**ACCESS Consortium**
**POINTS TO CONSIDER FOR STRAIN CHANGES IN AUTHORISED COVID-19 VACCINES IN AN ONGOING SARS-COV-2 PANDEMIC**

## Executive Summary


- This Points to Consider document lays out a regulatory approach for updating authorised coronavirus vaccines should mutations at any time make them less efficacious due to insufficient cross-reactivity.
- It is only applicable to Covid-19 vaccines which have already been authorised, based on adequate data on pharmaceutical quality, safety and efficacy from pivotal clinical trials.
- On public health and scientific considerations, Regulatory Authorities do not consider an updated coronavirus vaccine to be an entirely novel product with the resulting requirement for lengthy full-blown clinical studies.
- Rather, a regulatory approach like for seasonal updates for influenza vaccines can be taken. Evidence gathered by the large pivotal clinical studies for initial authorisation and by mass vaccination campaigns is a strong foundation for this approach, as is ongoing research on the “correlate of protection” (i.e., what immunological readouts correlate with clinical protection from Covid-19 disease).
- It is considered that, in a rapidly evolving pandemic and public health need, international harmonisation of both the definition on key virus variants and regulatory requirements are desirable but not a prerequisite for moving ahead in effective and enabling regulation of vaccine updates.
- From a pharmaceutical quality perspective, details of the virus sequence, its history and any updates to the already established manufacturing process should be provided, supported by appropriate batch analyses and stability data.
- From a non-clinical perspective, non-clinical immunogenicity data, both humoral and cellular, in a relevant animal model can be of support for an application.
- From a clinical perspective, clinical efficacy studies prior to approval are not required. Regulatory Authorities request bridging data on immunogenicity from a sufficient number of individuals; an immunogenicity and reactogenicity study may include both vaccine-naïve and subjects already vaccinated with the current vaccine version. For a vaccine using a viral vector, antibodies against the viral vector should be measured.
- An updated Risk Management Plan (RMP) would have to be submitted for review to ensure that the pharmacovigilance and risk minimization activities for both variant and prototype vaccine are in place.
- For Covid-19 vaccines which are not yet authorised where an update to the SARS-CoV-2 strain is considered, some considerations of this document may apply. Such scenarios will depend on the stage of development, the format of the vaccine, and on the evidence on immunogenicity, safety and efficacy already gathered at the time of updating the SARS-CoV-2 sequence. Any concept should be discussed with Regulatory Authorities.

## Background

1. In December 2020, a new mutant of SARS-CoV-2 was detected in the UK which is suspected to be substantially more infectious (VUI-202012/01 variants with several described mutations, with an N501Y mutation being the most significant one). At the same time, another strain was detected in South Africa, also with a distinct infectivity profile (501.V2). More recently a new viral lineage was reported in Brazil, featuring the N501Y mutation and changes to E484 and K417, along with other mutations in the spike gene. Mutations and deletions in the spike protein are of concern since this is also the major target of current coronavirus vaccines.

2. While developers and other stakeholders are working on testing cross-reactivity of sera from vaccinated people with the new strain in relevant assays, it is important that there is a regulatory approach ready to be implemented should virus mutations at any time make vaccines less efficacious due to insufficient cross-reactivity, and an update of already authorised vaccines is needed. This paper lays out scientific and regulatory considerations. It does not cover unauthorised vaccines currently under development. While the considerations in this paper have been written for vaccines, they may also apply, on a case-by-case basis, for other targeted therapies like monoclonal antibodies.

3. In a most conservative approach, regulators would consider a strain change in an authorised vaccine a new product and require new clinical trials to demonstrate safety, immunogenicity and efficacy. This would result in a considerable delay in getting the new version of the vaccine ready for deployment, since the rate-limiting step is the generation of efficacy data, relying on spontaneous infections, including in a comparator group. This may also be problematic from a public health perspective since delay in updating a vaccine, where needed, bears the risk that the virus is evolving even further, potentially making a new vaccine version outdated at the time of approval again. Therefore, a scientific and regulatory concept should be developed that strikes the right balance between evidence on quality, safety and effectiveness of an update vaccine against feasibility and speed.

4. This is not an unprecedented situation; it may be feasible to apply concepts from the regulation of influenza vaccines. The influenza virus is known to constantly mutate due to errors made in its replication, evolutionary pressure, and reassortment of viral genomes from different influenza viruses co-infecting one host. There are regulatory principles which have been developed for influenza viruses which may well be applicable to other viruses like SARS-CoV-2.

## Regulatory concepts for influenza virus vaccines

5. Constant mutational changes in influenza viruses are based on two phenomena which have been reflected in tailored regulatory approaches as compared to other vaccines where the pathogen does not evolve at such a significant rate that a vaccine against a particular immunotype becomes rapidly obsolete.

6. **Antigen drift:** Gradual change due to mutations, is typically the underlying reason for **seasonal strain changes** and updates. The general population, if vaccinated, will usually have a certain background immunity from cross-reactivity from previous vaccine versions. Vaccines are typically updated with relevant data on pharmaceutical quality, usually without underlying non-clinical and clinical data. The omission of requiring clinical safety data was implemented by most global regulators some years ago with a view to not delaying the manufacturing of the next season's vaccine candidates, and due to the

experience of safety with the respective vaccines in general. However, post-authorisation measures must be in place.

7. **Antigen shift:** Usually via reassortment of genes, creating a novel influenza virus, with **pandemic potential**. This is a phenomenon specific to influenza viruses which carry a segmented genome which allows reassortment in case of co-infection of one host. In this scenario, the general population, if vaccinated, will not have sufficient background immunity. This would imply that a new version of a previously authorised vaccine would be decisively different to a previous version. Such pandemic vaccines may differ from seasonal influenza vaccines, e.g. by the adjuvant that is used in order to provide strong and rapid protection already after the first dose, especially where such strains are poorly immunogenic. For pandemic preparedness in a pre-pandemic setting, the manufacturing process and vaccine design for a pandemic vaccine can already be determined before a pandemic is declared, even without knowing the actual pandemic strain yet.

8. This has prompted the development of the **mock-up concept** (generally termed "pandemic preparedness vaccines") by which a vaccine is developed as a "pre-pandemic" vaccine (now termed "zoonotic influenza vaccine") with a strain that is emerging and that may have pandemic potential. Pharmaceutical quality, safety, immunogenicity and efficacy data (where at all possible, since the pathogen may not circulate in the human population) are then studied with this pre-pandemic strain, forming a "**core dossier**", which is then swiftly changed at the time the pandemic strain is known to the actual pandemic variant. This would then not require the same amount of data, enabling swift production of the respective vaccine and rollout with the pandemic strain being linked to the pre-pandemic vaccine via a variation application. This was successfully applied in the 2009 H1N1 "swine flu" pandemic, where the pre-pandemic strain H5N1 ("bird flu") was used to develop the vaccines, and H1N1 could swiftly be substituted as the actual strain.

9. Such variation can be based on quality data only, although the relevant European Medicines Agency (EMA) guideline recommends as preference to have some clinical data indicative of the likely immunogenicity of the strain. If not possible, such data would have to be obtained as a condition after authorisation, and plans including vaccine effectiveness should be activated and results reported in pre-agreed timeframes. Scientific advice on requirements is recommended in an inter-pandemic scenario.

10. Interestingly, for zoonotic influenza vaccines in a situation where a strain change for the same subtype is needed (e.g., one H1N1 variant against another H1N1 variant), the guideline recommends, where feasible, that the new version of the vaccine is administered to subjects who previously received the initial vaccine to assess the degree of cross-priming, although such data may be submitted after the strain change variation has been approved.

## Guidance for adapting authorised Covid-19 vaccines for SARS-CoV-2 mutations in an ongoing pandemic

<u>General considerations</u>

11. The regulatory concepts for influenza vaccines have been developed based on ample experience gained through years of seasonal vaccinations, and the 2009 H1N1 pandemic. One could stipulate that with SARS-CoV-2 vaccines, in a mass vaccination setting, there is considerable safety experience accumulating as the pandemic progresses and vaccines are rolled out, and efficacy has been established for the initial vaccine candidate via large clinical Phase 3 studies. This is a clear advantage as

compared to the influenza mock-up concept where a pre-pandemic strain is used to estimate the safety and efficacy of a future candidate vaccine.

12. It should be noted that the concept of a pandemic preparedness (mock-up) influenza vaccine has been developed in order to allow for generation of bridging data **before** a pandemic is declared. In the context of an ongoing coronavirus pandemic, these principles are not readily applicable: First, in an ongoing pandemic, there will be limited time to generate large datasets; second, there are no coronavirus vaccines that have been designated as seasonal, and the previous version of a given vaccine already was a pandemic vaccine, proven to be efficacious in a pandemic setting. This allows for the generation of bridging data on potency and immunogenicity with the initial coronavirus vaccine.

13. On the other hand, SARS-CoV-2 is a novel pathogen and its scientific characterisation is not as mature as that for the influenza viruses. In addition, many of the vaccine formats are new formats with little long-term clinical experience but might be amenable to a more straightforward update.

14. **Regulatory Authorities will therefore handle a vaccine update for an already authorised coronavirus vaccine by an approach that is based on the regulatory principles of seasonal influenza updates plus adequate non-clinical or clinical data. Likely, in an ongoing pandemic, it is desirable to test the updated vaccine directly in humans and generate adequate clinical data on immunogenicity and safety.**

15. Cross reactivity data from studies with sera from vaccinated humans suggesting that the current vaccine does not offer protection from a new variant of the virus will be the stimulus to create a new version of the vaccine which is able to offer protection from the new variant. Moreover, a drop in vaccine efficacy reported in effectiveness studies/ surveys would constitute a strong signal for updating current vaccines.

16. One important aspect to be considered is if regulatory control should be a requirement for the sequence of the updated antigen. If introduced, this would harmonise many aspects of vaccine effectiveness and ensure that once available, the updated vaccine sequences would be based on certain fundamental research performed by laboratories as discussed elsewhere in this document. However, this would likely slow down the introduction of new vaccines and may result in an outdated vaccine upon introduction since the laboratory studies and process of obtaining agreement on the required strains within the scientific and regulatory community would introduce delay. Regulatory Authorities will proactively engage relevant stakeholders internationally, including the World Health Organisation WHO. It is considered that, in a rapidly evolving pandemic and public health need, international harmonisation of both the definition on key virus variants and regulatory requirements are desirable but not a prerequisite for moving ahead in effective and enabling regulation of vaccine updates. In a situation where little is still known about a new virus variant, harmonising all the vaccines on one or a few sequences may not be straight-forward, and vaccines with a variety of sequences, developed as quickly as possible by the manufacturers may be a pragmatic and rapid means of introducing updated vaccines at this stage in the pandemic. More sophisticated regulatory control could be introduced once the virus is better understood.

17. Scientific dialogue with Regulatory Authorities as early as possible is highly recommended.

Quality considerations

18. Manufacturers will have to submit a minimum data set to update their vaccines regardless of the regulatory mechanism. Although ultimately it would be for the company to decide and justify this dataset based on the vaccine type and adjuvants (if relevant) involved, the following quality aspects would need to be considered:

    a. The segments and sequence of the full vaccine moiety compared to the already licensed vaccine.
    b. Confirmation of the sequence of the novel antigenic component compared to the desired sequence, and data verifying homogeneity with the desired variant.
    c. Details about the construction and synthesis of the vaccine starting material and the novel sequence.
    d. Risk assessment of adventitious agents related to any cell banks/virus seed lots etc. associated with manufacture. Testing of cell banks and seed lots according to ICH guidelines where found necessary by the risk assessment.
    e. Details of manufacturing development and changes to the manufacturing process necessary due to the novel sequence. It is desirable to have an overview of the manufacturing process that confirms compliance with the strategy of the original manufacturing process and any amendments/variations that have so far been approved, including validation of critical steps of the manufacturing process.
    f. Process validation. Any platform specific aspects as well as at a sufficient number (at least two) commercial scale (pre-) PPQ batches per manufacturing facility (possibly with supporting smaller development batches).
    g. Characterisation/comparability of the updated vaccine to the licensed vaccine.
    h. Update and re-validation of assays and standards required due to the novel sequence.
    i. Shelf life data. In analogy to flu vaccines, and on the basis that the changes to the sequence are minor, it is proposed that available data should be submitted but initially, the shelf life be based on the originally licensed vaccine or updated versions where sufficient data is available.
    j. Where the updated version is manufactured on the same manufacturing line, adequate data on avoidance of cross-contamination (identity) are expected.

Non-clinical considerations

19. Absence of non-clinical data on toxicology, including reproductive toxicology, with the updated vaccine candidate need to be duly justified, although such an approach is likely acceptable where the only change is to the immunogen and the rest of the vaccine construct is unaltered.

20. Non-clinical immunogenicity data, both humoral and cellular, in a relevant animal model will be informative. Comparisons of the prototype and variant vaccines are recommended. Such studies should be accompanied with generation of cross-reactivity data.

21. Non-clinical protection data from a suitable challenge model may be useful additional data. Where justified, such studies can be performed in parallel to clinical studies. Cross-protection data in animals could test whether the new version of the vaccine is able to provide protection against the existing virus to inform on whether vaccination against both versions of virus should be considered.

Clinical considerations

22. Clinical requirements may differ depending on the variant vaccine platform and formulation. The context of the pandemic and public health within each region will be taken into account when deciding the level of clinical evidence required to support market access.

23. An updated coronavirus vaccine may incorporate a change in the sequence (active substance) related to the new variant or the addition to the current vaccine of another sequence (active substance) related to the new variant. The requirements will be different in these two situations.

24. A study of clinical efficacy, which has been established for the vaccine principle already by the initial pivotal study, will not be required. However, immunogenicity (both humoral and cellular) and safety data will usually be required for approval. In addition, post-approval effectiveness/surveillance data will need to be collected. Applicants should propose a plan for post-approval effectiveness studies.

*25. Change in sequence related to the new variant*

If *in vitro* assays from sera of subjects vaccinated with the current vaccine have shown that cross-reactivity with the new variant is not sufficient, a comparative study of the two vaccines may not be in the best interest of trial subjects. Therefore, a stand-alone study is considered appropriate although other designs would also be acceptable (see also below on non-inferiority).

A **stand-alone** immunogenicity and reactogenicity study may include both vaccine-naïve and subjects already vaccinated with the current vaccine version; depending on vaccine coverage, the latter may be the main focus of the study. Each cohort should ideally include adults and older subjects > 65 years old.

If the vaccine requires a prime-boost regimen, the cohort of subjects already vaccinated with the current vaccine version may be randomised to the prime-boost regimen or one single injection to investigate the potential for cross-priming and whether one single injection is sufficient to elicit the same magnitude of response against the new variant as the prime-boost regimen. It may be possible to include this type of design as a sub-study or extension study to the ongoing follow-up of the pivotal trial.

In all subjects, the immune response should include determination of binding antibodies, neutralising antibodies and T-cell response (at least an Elispot assay). Responses should be measured against the current and new targets; the same assay should preferably be used with a change in the target analyte. In the absence of known correlate of protection, comparison of sera from individuals vaccinated with prototype vaccine from the same platform should be undertaken. Demonstration of comparable titres may not assure similar level of protection as the correlation of antibody titres to effectiveness is not established. Hence, a comparison to a panel of sera from convalescent patients infected with the new variant could be useful. A WHO (NIBSC) International Standard and Reference Panel for anti-SARS-CoV-2 antibody as use of standardised reference material for assay validation will facilitate such analyses.

Only short-term results will be required, up to 2 months depending on the vaccine regimen (e.g., up to 1 month after the second dose in a prime-boost regimen with a dosing interval of 4 weeks); 7-day reactogenicity data after each dose and unsolicited adverse events during this follow-up period should be collected.

The number of subjects exposed should ideally be sufficient to inform about reactogenicity and immunogenicity. For example, around 300 per cohort in a stand-alone study (*e.g.,* 300 vaccine-naïve subjects or 300 subjects already vaccinated with the current vaccine version) would achieve a precision of about ±5% in the estimate of reactogenicity based on the 95% confidence interval (CI). This number would also be expected to allow for an acceptable level of precision for antibody data; for example, assuming a standard deviation on the log scale of about 1.25, 300 subjects would give precision of about 15% for geometric mean titres (*e.g.*, if the point estimate was 100, the 95% CI would go from about 87 to 115). Deviations are possible, including those potentially necessary in actual public health circumstances, and should ideally be discussed with Regulatory Authorities. The number of subjects enrolled in the study should be clearly justified based on the design and objectives of the study.

Where a **non-inferiority design** is chosen, comparing neutralising antibody titres raised against the variant after administration of the updated vaccine with those raised against the initial strain after administration of the current vaccine, adequate justification for the choice of the non-inferiority margin and the design of the study (head-to-head or a comparison to sera from previously immunised individuals) is expected. Regulatory authorities will look at the totality of evidence presented at the time of approval.

For a vaccine using a viral vector, antibodies against the viral vector should be measured as well. Enrolling subjects previously vaccinated within the pivotal trial might provide within-subjects evaluation of the kinetics of antibodies against the viral vector and their potential impact on the immune response to repeated vaccinations.

Additional studies of interest may be envisaged on a case by case basis, such as the evaluation of homologous *vs* heterologous prime-boost regimen, either of the same vaccine (current and new vaccine versions) or mixing with a vaccine from another platform.

It may be envisaged that updated Covid-19 vaccines are administered concomitantly, or in close timely relation, to influenza vaccines. Data on concomitant vaccination (safety including reactogenicity, and immunogenicity) with either the original or the variant vaccine are therefore welcome.

*26. Addition of a new sequence*

Combination of a new sequence with the current sequence in the new vaccine version (i.e. generation of a bi- or multivalent vaccines) may necessitate additional immunogenicity studies to define the appropriate dose for each sequence and to investigate whether the addition of a second (or subsequent) sequence(s) does not result in an inferior immune response to vaccines with a single sequence. For example, competition at an mRNA level may occur and hamper immunogenicity. Furthermore, the reactogenicity of the combination should be evaluated, for example in comparison to the single sequence vaccine. The approach of a multivalent vaccine would therefore require additional data and should preferably be discussed with the Regulatory Authorities.

27. *Other approaches*.

It is recommended that approaches like different level of antigens for a booster dose are discussed with Regulatory Authorities.

28. Since an updated vaccine variant will build on a previously authorised parent version with established quality, safety and efficacy; from a public health perspective, it may be

justifiable to roll out the new vaccine candidate already in parallel with the previous version in absence of clinical immunogenicity and safety data while these studies are ongoing. Such approach, only based on non-clinical data, will have to be discussed with Regulatory Authorities.

29. From a Pharmacovigilance perspective, the Risk Management Plan (RMP) would have to be updated, and the deployment system would have to be reviewed in order to make sure that the appropriate version of the vaccine can be captured in adverse event reports. Previous vaccinations should be captured in people vaccinated with the new vaccine version.

    Vaccines authorization of variant changes are subject to all of the post-market reporting requirements in the Regulations including the requirement to collect and assess safety information on an ongoing basis, determine whether there has been a significant change in what is known about the risks and benefits for both variant and prototype vaccine versions, and notify regulatory authority without delay of such changes.

    Updated Risk Management Plan (including country-specific Annex/Addendum) would be required to ensure that adverse events can be appropriately captured for both the variant and prototype vaccine versions. The RMP format should follow appropriate guidance and should include the following in the context of both variant and prototype vaccine versions:

    i. a safety specification that details the identified risks, potential risks, and missing information
    ii. a pharmacovigilance plan that details specific measures to be taken to identify and report safety issues in COVID-19 patients, including adverse reaction reporting, periodic reporting, and ongoing/planned studies
    iii. a risk minimization plan, if applicable, to manage risks that may require additional measures beyond those considered routine (for instance, labelling)

Traceability of the brand and batch, distinguishing suspected ADRs with new and old formulations and collecting quality information on immunisation and medical history need to be a key focus of the updated RMP.

Where relevant, national guidance should be followed.

<u>Regulatory considerations</u>

30. Regulatory Authorities are open to discuss any impact of changes in strains in an ongoing pandemic on existing post-authorisation commitments.

**Considerations for Covid-19 vaccines under development**

31. For Covid-19 vaccines which are not yet authorised where an update to the SARS-CoV-2 strain is considered, some considerations of this document may apply. Such scenarios will depend on the stage of development, the format of the vaccine, and on the evidence on immunogenicity, safety and efficacy already gathered at the time of updating the SARS-CoV-2 sequence.
32. Due to its case-by-case nature, Applicants are encouraged to discuss their plans early with Regulatory Authorities.

**Future outlook: Considerations for future novel coronaviruses unrelated to SARS-CoV-2 (pandemic preparedness)**

33. At a future point in time, guidance will be further developed in order to prepare for a potential next pandemic. Coronaviruses appear to be zoonotic pathogens with high pandemic potential, as evidenced by three major outbreaks since the early 2000s (MERS, SARS, Covid-19).

34. A path worth exploring could be to consider authorised SARS-CoV-2 vaccines and their related data dossiers as “core dossiers” for a future coronavirus vaccine where a similar construct and manufacturing process is used. In such a scenario, an emerging coronavirus sequence could be cloned into existing constructs and be studied similarly to the process laid out above. The possibility for this will depend on the particular vaccine construct.