



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

16 November 2020  
EMA/592928/2020  
Committee for human medicinal products (CHMP)

## EMA considerations on COVID-19 vaccine approval

Draft agreed by ETF <sup>1</sup>	12 November 2020
Adopted by CHMP	16 November 2020

Keywords	COVID-19, SARS-CoV-2, vaccine, clinical requirements, clinical efficacy, clinical safety
----------	--

<sup>1</sup> COVID-19 pandemic EMA Task Force (ETF); <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/emas-governance-during-covid-19-pandemic# covid-19-ema-pandemic-task-force-section>



# EMA considerations on COVID-19 vaccine approval

## Table of contents

<b>1. Introduction.....</b>	<b>3</b>
<b>2. Discussion.....</b>	<b>3</b>
Clinical requirements for marketing authorisation (MA) .....	3
Clinical efficacy.....	3
Clinical safety.....	4
Post-approval follow-up for safety and efficacy .....	4
<b>3. Conclusion .....</b>	<b>4</b>
<b>4. References.....</b>	<b>5</b>

# 1. Introduction

The ongoing SARS-CoV-2 pandemic is still far from being under control with more than 1 million deaths already recorded. While the unprecedented scenario of the pandemic requires special considerations on the regulatory requirements for approval, the benefits and risks of COVID-19 vaccines need to be properly assessed based on detailed information on manufacturing, nonclinical data and well-designed clinical trials.

Given the global nature of the pandemic and the need to ensure that vaccine developers generate robust evidence that meets the needs of regulators around the globe, EMA and international medicines regulators (ICMRA) have agreed [key principles of trial design for COVID-19](#).

Procedures are in place to allow rolling review of the quality, nonclinical and clinical data as they are submitted to EU regulators. Marketing authorisation can be granted in the EU when the evidence for any one COVID-19 vaccine shows that the benefits of vaccination are greater than any known or potential risks.

## 2. Discussion

### ***Clinical requirements for marketing authorisation (MA)***

The EMA has been in touch with developers of vaccines since early in the pandemic to discuss their overall development strategies. Advice has been given on regulatory requirements to facilitate progression into clinical trials and from safety and immunogenicity trials to efficacy trials.

The EMA expects that at the time of MA vaccine safety and efficacy will have been demonstrated in adults and should include individuals with pre-existing comorbidities and individuals aged above 65 years.

### ***Clinical efficacy***

Currently, it is expected that at least one well-designed large-scale phase 3 efficacy trial would be required to support the marketing authorisation of a COVID-19 vaccine.

The primary endpoint in pivotal vaccine efficacy trials should be laboratory-confirmed COVID-19 disease of any severity. The primary analysis of efficacy should be restricted to study participants who were seronegative for the virus at baseline as it is important to show that the vaccine protects subjects not likely to have been exposed to the virus before.

Developers of vaccines have been advised to design and power their Phase 3 efficacy trials to provide a convincing demonstration of efficacy based on stringent trial success criteria. In doing so, they need to make assumptions about possible rates of vaccine efficacy that might be observed, in order to estimate the number of participants to enrol and when to analyse the data. Specifically, they have been advised when designing trials to consider a point estimate of vaccine efficacy that is at least 50% and a lower bound of the 95% confidence interval around the point estimate that is above 20% and preferably above 30%. If the actual results meet these criteria, they would be sufficient to provide a convincing demonstration of vaccine efficacy and, if accompanied by an acceptable safety profile, would support a regulatory decision.

It is recognised that the actual results of a vaccine efficacy trial may show that the lower bound of the 95% confidence interval around the point estimate of vaccine efficacy is above zero (i.e. the vaccine is superior to the control) but it may not exceed 30% or even 20% in some cases. In such instances, the point estimate of vaccine efficacy may not exceed 50%. In all cases, the clinical assessment by EU

regulators will take into account the actual point estimate of vaccine efficacy, the precision around that estimate (based on the confidence interval) and the safety profile. Therefore, if the actual results show that the vaccine is superior to the control group, i.e. the vaccine is efficacious, vaccine developers are encouraged to discuss the data with the EMA.

The secondary analyses of efficacy should include an estimate of protection against symptomatic disease in study participants regardless of whether they were seronegative or seropositive for SARS-CoV-2 at study baseline. It is also recommended that the trials attempt to assess vaccine efficacy against severe disease, subject to accrual of sufficient cases to support an analysis. The definition of severe disease should follow acceptable and standardised criteria such as those defined by [WHO](#). Collection of data on acquisition of SARS-CoV-2 with or without clinical symptoms to provide an estimate of prevention of infection is also of interest and, if shown, may be important to inform public health vaccination strategies.

### ***Clinical safety***

The evaluation of safety of SARS-CoV-2 vaccines will follow the standard principles outlined in [EMA guidance documents](#). Since pre-licensure vaccine efficacy trials will have been conducted, it is anticipated that several thousand individuals will have been exposed to the vaccine at the time of initial marketing authorisation, which will allow an assessment of uncommon risks. Most adverse reactions to vaccines occur within 4-6 weeks from vaccination. In principle, conditional marketing authorisation for a COVID-19 vaccine could be based on review of at least 6 weeks post-vaccination safety data.

### ***Post-approval follow-up for safety and efficacy***

Whenever feasible, the EMA has recommended that clinical trial participants should be followed for safety and efficacy within their randomised groups for at least one year after completing vaccination. This is recommended even if a conditional approval based on a convincing interim analysis of efficacy has occurred before all study participants have reached one year. These longer-term data are important to document any late adverse reactions and to assess whether there is waning of protection against SARS-Cov-2 disease over time.

Suitable pharmacovigilance system has to be in place across the EU at the time of initial marketing authorisation to gather and promptly report data on adverse reactions during vaccination campaigns. A core Risk Management Plan has been drafted to structure the requirements for post-approval monitoring and enhanced safety surveillance as soon as the vaccines are deployed, so that EMA can act as fast as possible when a signal is detected.

Studies that estimate vaccine effectiveness during campaigns will be important to better understand immediate and longer-term protection in a broader range of individuals (e.g. based on age and other host characteristics) than included in pre-licensure trials. EMA is collaborating with ECDC and the Member States to allow the definition of networks across Europe capable of conducting safety surveillance and effectiveness studies.

## **3. Conclusion**

The EMA has recommended that vaccine developers should plan the pivotal efficacy trials with stringent success criteria, aiming to provide a convincing demonstration of efficacy in the population studied. Nevertheless, if vaccine efficacy is demonstrated based on less stringent criteria, vaccine developers are encouraged to submit the results for regulatory review. In all cases, the clinical assessment by EU regulators will take into account the actual point estimate of vaccine efficacy, the

precision around that estimate (based on the confidence interval) and the safety profile. Follow-up of study participants for safety and efficacy after MA is considered important, along with assessment of safety and effectiveness of COVID-19 vaccines during vaccination campaigns.

## 4. References

EMA, 2020; *International regulators align positions on phase 3 COVID-19 vaccine trials*

<https://www.ema.europa.eu/en/news/international-regulators-align-positions-phase-3-COVID-19-vaccine-trials>

WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection; [A minimal common outcome measure set for COVID-19 clinical research](#). *Lancet Infectious Diseases* 2020;20: e192-97

EMA, 2020; *Guideline on clinical evaluation of vaccines*

[https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-evaluation-vaccines-revision-1\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-evaluation-vaccines-revision-1_en.pdf)