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European Medicines Agency

Dear Honourable Members of Parliament Marcel de Graaff, Gilbert Collard, Francesca Donato, Joachim Kuhs, Mislav Kolakušić, Virginie Joron, Ivan Vilibor Sinčić and Bernhard Zimniok

Thank you for your letter of 4 October 2023 in which you call for the suspension of the marketing authorisations of the mRNA COVID-19 vaccines Comirnaty and Spikevax.

The European Medicines Agency is committed to protecting public health by conducting thorough scientific assessments of medicinal products for the EU. We are equally dedicated to ensuring that the public and their representatives in the European Parliament are informed of the reasons why their medicines are authorised and of the measures we take to monitor them once they are available.

We should also emphasise that EMA focuses mainly on one aspect of EU health policy, namely the authorisation and monitoring of medicines and vaccines. When our scientific committees issue recommendations, other bodies, such as the European Commission, the European Centre for Disease Prevention and Control (ECDC) and national health and vaccination authorities can consider them as they develop immunisation policies to protect the public.

Please find below direct responses to the questions you raise in your letter.

1. The authorised indications

   You state that based on the authorised indications, the vaccines 'should only be administered to individuals who seek personal protection, and they are not authorised for the purpose of reducing transmission or infection rates (transmission control)'. You also state that the authorised indication does not align with uses promoted by 'pharmaceutical companies, politicians, and health professionals'.

   You are indeed correct to point out that COVID-19 vaccines have not been authorised for preventing transmission from one person to another. The indications are for protecting the vaccinated individuals only.

   The product information for COVID-19 vaccines clearly states that the vaccines are for active immunisation to prevent COVID-19. In addition, EMA's assessment reports on the authorisation of the vaccines note the lack of data on transmissibility.

EMA will continue to be transparent about the approved uses of COVID-19 vaccines and identify areas where we need to tackle misconceptions.

2. Authorisation of vaccines targeting the Omicron XBB.1.5 subvariant

You note that data from clinical trials are not available for adapted vaccines targeting Omicron XBB.1.5 subvariant. Given this and the fact that the international public health emergency is over, you question the need for authorising the adapted vaccines at this time.

We would like to stress that the authorisation of adapted COVID-19 vaccines is not contingent on the continuation of the public health emergency. The authorised indications do not restrict the use of the vaccines to an emergency.

Furthermore, data from clinical trials were not a scientific requirement for the Omicron XBB.1.5 adapted vaccines because of the information derived from the originally authorised and earlier adapted vaccines.

In its decisions to recommend authorisation of vaccines targeting the Omicron XBB.1.5 subvariant, EMA's human medicines committee (CHMP) considered all the available data on both the originally authorised vaccines and earlier adapted ones, including data on safety, efficacy and immunogenicity (how well they trigger immune responses). In addition, the Committee assessed laboratory data on the responses of the adapted vaccines against XBB.1.5 and related strains of SARS-CoV-2, the virus that causes COVID-19. Please also note that for Spikevax XBB.1.5, the Committee assessed some clinical data from an ongoing study.

Where the ending of the public health emergency may be relevant is in the vaccination strategies of EU Member States and the advice given to the general population. In this regard, the product information for COVID-19 vaccines state that the use of the vaccines 'should be in accordance with official recommendations'.

3. Environmental risk assessments for genetically modified organisms (GMOs)

I understand you have concerns about Regulation (EU) No 2020/1043/EU ("the Regulation") which, as stated in its Article 2 of the Regulation, allows for the conduct of some clinical trials with products containing GMOs without a prior environmental risk assessment.

You also note that, according to Article 4, the Regulation shall 'apply as long as WHO has declared COVID-19 to be a pandemic or as long as an implementing act by which the Commission recognises a situation of public health emergency due to COVID-19'.

It is important to first clarify that mRNA vaccines are not considered genetically modified organisms. It is our understanding that the Regulation was intended for other vaccines, such as vaccines that 'contain attenuated viruses or live vectors, which may fall within the definition of a GMO.'[1]

That said, we can provide you with information on the status of the environmental risk assessments for Comirnaty and Spikevax.

At the time of the initial authorisations of Comirnaty and Spikevax, the CHMP noted in its published assessment reports that, due to their nature, 'vaccines and lipids are unlikely to result in a significant risk to the environment'. The Committee further noted that it was acceptable for environmental risk assessment studies not to be provided in the applications for marketing authorisation. You can find more information in the published assessment reports on EMA's website

[1] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R1043

as well as the *CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use*.[2]

On the basis of the Regulation, you also imply that with the end of the public health emergency, companies should now provide prior environmental risk assessments for adapted vaccines.

Having clarified that the vaccines are not GMOs and the Regulation does not therefore apply, we would also like to clarify that adapted vaccines are not new vaccines with marketing authorisations separate from those of the originally authorised vaccines. Any theoretical environmental risks they may pose are considered to be the same as those of the originally authorised vaccines.

On a separate note, national authorities approve clinical trials in the EU and would therefore be the authorities to receive any environmental risk assessments required before the start of a clinical trial.

4. Safety, efficacy and quality of vaccines

Safety

In response to your comments about the safety of the vaccines, we would like to point out that EMA and national authorities continuously monitor data on reported side effects. It is also important to clarify that a report of a suspected side effect is not in itself evidence that a vaccine caused the adverse event in question.

Such adverse events can occur for other reasons in vaccinated people, as they do in unvaccinated people. With a large proportion of the general population having had the vaccines, we expect many reports of conditions occurring at or soon after vaccination.

To determine whether a vaccine caused an event, authorities have to assess all the relevant data, including data that might indicate that the condition occurs at a higher rate in vaccinated or recently vaccinated people than in others.

As shown in the product information for both vaccines, most side effects are mild, although more serious ones can occur. You note the risk of myocarditis and pericarditis, which EMA has assessed and described in the product information.[3,4] All safety information should be considered carefully before administering or recommending vaccination.

Efficacy

You say that 'a fundamental requirement for a vaccine is to stimulate long-term immunity', noting that 'if a vaccine only offers protection for less than a year, it falls short of this crucial criterion'. We take from your comment that no vaccine should be authorised without evidence of long-term protection.

While long-term protection is always desirable, imposing such a requirement would have severe consequences for public health and put vulnerable people in danger. Establishing long-term protection may also not be feasible and, in the case of COVID-19, will be complicated by the evolution of SARS-CoV-2, a situation that we also observe with influenza.

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[2] https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use-scientific-guideline

[3] https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-29-november-2-december-2021

[4] https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-myocarditis-pericarditis-tozinameran-covid-19-mrna-vaccine_en.pdf

When EMA recommends the authorisation of a vaccine, it provides information on the data it assessed to help vaccination authorities and healthcare professionals make recommendations to the wider public.

Qualitative and quantitative properties

In your section 'Lack of declared qualitative and quantitative properties', you refer to the lack of data on the prevention of transmission rather than the qualitative and quantitative properties of the vaccines. We have addressed the issue of transmissibility above.

Quality of submitted documentation

In arguing against the authorisations of the vaccines, you refer to 'irregularities and illegalities in altering the categorization of medicines' and 'changes in the rolling review and conditional marketing authorization procedures, as well as modifications to the definitions of vaccines and immunity'. We comment on these concerns, to the extent that we can, in the sections below.

You also cited a BMJ article by Paul D Thacker about Ventavia, a contract research organisation that worked on some clinical trial sites for Comirnaty.[5]

EMA, in close collaboration with the US Food and Drug Administration (FDA), looked into the issues reported in the BMJ and concluded that the deficiencies identified do not jeopardise the quality and integrity of the data from the main Comirnaty trial and have no impact on the benefit-risk assessment.

The main trial that supported the authorisation of Comirnaty included around 44,000 people and was conducted in about 150 sites around the world. Ventavia enrolled around 1,000 subjects in 3 sites in the United States, representing less than 3% of the total study population. The issues affected one of those 3 sites and mainly concerned a lack of trained staff which resulted in deficiencies such as delays in data entry and query resolution. The marketing authorisation holder audited the company at the end of 2020, and corrective actions were taken, including oversight visits and hiring of additional staff. These actions were deemed appropriate.

Ventavia also recruited participants in studies on the use of Comirnaty in children and as a booster (representing about 1.6% and 3.5% of the total study populations respectively). As with the main study, EMA looked at the relevant data and concluded that the issues reported at the concerned site have no impact on the assessments of the benefits and risks of the vaccine for these uses. The corrective actions taken by the company were put in place before these later trials started enrolling participants.

Summaries of product characteristics and package leaflets

You note that the summaries of product characteristics (SmPCs) for Comirnaty and Spikevax 'are so voluminous that they have become de facto illegible for both doctors and citizens making informed consent impossible'. You also note a similar problem with the package leaflets.

These documents have indeed grown in size as new strengths and new adapted vaccines have been approved. EMA is currently considering ways to improve the way information is presented in SmPCs and package leaflets, not only for COVID-19 vaccines but for all medicines evaluated centrally in the EU. We are also looking at other ways to present information in our lay language questions and answers (Q&A) documents (what we call medicines overviews).

Good manufacturing practices

[5] Thacker PD. Covid-19: Researcher blows the whistle on data integrity issues in Pfizer's vaccine trial. BMJ. 2021;375:n2635. Published 2021 Nov 2. doi:10.1136/bmj.n2635

You refer to emails released by hackers, some referring to the quality of Comirnaty. It is important to note that during the evaluation of medicines, issues arise which need to be resolved before EMA can recommend an authorisation. A collection of selected emails cannot provide an accurate or full picture of what the issues were or how they were resolved. In this case, the issue concerned mRNA integrity (i.e. whether mRNA in the vaccine remained intact as expected).

While some truncated mRNA pieces were found in the vaccine, the CHMP concluded in 2020 that 'proposed specifications for RNA integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product, and considering clinical experience, are considered important to confirm the adequacy of these specifications, and these data should be provided post-approval as specific obligations to the MA [marketing authorisation]'.

The company has since provided all the required information, and the specific obligations have been fulfilled. The CHMP has accepted the latest specifications proposed by the company.[6]

5. Legal status of EU authorisations of Comirnaty and Spikevax

You have raised a number of concerns about EU Regulations and Directives. You question the initial conditional marketing authorisations of Comirnaty and Spikevax, as you believe that Regulation (EU) 2019/5[7], Regulation (EU) No 2020/1043[8] and Regulation (EU) No 2021/756[9] do not meet the framework laid down:

- on environmental risk assessment and reporting in Regulation (EU) No 2001/18[10] and Directive 2009/41/EC[11];
- on safety for medicinal products laid down in Directive 2001/83/EC[12], Commission Directive 2003/63/EC[13] and Regulation (EC) No 1394/2007[14];
- concerning the granting of a union licence laid down in Regulation (EC) No 2004/726[15] and Regulation (EC) No 2008/1234[16].

You also state that the changes in Regulation (EU) 2019/5 'should not be used to go outside the framework of existing classification and categorisation, only clarification is allowed, no categories can be added that conflict with the current system, full legislation is needed for that.'

Further, you state that 'the addition of codes/sequences' in Regulation (EU) No 2021/756 'conflicts with the classification and categorisation' of Directive 2001/83/EC, Directive 2003/63/EC and Regulation (EC) No 1394/2007.

You also assert that parts of Regulation (EU) No 2020/1043 (concerning trials of GMOs for COVID-19) and Regulation (EU) No 2021/756 (concerning variations to marketing authorisations of coronavirus vaccines) are 'contrary to Articles 141 and 168' of the Treaty on the Functioning of the

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[6] https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-r-0137-epar-assessment-report-renewal_en.pdf
[7] Amending Regulation (EC) No 726/2004, Regulation (EC) No 1901/2006 (concerning medicines for children) and Directive 2001/83/EC
[8] Concerning trials of GMOs for COVID-19
[9] Concerning variations to marketing authorisations of influenza and coronavirus vaccines and amending Regulation 2008/1234
[10] Concerning GMOs in the environment
[11] Concerning use of GMOs
[12] Concerning human medicines in the EU
[13] Amending Directive 2001/83/EC
[14] Concerning advanced therapy medicines
[15] Concerning the establishment of the EMA and the centralised procedure
[16] Concerning variations

European Union. Furthermore, you say that Regulation (EU) 2019/5 was used in violation of Article 290(1) of the Treaty.

We read these concerns as being related to the Regulations and Directives themselves. While EMA is bound by them, we are not in a position to comment on the appropriateness of Regulations or Directives adopted by Parliament and the Council or on their compatibility with the Treaty.

With regard to extensions of marketing authorisations, you note that Regulation (EU) No 2021/756 (concerning variations to marketing authorisations of influenza and coronavirus vaccines) was adopted after the authorisations of Comirnaty and Spikevax. The implication is that the Regulation does not apply to adapted Comirnaty and Spikevax vaccines. Please note that the text of the regulation clearly recognises that 'based on the scientific assessment by the European Medicines Agency, the Commission has thus far authorised several COVID-19 vaccines', and the Regulation provides for variations to the authorisations of these and future vaccines.

You also highlight Article 19 of Regulation (EC) No 2008/1234 (concerning variations), which states that 'an extension shall either be granted a marketing authorisation in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates or be included in that marketing authorisation'. Please note that this article does not preclude relying on relevant data from the initial marketing authorisation. Furthermore, and as noted above, the authorisation of the adapted vaccines for Comirnaty and Spikevax are covered by Regulation (EU) No 2021/756, which amends Regulation (EC) No 2008/1234.

With regard to Article 1 (4) of Directive 2001/83/EC, vaccines are listed as agents used to produce active immunity. You say that there is no evidence that these vaccines provide immunity (i.e. protection against infection or disease).

It is true that the protection wanes over time as the virus itself evolves, and this is one of the reasons why adapted vaccines have been authorised. It is important to note that with SARS-CoV-2, people may be exposed to the virus several times and repeated exposure may increase the chance of infection even in vaccinated people.

COVID-19 vaccines also provide protection against severe disease, including hospitalisation. This is particularly important for vulnerable people who are at increased risk.

You also state that 'a vaccine must contain an antigen; this antigen requires its own registration in the Vaccine Antigen Master File (VAMF)' as laid down in Directive 2003/63/EC. 'The reason for this method', you say, 'is that homogeneity and quality and active dose can be determined per treatment. This is not the case with coding sequences.'

It is important to note that for mRNA vaccines, the antigen (the particle that triggers an immune response) is not the mRNA active substance itself but the spike protein formed after vaccination.

That said, we would like to clarify what a VAMF is. EU legislation provides for the option of presenting all required information on a vaccine antigen as a VAMF (i.e. as a stand-alone part of the marketing authorisation application (MAA) dossier for a vaccine). A VAMF is particularly useful when a specific vaccine antigen is used in different vaccines. In such cases, with a single evaluation of a VAMF, authorities can assess the same antigen used in several vaccines at the same time. The VAMF system is therefore only aimed at simplifying the evaluation of vaccines, and the use of VAMFs is optional. When the option of a VAMF is not used, companies, like for any other medicine, have to include the relevant information on the vaccine antigen directly in the MAA dossier concerned.

You can find more information in the *Guideline on Requirements for Vaccine Antigen Master File (VAMF) Certification* on EMA's website.[17]

6. EMA reflection papers

Citing EMA's *Reflection paper on the classification of advanced therapy medicinal products*[18] and EMA's *Reflection paper on criteria to be considered for the evaluation of new active substance* (NAS) *status of biological substances*, you make the following case: that mRNA is considered an example of gene therapy and therefore any significant change in the sequence of mRNA requires a new application.

As you noted in your letter, Commission Directive 2009/120/EC does not consider vaccines against infectious diseases gene therapies, as the aim of vaccination is not to restore, correct or modify human genes. Furthermore, the extensions to marketing authorisations of COVID-19 vaccines are covered by Regulation (EU) No 2021/756.

Finally, we take note of your call for immediate action to suspend the marketing authorisations of Comirnaty and Spikevax, including the authorisations of the adapted vaccines targeting the Omicron XBB.1.5 subvariant.

EMA's CHMP can only recommend suspensions of the marketing authorisations if the evidence shows that the risks outweigh the benefits. The evidence continues to show that the vaccines provide protection, which is particularly important for vulnerable people. Removing these vaccines as an option for EU Member States and for healthcare professionals without due regard to available data would therefore be a great disservice to the EU and to public health.

I would like to thank you for writing to the Agency and I hope this reply addresses your concerns.

Yours sincerely,

Emer Cooke
Executive Director

[17] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-vaccine-antigen-master-file-vamf-certification_en.pdf
[18] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf