highly accelerated timelines. It 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 scepticism 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. However, in some countries batch release data cannot be shared due to legal restrictions. On the other hand, 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/NRLs outside EU/EEA (see more on OCABR below).

Several RAG members pointed out that NRAs/NRLs should focus on a minimum set of harmonised 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 recognised globally for each vaccine. However, at present, neither a global mechanism for mutual recognition nor establishing harmonised batch release guidelines are available.

The WHO network of national regulatory authorities (NRAs) and national control laboratories (NCLs) responsible for testing and release of WHO-prequalified vaccines could potentially facilitate a higher degree of batch release recognition even if the network members have no legally binding obligation to recognise 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.

At the European level, EDQM coordinates actively the Official Medicines Control Laboratories (OMCLs)/Official Control Authority Batch release (OCABR) network to ensure the continuity of the batch 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 recognised 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.

For more information, please see EDQM batch release for vaccines: https://www.edqm.eu/en/batch-release-human-biologicals-vaccines-blood-and-plasma-derivatives

The EU batch release process (OCABR) is well structured and the OCABR certificate is already recognised 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).