INN Working Doc. 21.520
April 2021
Distr.: PUBLIC
ENGLISH ONLY

International Nonproprietary Names for Variant COVID-19 Vaccine Active Substances

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Background

International Nonproprietary Names (INN) improve safe prescribing, good pharmacovigilance practice and worldwide recognition of medicinal products. Well-defined vaccine active substances such as mRNA, DNA, viral vectors and recombinant proteins can be assigned INN, and indeed some have, including COVID-19 vaccines[1]. Current COVID-19 vaccines with proven efficacy are based upon the viral spike glycoprotein S, or a gene encoding it, with the precise structure based upon sequences of the S protein gene made available to the scientific community in early 2020. As the pandemic has progressed, the SARS-CoV-2 virus has undergone mutation particularly in the spike glycoprotein. This has led to a decrease in the effectiveness of some vaccines against new variants of concern (VOC) of SARS-CoV-2 virus and some vaccine manufacturers are re-designing their vaccines to provide improved protection against these VOC. The modified vaccines are likely to have minimal changes to their RNA, DNA or protein structure, potentially involving a small number of codons or amino acids. Since it will be difficult and time consuming to prove the efficacy and safety of these modified vaccines through full scale, controlled, phase III trials, a consensus among regulators worldwide is developing that where an already authorised COVID-19 vaccine, with proven efficacy in a pivotal phase III study, is modified to target a VOC the new vaccine can be approved by an abbreviated process focussing on immunogenicity[2].

INN for Variant COVID-19 Vaccine Active Substances

Any change to the structure of a medicinal active substance will trigger a requirement for a new INN to be assigned. To highlight the close relationship of a variant COVID-19 vaccine substance to the original vaccine active substance, the INN of the variant active substance will be linked to the original INN (where one exists) by the addition of a short, random, two or three-letter syllable as a prefix to the original INN. This approach will be applied only to COVID-19 vaccine substances in which changes have been made to an original substance in order to direct the immune response to a VOC, i.e., a strain change, and where regulators are likely to authorise the variant vaccine by an abbreviated procedure. Any other change to the structure of the active substance, e.g., a change that alters the structure for other reasons such as improved antigen stability, or a change that improves expression or otherwise of a nucleic acid or vector, will be assigned a new unique alternative INN, not necessarily related to any preceding INN (where one exists). It is highlighted further that each active substance of a multivalent COVID-19 vaccine requires its own INN.

The INN Programme also recognises that for the INN of new variant COVID-19 vaccines to be useful, the INN must be assigned and adopted within a much shorter time frame than is usual (assignment and approval of a recommended INN usually takes > 1 year). To this end, following submission of a request for an INN for a variant COVID-19 vaccine active substance, where the original vaccine substance has already been assigned an INN, the INN Programme will exceptionally review such an application *ad hoc* rather than assessing them at a biannual INN Consultation. Following receipt of an official request for such an INN, the INN Expert Group will review and reach consensus agreement on the new INN within 4 weeks of receipt of the request, following which the applicant will have 2 weeks in which to accept (or not) the proposed new INN. From the outset, the applicant must also submit all relevant information concerning the substance, but especially the sequence, in order for the INN Definition to be drafted, with the intention of finalising the Definition within 4 weeks of the submission of the application. Following acceptance by the applicant, the proposed INN will be published on the WHO INN web site for public comment for two weeks after

[1] INN Proposed List 124 -COVID- (who.int)

[2] Access Consortium statement on authorisations of modified Covid-19 vaccines for variants (swissmedic.ch)

which (assuming no major objections) the INN will be acknowledged as an extraordinary approved variant vaccine INN, available for use by the applicant.

The fee for a request of an INN for a variant COVID-19 vaccine active substance where a previous INN has been assigned to the original vaccine substance will be waived. Standard fees will apply to all other COVID-19 vaccine INN requests although a reduced time frame in assigning the INN may be considered.

Vaccine developers are encouraged to apply for an INN for a variant COVID-19 vaccine as early as possible. The INN Programme will endeavour to complete the assignment of an INN to a variant COVID-19 vaccine within the time frame outlined above but ultimately this will depend on good communication and collaboration with the applicant. These are interim measures to provide for an optimal solution in assigning INN to 'strain change' vaccines during the COVID-19 pandemic and may be changed with experience and accrual of information. The INN Programme is also considering a proposal to establish a database of information related to a vaccine, including the site of manufacture, and which could be incorporated into the INN in the form of a Vaccine Identifier, as yet to be defined.

Summary of proposals for assigning INN to COVID-19 vaccine substances

Nature of vaccine	**INN assignment process**	**Nature of INN to be assigned**	**Fee**
Original SARS-CoV-2 vaccine	Standard process but reduced timeframe may be considered	New INN based upon applicant's suggestions and conforming to INN rules of nomenclature	Standard fee
Strain change of pre-existing vaccine with pre-existing INN	Accelerated process (see above text for details)	Short random syllable of 2-3 letters added as prefix to pre-existing INN	Fee waived
Strain change of pre-existing vaccine with no INN previously assigned	Standard process but reduced timeframe may be considered	New INN based upon applicant's suggestions and conforming to INN rules of nomenclature	Standard fee
Modifications to a vaccine substance with or without a pre-existing INN over-and-above strain changes such as changes resulting in non-antigenic structural changes or in the control of expression	Standard process but reduced timeframe may be considered	New INN based upon applicant's suggestions and conforming to INN rules of nomenclature	Standard fee