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Approval process for COVID-19 vaccines v.2

Adaptation of vaccines to new SARS-CoV-2 variants

Introduction

On 23 December 2020, two days after the European Medicines Agency (EMA) issued its favorable opinion on the authorization of the Covid-19 vaccine developed by BioNTech and Pfizer and, in a context in which there were voices expressing certain concern about the safety of the vaccines, we published a special CAPSULAS aimed to dispel any doubts regarding their approval process, highlighting the rigorous nature of conditional marketing authorizations. This CAPSULAS is an update focused on recent developments at the regulatory level that have an effect on said authorization process.

We refer to the Reflection Paper that EMA's Committee for Medicinal Products for Human Use (CHMP) approved on 23 February 23 2021 on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2, which defines an accelerated process for the approval of the adaptations of the vaccines to new variants of the virus and provides guidance to manufacturing laboratories on the requirements to be fulfilled and steps to be followed. The EMA is, thus, addressing another of the most recent concerns surrounding vaccines. It does so with a twofold objective: to be sufficiently agile in its response to the evolution of the virus and to guarantee the efficacy and safety of the variant vaccines that are developed. To this effect, the Reflection Document refers to the content of modules 3, 4 and 5 of the dossier to be submitted to obtain authorization for new vaccines against SARS-CoV-2) variants.

The starting point

CHMP guidance starts from the assumption that a new variant vaccine would be based on the same technology and platform as the original vaccine, a vaccine already approved in the EU for the prevention of COVID-19. The difference would be on the antigen (the substance that triggers the production of antibodies) selected to generate the immune response.

Quality and manufacturing data for Module 3

The variant vaccine is expected to be produced by the same manufacturer, in line with the processes and controls of the original vaccine. The manufacturer should generate data demonstrating that the quality of the variant vaccine meets the approved standards for the original vaccine.

Non-clinical data (laboratory studies) for Module 4

No further laboratory studies are required to support the development of variant vaccines. However, if the applicant conducts such studies their results will be evaluated and taken into consideration by the CHMP along with the clinical data.

Module 5 clinical data (clinical trials)

This is the most relevant aspect for the purpose of analyzing the efficacy and safety of vaccines. For this reason, it is the module on which the Reflection Paper has the greatest impact. CHMP

considers that it is not necessary to require large -scale safety and efficacy studies, since they have already been analyzed for the authorization of the original vaccine and, moreover, they would present feasibility limitations. What is required is to demonstrate the efficacy of variant vaccines through immunogenicity studies (i.e., measuring the ability of an antigen to activate our defenses) designed to investigate the immune response triggered by the variant vaccine against the variant virus.

The Paper differentiates between two different situations, for which the efficacy of the variant vaccine must be analyzed: (i) when this variant vaccine is administered as a primary vaccination (i.e. the first vaccination ever received by the subject against the virus) and; (ii) when a single dose of the vaccine is administered to subjects who have previously received a primary vaccination with the original vaccine (as a booster to protect them from the new strain of the virus).

In the first case, EMA recommends conducting at least one clinical trial on unvaccinated subjects who have never been infected with SARS-CoV-2. In this trial, subjects will randomly receive either the original vaccine or the variant one. The aim is to gather evidence to compare and demonstrate that the immune response generated by the variant vaccine against the variant virus is of the same magnitude as the immune response elicited by the original vaccine against the original virus (by measuring the levels of neutralizing antibodies generated).

Regarding the second case, EMA considers that the immune response induced by a dose of the variant vaccine against the variant strain should be compared with the available data of the immune response recorded during the clinical trials that were conducted with the original vaccine. In this regard, the trial should be conducted with subjects with prior vaccination having the original vaccine fully documented (preferably those who have already participated in clinical trials with the original vaccine), administering to all participating subjects a dose of the variant vaccine and comparing the immune response generated by the original vaccine against the original strain of the virus with the response generated by the variant vaccine against the variant strain. If this is not possible, the antibody data generated after the original vaccination should be drawn from a population that matches the population enrolled in the prospective trial of the variant vaccine, based on age, sex, and the presence of significant underlying comorbidities.

Conclusion

Although nowadays the main concern is still controlling the pandemic, we must also prepare ourselves to live with the virus and the new challenges it may entail in the future. To this end, it is essential that, just as the virus evolves over time, so does the regulator. It is good news that EMA is equipping itself with the means to move in this direction and to not lag behind in this battle.