8 June 2022
EMA/175959/2021 Rev.2
Human Medicines Division

Procedural guidance for variant strain(s) update to vaccines intended for protection against Human coronavirus

Regulatory and procedural requirements

Consulted by PRAC	20 May 2021
Consulted by NRG	26 May 2021
Consulted by BWP	15 June 2021
Adoption by CHMP	24 June 2021
Revision 1 adopted by CHMP	16 December 2021
Revision 2 adopted by CHMP	13 June 2022

Keywords	***Procedural requirements, regulatory requirements, submission, variation, covid-19 vaccines, pandemic, variants update, pandemic strain update, COVID-19, SARS-CoV-2, vaccine, variant strain, variant vaccine, parent vaccine, human coronavirus***

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1. Introduction

In order to ensure the continued effectiveness of authorised COVID-19 vaccines, it may be necessary to modify the authorised human coronavirus vaccines composition so as to protect against new or multiple variant strain(s). Such changes, which include the replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences, should be considered as variations to the marketing authorisation in accordance to the Commission Regulation (EC) No 1234/2008 as amended by Commission Delegated Regulation (EU) 2021/756, provided the technological platform of the vaccine remains similar. The same approach should be followed for all human coronaviruses as set out in the Commission Delegated Regulation (EU) 2021/756. This guideline lays down the procedural aspects related to the submission of a variation to change the composition of a marketing authorisation for COVID-19 vaccines in the centralised procedure.

2. Scope

This module provides guidance on variation applications for updates of vaccine composition for centrally authorised vaccines against COVID-19 disease.

3. Legal basis and relevant guidelines

This guidance should be read in conjunction with Regulation (EC) No 1234/2008 as amended by Commission Delegated Regulation (EU) 2021/756 and the Addendum to the Variation Guidelines (2021/C 215 I/01).
This guidance should also be read in particular in conjunction with the EMA Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2.

4. Regulatory and procedural requirements for applications to change vaccine composition (pandemic strain change) during a pandemic situation

Where a pandemic situation is duly recognised by the WHO or the Union, a variation application may be accepted to include pandemic strain(s) in the pandemic vaccine, if appropriate.

4.1. Variation classification

According to Annex II of the Commission Regulation (EC) No 1234/2008 (the Variations Regulation) as amended by Commission Delegated Regulation (EU) 2021/756, an update of the composition of a parent COVID-19 vaccine, should be submitted as a type II variation to the marketing authorisation.

This update can consist of a replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences.

This type II variation should be submitted under scope B.I.a.6. provided the technological platform of the vaccine remains similar. Other changes should be submitted as appropriate through a grouped variation (e.g. addition of a new manufacturing site) together with the strain change / addition.

The MAH should clearly indicate in the 'Present/Proposed' section all changes introduced vis-à-vis the parent vaccine.

4.2. Procedural steps

4.2.1. Pre-submission step

Based on the pandemic situation, it could be necessary to have vaccines available that allow dedicated response to different variants circulating. The selection of the variant(s) of concern would be a 'case-by-case' discussion taking into account the epidemiological situation, the urgency, relevant recommendations from authorities and the vaccination campaigns in the Member States. Furthermore, for such type II variation, due to the substantial amount of data expected, significant assessment resources need to be committed by the Rapporteurs. In that respect, the MAH should initiate discussions with the competent authority and, in particular, seek scientific advice as early as possible especially to discuss selection of the variant(s) of concern and whether the new selected strain(s) should be added or rather replace the existing one(s), as well as the supportive data package in that regard.

In addition, the MAH is invited to discuss with the EMA any adaptation of the Paediatric Investigation Plan to reflect the potential impact of the change in the strain(s) on the paediatric development, taking into account the epidemiological situation.

The timetable needs to be discussed in advance of the submission. For this reason, MAHs are requested to give advance notice of their intention to submit such variation, ideally 3 months in advance of the planned submission. This can be achieved by means of an email to the Product Lead, summarising the scope of the intended application and specifying the target submission date. The information will be used for planning purposes by the Agency and the Rapporteurs' assessment teams.

4.2.2. Submission

4.2.2.1. Format

The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

Applicants are advised to consult the relevant aspects of the post-authorisation procedural advice on type II variations as published on the Agency's website. In addition to the requirements foreseen in the question 'How shall I present my type II Variation application?', the following considerations specifically apply to these applications:

- Module 1 - Changes made in all modules and the product information to accommodate the new strain(s) should be detailed in the present and proposed section of the application form. The description of the variation scope should clearly indicate whether it relates to a replacement or addition of new strain(s).
- Module 1.6 – Environmental Risk Assessment (ERA), where applicable. Expert assessment with or without study report(s) or justification why they are not considered necessary and, the CV and signature of the expert should be provided.
- Module 1.8.2 - Updated RMP (with revision date and version number) describing the traceability, routine and possibly additional pharmacovigilance activities that would ensure a robust signal detection and observational research plan to be in place to monitor the safety profile of the new version of the vaccine.
- Module 3 – in case of only a replacement of the current strain(s), the current modules 3.2.S and 3.2.P should be updated as needed. In case that both original and new variant strain versions will

co-exist within the marketing authorisation, separate module 3.2.S (for each new variant strain) and module 3.2.P are needed.

- Module 5 (and Module 4, in case of non-clinical data) - The supporting documentation should be included within the variation application, taking into account the EMA Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2.

Applicants are strongly advised to include the summary of the main quality and efficacy results as part of the 'working documents' outside the eCTD structure. Provision of this document would facilitate the scientific assessment by the relevant scientific bodies. Further details can be found in the Harmonised Guidance for eCTD Submissions in the EU.

The fees for type II variations as provided in the Explanatory note on fees available on the Agency's website should be applied.

4.2.2.2. Product information, traceability and naming

4.2.2.2.1. Product information

In case the 'strain variant update' to the parent vaccine would consist of the addition of an active substance or combination of active substances, it may result in the co-existence of different versions of the vaccine under the same marketing authorisation which are potentially placed on the market at the same time. In order to distinguish the instructions for use for the various versions of vaccine, there should be separate product information *per* version of vaccine.

4.2.2.2.2. Traceability and naming

For vaccines that already have an international non-proprietary name (INN), the variant vaccine substance will be identified by the addition of a two or three-letter syllable as a prefix to the original INN, *as per* WHO INN Working Doc. 21.520.

The common name of the active substance is reflected in the Product Information. Of note, the type of vaccine is included in the common name as it is important information for HCPs. The common name of the active substance is anticipated to remain unchanged. The number of valences may be included in the common name if appropriately justified.

- Addition of a qualifier to the vaccine name for the specific variant strain presentation

MAHs should use qualifiers/abbreviations as part of the vaccine name in order to ensure adequate differentiation between the versions of the vaccine and help healthcare professionals and/or patients to administer/identify the appropriate version of the vaccine. The use of a qualifier, in addition to the batch number, will also facilitate traceability.

In the choice of an appropriate qualifier/abbreviation, MAHs may consider the standardised nomenclature for the naming of COVID-19 variants of concern and interest published by the WHO on 31 May 2021 (see https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ and https://www.who.int/news/item/31-05-2021-who-announces-simple-easy-to-say-labels-for-sars-cov-2-variants-of-interest-and-concern).

It is important to note that the choice of qualifier should be primarily targeting the differentiation between the vaccine versions and is not intended to provide information about variant strain coverage for immunisation.

It is the responsibility of the MAH to submit a proposed qualifier for the vaccine name which will be subject to NRG review. Proposed qualifiers will be reviewed on a case-by-case basis. MAHs should take into consideration the reduced space on the immediate labelling when proposing a qualifier (see next subsection 'Labelling aspects').

The addition of the qualifier should apply to both invented names and names with INN/common name + company name/trademark structure. In the case of INN/common name + company name/trademark, the qualifier should be placed directly between the INN/common name and the MAH name, to avoid that the qualifier might be inadvertently missed in electronic prescribing and dispensing lists.

Under normal circumstances qualifiers/abbreviations should not require translation, however, in this exceptional case, to support differentiation and safe use, and depending on the agreed qualifier, it might be translated into all the languages.

These will result in the following general constructions:

Invented name structure: Invented name + qualifier

INN+MAH structure: Prefix + INN + qualifier + MAH

Common name + MAH structure: Common name + qualifier + MAH

- Labelling aspects

COVID-19 vaccines are currently supplied in small vials. Therefore, in order to ensure readability and proper identification of the correct variant strain presentation, it needs to be guaranteed that any name including qualifier, will fit on the label of the primary packaging.

Furthermore, in order to ensure clear identification of the different strains covered by the same MA, packaging differentiation will be paramount. Due consideration must be given to other labelling aspects, such as the prominence of the INN(s), common name(s), strength and colour differentiation. The number of valences may also be reflected in the labelling, as necessary. Therefore, applicants will be requested to submit mock-ups addressing this requirement.

To further strengthen the traceability and pharmacovigilance monitoring, the variant vaccines may be differentiated at the level of the batch-code which will strengthen the differentiation between variant vaccine versions.

4.2.3. Evaluation steps

A pandemic variation will be assessed following an expedited timetable. It is emphasised that efficient interaction with the EMA to discuss critical issues in advance of the submission would be essential to allow acceleration of the variation procedure and, as relevant, potential rolling review.

As per Article 21 of Regulation (EC) No 1234/2008, it may be exceptionally and temporarily acceptable that certain quality, non-clinical or clinical data are missing. In this case, the MAH will have to identify these data as early as possible to the Agency with appropriate justification and submit the missing quality, non-clinical and/or clinical data within the time limit set in the marketing authorisation.

Once adopted by the CHMP, the opinion will be forwarded to the Commission for the decision-making process which may be accelerated as appropriate.

MAHs are reminded to engage with the relevant Official Medicines Control Laboratory (OMCL) early on to ensure that necessary tests/adaptations are made to permit release of the new variant product in a timely manner.

The post-authorisation procedures to submit the missing data and to vary the terms of the marketing authorisation may be reviewed under an accelerated timeframe if appropriate.