EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Marcel de Graaff
[redacted]

4 July 2024
EMA/277138/2024

Dear Mr De Graaff,

Subject: Responses to your follow-up questions of 3 June 2024

Thank you for sharing the list of questions that you wish to discuss with EMA experts in person.

After carefully reviewing these questions and considering that we have already addressed the majority of these matters in our previous extensive correspondence, we do not consider that a meeting would be very helpful.

We have, however, prepared further written responses to your questions which we hope you find useful.

1. Transmission control

Why did the EMA not intervene when all member states were advocating and using the C19 injections for transmission control as with the digital covid certificate, although no marketing authorisation was grated for this purpose. Moreover no data supports this application.

EMA has made it clear that COVID-19 vaccines have been authorised to protect vaccinees against COVID-19. At the time of the first approval of a vaccine for COVID-19, EMA also stated explicitly that there were no data on the effect of vaccination on transmission.

As with other vaccines, this does not mean that they cannot be used with the additional aim of reducing transmission. Vaccines are rarely authorised specifically for reducing transmission of a disease. Decisions on the use of the digital covid certificate are not within the remit of EMA.

We addressed this point in our reply to your letter of 1 December 2023.

2. Batch related adverse events reports

In which extent has EMA looked into the batch dependencies themselves. As more scientific evidence indicate batch dependency in the adverse effects reporting we expect EMA to have looked into this problem as well. Can EMA provide us this analysis? Can we have the OCABR reports of all batches used in Europe?

When EMA monitors medicines, we check for safety signals, which are essentially new data or information about possible side effects. During the investigation of a signal, we consider whether there are data indicating that a side effect could be batch-specific.

For example, when serious blood clots were first reported with Vaxzevria, it was thought that the adverse event could be batch specific and some countries stopped using the batch in question. A

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further investigation by EMA's safety committee (PRAC) taking into account all the evidence showed that the blood clots were not linked to any particular batch. As you may know, serious side effects of Vaxzevria did not affect all age groups in the same way, and differences in reporting per batch would be expected if batches are not used in the comparable populations.

Batch specific side effects can occur if some batches are defective, which is why the EU regulatory network has stringent rules to prevent defective products from being placed on the market. We would like to highlight that Official Medicines Control Laboratories (OMCLs) in EU Member States check data on the quality of all batches of COVID-19 vaccines before they are released for use in the EU. Only batches that comply with EMA's approved quality specifications can be used in the EU. Please note that the results of the tests are held by the OMCLs.

We addressed this point in our reply to your letter of 1 December 2023.

3. Sex difference reporting

As 70-75% of all SAE-reports are related to women, what have EMA done in this light? And what have withheld EMA from warning women? What does the EMA analysis say about this anomaly? General uptake is 50-50.

It is not unusual to have a disparity in the number of reports from men and women. Some gender-based side effects (e.g. gynaecological symptoms) could contribute to this disparity as well as the fact that some side effects affect one group more than the other. For example, myocarditis and pericarditis were reported more frequently in young men than in young women. EMA ensures the summaries of product characteristics (SmPC) and package leaflets contain the relevant up-to-date information.

When assessing signals, EMA stratifies the data by age and gender and considers other possible contributory factors.

4. Underreporting

Most of the reports concerning SAE to mRNA-injections are done by recipients, normally health professionals do the reporting. Why did doctors and medical workers refrain from reporting? What has EMA done to secure proper reporting from health professionals?

In the EU, suspected side effects should be reported either directly by the patients themselves or via their healthcare professional to their national competent authority or to concerned marketing authorisation holder.

Member States have put in place reporting channels in their national languages which should facilitate spontaneous reporting. Please note that reports concern suspected side effects and a healthcare professional will only send a report if they consider an adverse event to be possibly linked to the medicine. In many cases, increased media or social media attention may explain spikes in reports from the general public.

EMA's role in this area is to share information and raise awareness about how to report side effects in the Member States and to help explain what type of information needs to be reported. You can find more information on our website.

While we are aware of the problem of underreporting in general, we have no reason to believe that this is a bigger issue with mRNA vaccines than with any other medicinal products. Furthermore, our assessment of safety data takes underreporting into account.

5. Long-term side effects (security surveillance)

Expected long term side-effects are cancer, immunodeficiency and infertility, multiple studies have indicated a rise in these ailments. Do you see this in the phase 4 trials? At what incidences would a substance be pulled from the market? How does EMA ensure the surveillance of long-term side effects. Can EMA provide data from the post marketing safety studies concerning the COVID19- vaccines?

Please refer to our replies to your letters of 1 December 2023 and 5 January 2024 as regards the work of EMA and national authorities in assessing safety data on COVID-19 vaccines. We noted that there has been no confirmed signal of cancer following COVID-19 vaccination.

We would also like to point out that our continuous assessment of safety data from mass vaccination campaigns across the world over 4 years does not show a link to any of the other conditions you list.

At the time of authorisation of Comirnaty and Spikevax, the marketing authorisation holders were required to provide additional safety data and submit final clinical study reports - by December 2023 for Comirnaty and December 2022 for Spikevax.

You can find information on the post-authorisation safety monitoring of COVID-19 vaccines on the web pages of each vaccine on our website, as well as on the dedicated webpage of the Vaccine Monitoring Platform, where a list of studies and links to detailed information in the HMA-EMA Catalogue of studies is included.

6. GMO / DNA contamination

As the commercial mRNA injections are produced using GMO bacteria legally the mRNA is GMO as well. Moreover the fragments of the broken-up plasmids are still present in the substances. As multiple scientific publications prove that these fragments contain intact promoter regions. (In the reports of the CAT of December 2020 and march 2021 it is clearly stated that the vector and the LNP-mRNA injections fall under the category of GMO-gene therapy.) Both with gene therapy as with GMO's products test have to be done for impact and integration assessment. Can you share the results of these tests? If not, how did EMA determine the current threshold for mRNA integrity and the threshold for DNA contamination?

We explained in reply to your letter of 4 October 2023 why mRNA vaccines are not GMO products. Some vaccines such as those that contain attenuated viruses or live vectors may fall within the definition of a GMO but not mRNA vaccines.

We also explained in the same letter why mRNA vaccines are not considered gene therapies: the aim of vaccination is not to restore, correct or modify human genes. Please note that the Committee for Advanced Therapies (CAT) did not conclude that mRNA vaccines are GMO products or constitute gene therapy.

In our reply to your letter of 5 January 2024, we explained that plasmid DNA is used to make a so-called linear DNA template, which is then transcribed to make the mRNA for the vaccines. The manufacturing process includes steps to break down the template DNA as it is no longer needed (DNase digestion). The manufacturing process is carefully controlled to ensure that the template DNA is removed. The DNA is broken up and only very small fragments may remain as residue.

With respect to residual DNA, the manufacturing process of mRNA vaccines is carefully designed and controlled to ensure that the level of residual DNA is below acceptable and safe levels. Furthermore the plasmid DNA used in production does not contain oncogenes and is not replication competent in mammalian cells.

7. Expert group for 2021/756

How can the expert group change the text into a law giving act? By adding the words 'coding sequence' in article 21 and 23 and annex I & II . Were employees of the EMA involved in this group?

Regulation (EU) 2021/756 of 24 March 2021 amending Regulation (EC) No 1234/2008 is a delegated act that is prepared and adopted by the European Commission. Questions about the text and preparatory work for the Regulation should therefore be addressed to the European Commission, as the responsible EU institution.

8. Efficacy determination

As studies show that the efficacy was grossly over-estimated and mostly because of previous infections that did give immunity and the seasonality effect. Does the EMA agree that none of these injections come close to the 50% threshold for approval?

At the time of first authorisations, efficacy clinical trials compared COVID-19 vaccines with placebo and showed that people who were vaccinated had significantly fewer cases of disease than those given placebo, with efficacy rates reaching as high as 95%. The studies demonstrating these efficacy rates and the assessment of these studies are clearly documented in the European Public Assessment Reports on our website.

Thank you for taking the time to write to us. While we will continue to make every effort to respond to questions you may have, please be aware that repeating the same questions several times takes away important resources that EMA could use to address enquiries from other EU citizens.

We will therefore no longer respond to repeat questions in the future. We appreciate your understanding in this matter.

Please refer to our previous replies for more detailed answers to some of your questions above.

Kind regards

Emer Cooke

Executive Director