1st Technical Brief: Regulation of COVID-19 Vaccines

Synopsis from the August to October 2020 COVAX RAG meetings

World Health Organization

Overview

The vaccine pillar, COVAX, of the 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 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 in the format of Q&As. It is also presented here for the benefit of all COVID-19 vaccine developers and for the wider community of regulatory authorities.

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

Technical Briefs are intended to serve to support COVID-19 vaccine developers but also make the wider community of Regulatory Authorities aware of questions and challenges vaccine developers are facing in development of COVID-19 vaccines.

Technical Briefs will be expanded as new questions are discussed at the COVAX Regulatory Advisory Group (RAG).

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

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1st Technical Brief: Regulation of COVID-19

General

Coordinated feedback from Regulators

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

Feedback:

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:

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 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.

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 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**?

Feedback:

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.

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:

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.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

Good manufacturing practice (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.

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

Feedback:

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.

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

Feedback:

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 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

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 '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.

Physical samples for batch release not required: a reminder for sponsors of biosimilars and biological medicines

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:

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 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. 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 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 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 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.

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 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.

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 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).

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 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 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 accepted globally.

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?

Feedback:

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 biotherapeutic 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.

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:

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.

Comparability to support manufacturing changes

Background

- 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 / 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:
    - 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).
    - consider matrixed and bracketed approaches across DS and DP

  - 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 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

- 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

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 excursions (e.g., ≤ 37°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 trails 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

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 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.

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

Feedback:

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

- 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.
- 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

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:

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.

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:

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

Clinical

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.

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:

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, 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.

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

Background

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 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

- 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

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?

   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?

   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 ≥50% with a lower bound confidence interval of >30%.

Feedback:

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 sever 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.