Dear Dr Mäkelä,

Thank you for contacting the CHMP and PRAC chairs and vice-chairs. Please allow us to provide some clarifications on the questions you raise:

**1) Have you required the Pharmaceutical Companies to investigate the biomolecular mechanisms of the SAEs reported from gene technology-based injections in order to evaluate whether there is a true causality between Covid-19 vaccines and reported SAEs?**

Based on your initial letter we assume that with 'gene-technology based' vaccine you are referring to mRNA vaccines (Comirnaty and Spikevax) and viral vector vaccines (Vaxzevria and COVID-19 Vaccine Janssen). Nearly all biological medicines currently available in the EU, including vaccines, are produced by recombinant cells (i.e. gene technology) and have been for many years.

Collecting reports of suspected side effects is one of the pillars of the EU safety monitoring system. The EU regulatory network continuously monitors EudraVigilance (the EU's centralised database of suspected side effects) to detect any new safety issues. All suspected side effects reported are collected in EudraVigilance and are assessed and analysed together with other similar cases (as well as with results of clinical studies and scientific literature) to determine whether they reveal unusual or unexpected patterns in the reporting which could indicate a possible new side effect — or a new aspect of a known side effect — and therefore require further investigation. This emerging information is known as a 'safety signal'. When a safety signal requires further investigation, EMA's safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), gets involved to carry out a full assessment; new data may be brought to bear and other bodies may be consulted. These data include clinical trial results, epidemiological studies monitoring the safety of the vaccine, toxicological investigations and any other relevant information. Plausible biological mechanisms are also considered. However please note that an investigation into such mechanism is not a requirement to establish potential causality and consider further regulatory action, such as an update of the medicine's product information or any other action to minimise or manage the risks.

Further details are described in the Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines. https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf

In addition to the signal detection and management activities performed by EMA, the marketing authorisation holders of the vaccines also have obligations to monitor all available data. Moreover, they need to submit to the authorities monthly safety reports and periodic safety updates reports which are routine safety and regulatory tools supporting the continuous monitoring to ensure that the benefits for the vaccine in question outweigh its risks.

In order to better understand how specific risks are monitored you may wish to refer to the medicines' risk management plans, which are available through the following links:

Comirnaty: https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

COVID-19 Vaccine Janssen: https://www.ema.europa.eu/en/documents/rmp-summary/covid-19-vaccine-janssen-epar-risk-management-plan_en.pdf

Spikevax: https://www.ema.europa.eu/en/documents/rmp-summary/spikevax-previously-covid-19-vaccine-moderna-epar-risk-management-plan_en.pdf

Vaxzevria: https://www.ema.europa.eu/en/documents/rmp-summary/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-risk-management-plan_en.pdf

**2) If so, within what time frame have the Pharmaceutical Companies already initiated these investigations and taken other necessary measures, such as recalling injections off the market and, if not, have you requested clarifications on these measures?**

A recall is a regulatory action that can be considered amongst other actions in case of a safety, efficacy or quality issue with a medicine that results in a risk that outweighs the benefits provided. Please note that to date no COVID-19 vaccine has been recalled. Certain serious but rare side effects have been identified. Nevertheless, these risks are outweighed by the vaccines' benefits in preventing COVID-19, a serious and potentially fatal disease.

However, some Member States may have suspended the use of a vaccine while EMA was investigating a safety signal (such as TTS for Vaxzevria) or may have chosen to restrict which groups should be given certain vaccines. These were decisions by the public health institutions guiding relevant national vaccination campaign and may vary from country to country.

Information on the outcomes of the assessment of safety data carried out by EMA's Pharmacovigilance Risk Assessment Committee and actions that have been taken in the context of the vaccines' regular safety monitoring can be found in the safety updates of the individual medicines, which are available on the following pages:

Comirnaty: https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

Spikevax: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax-previously-covid-19-vaccine-moderna

Vaxzevria: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca

Covid-19 Vaccine Janssen: https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen

**3) What have you done / intend to do to prevent the growing number of deaths and other serious injuries experienced by the vaccinees in the future?**

As for all medicines, EMA is monitoring all COVID-19 vaccines for side effects. In comparison with other medicines, the monitoring of COVID-19 vaccines is far more intense. Although EMA receives many reports of suspected side effects, this does not mean that the adverse events or deaths reported were caused by the vaccine. In the end, the great majority of such reports cannot be shown to be linked to the vaccine. Only careful review and analysis, taking into account data from relevant sources such as clinical and laboratory studies, background rates of events and the consideration of a plausible mechanism, allows a conclusion that a particular event is likely to be caused by the medicine. It is also important to consider that the vaccines would not prevent deaths from other causes.

Any numbers have to be seen in the context of the huge numbers of persons given the vaccines (298 millions full vaccinations in the EU/EEA), as well as in comparison to the burden of the disease, i.e. the number of deaths associated with COVID-19 infection (currently estimated by ECDC to be over 700,000 in the EU/EEA, see https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea#:~:text=COVID-19%20situation%20update%20for%20the%20EU%2FEEA%2C%20as%20of,%20%207.40%20%2027%20more%20rows%20).

As part of the ongoing safety monitoring, a few rare and serious side effects of the different vaccines have been identified and, following review, prompt actions have been taken. We have described these, and the very small numbers of fatal cases in the associated reports, in the monthly safety updates we publish for each vaccine (see https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/safety-covid-19-vaccines).

We hope the above reassures you that enhanced and stringent safety monitoring is in place for all COVID-19 vaccines, to ensure that the benefits always outweigh the risks.

Kind regards,

Juan Garcia Burgos,

Head of Public and Stakeholders Engagement