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On progress with the collective letter (NORTH Group)

The Ministry of Health has examined the North Group's letter of 25 November 2024 on concerns regarding on the safety of the mRNA Covid-19 vaccine and provides a response based on information provided by the National Medicines Agency.

I. What is required to set up an independent and transparent public and forensic inquiry into the regulatory processes leading to the approval of these products?

We would like to draw your attention to the fact that the mRNA technology Covid-19 vaccines used in Latvia are registered and supervised medicines in accordance with the requirements set out in the legislation of the European Union and the Republic of Latvia.

The European Medicines Agency (hereinafter referred to as the EMA) is responsible for scientific evaluation of centrally authorised medicinal products in the European Union, including Covid-19 vaccines, The European Commission issues the marketing authorisation decision, taking into account the recommendations made by the EMA following the above-mentioned scientific evaluation. In addition, measures are being taken to healthcare professionals and the public are properly informed of the considerations underlying each specific medicinal product marketing authorisations and their follow-up after marketing authorisation. Experts from all countries of the uropean Economic Area, representing the different scientific disciplines relevant to the scientific evaluation of medicinal products, participate in the work of the EMA and in the scientific evaluation and post-authorisation supervision of medicinal products. Thus, the monitoring of medicines, including the expertise on the regulatory processes leading to their approval, is already being carried out.

Below is an explanation of the concerns raised in your letter:

1. Plasmid DNA

You state that there is excessive use of Covid-19 mRNA vaccine contamination with residual plasmid DNA of bacterial origin. We would like to clarify that the mRNA in Comirnaty and Spikevax vaccines is produced using plasmid DNA. A plasmid is a small, circular DNA molecule that is not part of the chromosome of a cell. Plasmids are naturally found in bacterial cells and contain information that may be useful for the survival of these bacteria. Production of plasmid DNA from transformed bacteria (Escherichia coli) cells is first used to create the so-called linear DNA template, which is then transcribed to produce mRNA, which is present in the vaccine. After mRNA transcription, the production process involves DNA cleavage and purification steps, as the DNA template is no longer needed. This is done using a special enzyme that degrades DNA. The production process is monitored to make sure that the vaccine is purified of the DNA template. The full composition of the vaccines is given in the respective product description and package leaflet. The final vaccine product does not contain the DNA template, but the presence of very small amounts of DNA fragments cannot be excluded. Appropriate limits have been set for the control of residual DNA fragments in vaccines. The manufacturing process and control strategy are designed to ensure that any potential residual DNA fragments do not exceed the permitted safe level. In addition, we would like to inform you that the principle of DNA recombination using plasmid DNA, as described above, is a standard method for the production of numerous active pharmaceutical ingredients and also the purification and control of DNA fragments in final pharmaceutical products is a well-known and established standard procedure. In general, the use of plasmids in pharmaceutical production is a widely used technology, e.g. in the production of therapeutic monoclonal antibodies, where plasmids are used to incorporate the relevant genes into drug-producing cells, resulting in the production of the relevant antibody. Monoclonal antibodies are one of the basic groups of biological medicines with decades of experience, and their number is only growing. They are most commonly used to treat oncological, rheumatological and ophthalmological diseases, but not only.

The Ministry of Health and the Medicines Agency have been informed of McKeran et al. 2023 and other reports claiming that mRNA has been found to have increased levels of residual DNA, but we have no objective information available to confirm this claims and the reliability of the data. As reported, the study investigated samples from four vaccine vials with unknown or unproven origin, storage conditions and traceability. These samples cannot be authenticated, neither can be considered as representative of commercial vaccines, nor the possibility of intentional or unintentional manipulation of these samples can be excluded. We are also aware of Prof. Phillip Buckhaults

speaking before the South Carolina Senate, in which allegations were made of commercial contamination of the Comirnaty series with plasmid DNA. Buckhault made the speculative claim that even if DNA the residue is within the EMA-accepted safety limits, it may cause some of the very rare but serious side effects observed. In addition, Buckhault suggests that this DNA may integrate into the genome of the transfected cells. Finally, theoretical concerns were raised that such integration could lead to oncological diseases (by inhibiting tumour inhibition of development or activation of oncogenes) or lead to autoimmune reactions against affected cells.

We would like to draw attention that no scientific data or research results have come to the attention of the competent authorities to justify the claims made by Buckhaults. In the safety monitoring programme, the EMA or national competent authorities, including the national authorities of Latvia, have not identified any signs of adverse reactions to mRNA vaccines that could be related to the presence of DNA material. The currently available scientific evidence does not suggest that the tiny residue of DNA fragments that might be present in vaccines or other medicines can integrate into the DNA of people who have received such medicines or vaccines. EMA and the competent authorities of the EU Member States continue to monitor the safety of all Covid-19 vaccines to ensure that any potential risks are identified and mitigated, and EMA is carefully assessing potential side effects to determine whether they are caused by the vaccine. The EMA has published a report on safety monitoring of vaccines during a pandemic, which is worth reading for anyone interested in this topic, as it contains useful information on the principles underlying the scientific evaluation and safety assessment of medicines, both pre- and post-authorisation.

We would like to reiterate that the production of mRNA vaccines process is carefully designed and controlled to ensure that the residual DNA does not exceed the limit that is acceptable and considered safe. For example, the manufacturer of Comirnaty is obliged to detect DNA residue levels in each batch of active substance produced. Before the release of any batch of vaccine manufactured using of the active substance in question, these results shall also be verified the official medicines control of the competent authority of the Member State official medicines control laboratory (*official medicines control laboratory*, OMCL). This independent check is called a series release from the official controlling authority (*Official Control Authority Batch Release*, OCABR). As a result, everyone in society can be confident that DNA levels in the vaccine are always within safe limits. To this date, no reliable scientific evidence has come to the attention of the competent authorities that any of the mRNA vaccines registered in the EU, including Latvia, have been found to have elevated levels of residual DNA above the permitted limit.

2. Efficacy of Covid-19 vaccines

Your letter suggests that the ability of Covid-19 vaccines to stop the transmission of the virus has not been tested. We explain that Covid-19 vaccines are registered to protect vaccinees from the harmful effects of Covid-19, and both initial clinical trial data and subsequent post-marketing data provide compelling evidence of their ability to reduce infection with the Covid-19 virus and to reduce severe disease or fatal outcomes. The requirements for the registration of vaccines do not include an obligation to demonstrate reduction of disease transmission and are not normally registered for that purpose (indication). For Covid-19 vaccines, at the beginning of the pandemic, pharmaceutical companies developing vaccine candidates were asked to prioritise clinical trials to assess the impact of the new vaccines on the severe course and fatal outcome of Covid-19, because conditions were critical - the risk to the public and to life was very high and this was the main reason why national governments were forced to take decisions on various restrictions. Thus, the vaccines were originally developed and registered to protect against symptomatic SARS-CoV-2 infection and to prevent the worst outcomes of Covid-19 (hospitalisation and death), and data were received from pharmaceutical companies that justified registration on the basis of these benefits of the vaccines. Subsequently, pharmaceutical companies were also required to conduct mandatory post-marketing studies on the effectiveness of vaccines on disease transmission, and for a time, while early variants of SARS-CoV-2 were circulating, this was convincingly observed, but with the very rapid development of new variants, such studies were for justified reasons no longer feasible.

We categorically reject the claim that the authorities misled people because both at the time of the initial registration of the Covid-19 vaccine, and at any other time, any member of the public had and have an access to completely honest and open information about what studies had been conducted and what the effects and benefits of the vaccines had been demonstrated. We would like to emphasise that the EU has particularly high requirements for openness and transparency of information and any interested party can use a variety of verified, evidence-based information resources to get the information and understanding they need about vaccine research, registration, safety surveillance or other aspects. One example of such a useful resource is the EMA website - https://www.ema.europa.eu.

3. Adverse reaction reports and their evaluation

In reply to the claim that the safety data for Covid-19 vaccines was not provided information to the public and professionals after the Covid-19 vaccines approval for use in EU countries, we would like to clarify that the

monthly Covid-19 vaccine safety reports were summarised in the EMA Medicinal Products Committee (*Pharmacovigilance Risk Assessment Committee*, *PRAC*) the latest safety data evaluation results from around the world. Monthly safety reports on Covid-19 vaccines were published on the EMA website and on the Latvian Medicines Agency (LMA) website: https://www.zva.gov.lv/lv/pacientiem-un-sabiedribai/covid-19-vakcinas/drosuma-parskats

Please note that if, during vaccine safety monitoring a signal of a suspected adverse reaction is detected (the signal is a new significant information about a reaction that has been linked to vaccination to be investigated and assessed), the signal is always considered during the investigation, whether there are data indicating that the reaction might be specific to a particular series of medicinal products. For example, when serious blood clots were first reported with Vaxzevria (thrombotic thrombocytopenia syndrome - TTS), it was initially thought that the side effect might be related to a specific series, and some countries stopped using that particular series. Further investigation and evaluation by the EMA PRAC in the light of all the evidence showed that TTS was not linked to a specific vaccine series. As already known, this side effect of Vaxzevria did not affect all age groups in the same way, and therefore differences in reporting are to be expected for each vaccine series if the series are not used in comparable populations.

It is false to claim that a single production and control in the absence of unified standards of production and manufacturing, some individuals may be at a much higher risk of vaccine-related adverse reactions than others. The European Union's regulatory network for medicinal products is strictly defined standards for manufacturing and control requirements, which include risk assessments for different risk groups, with particular consideration of the impact on pregnant women and children, but also on other particularly sensitive groups.

Evidence is now available on the safety of Covid -19 vaccines after several billion doses. European Union countries, including Latvia, have a very well-developed and detailed safety monitoring system for medicines, including vaccines, which continuously collects and analyses reports of possible adverse reactions.

By March 2023, more than 13 billion vaccine doses had been administered worldwide. This includes hundreds of millions of doses of mRNA vaccine administered to children and pregnant women. Data from vaccination campaigns show that vaccines have an overwhelmingly positive safety profile. The long-term safety data for Covid-19 vaccines include data from tens of thousands of volunteers in some of the largest clinical trials ever conducted, as well as data from mass vaccination campaigns spanning more than three

years. As with all medicines, the more people receive the vaccine, the more likely it is that very rare but potentially serious side effects will be detected. In many cases, these rare medical events (such as myocarditis) can also be caused by SARS-CoV-2 infection itself, and are more frequent and more severe in unvaccinated people than in vaccinated people.

The most common side effects caused by Covid-19 vaccines are mild and transient. These include fever, swelling and pain at the injection site and occur in up to 1 in 10 people. The fact that a medical event has been reported as possible (probable) does not mean that the vaccine definitely caused it. Most of the reported possible (suspected) side effects that occurring during a period of time apparently related to vaccination are not due to the vaccine.

Anyone can report a possible side effect, including members of the public and healthcare professionals. Regulatory authorities are continuously nalysing these reports to establish a causal link to the vaccine. One method used to assess a possible association is to compare the frequency of medical events in vaccinated people with the frequency of events in the general population and reports for other medicines. As part of this rigorous and ontinuous safety monitoring, regulators also review reports of potential safety signals and take into account any other available evidence, such as studies.

If a safety problem is detected, regulators act quickly, as this happened when rare cases of abnormal thrombus formation were reported cases of adenovirus vector vaccines causing thrombosis and thrombocytopenia syndrome (TTS).

International safety monitoring systems, including those in the European Union (including Latvia), collaborate and share their territorial vaccine safety data, making an invaluable contribution to vaccine safety monitoring worldwide.

For example, myocarditis and/or pericarditis are very rare mRNAs side effects of vaccines. They usually affect younger men and disappear after ppropriate treatment. Myocarditis and pericarditis are also known complications of SARS-CoV-2 infection in unvaccinated people. Large-scale studies have shown that the likelihood and severity of myocarditis due to SARS-CoV-2 infection is significantly higher than the likelihood and severity of myocarditis due to vaccination.

Abnormal blood clots combined with low platelets count (thrombotic thrombocytopenia syndrome or TTS) is very rare but serious side-effect of adenovirus vector vaccines. This side effect was immediately detected by national safety surveillance systems based on the health professionals' reports. European regulators were the first to identify this reaction and took action to protect citizens. The summary of product characteristics and package leaflet were promptly updated to inform healthcare professionals,

public health authorities and the general public about this rare side effect.

We certify that we have been informed of the decision of Mr J. Hauser in the European Parliament on 18 September 2024, stating that by 2 September 2024 there have been 29 000 deaths and a total of 2.3 million adverse reactions. As with other medicines, the EMA has received reports of fatalities following vaccination with Covid-19. We clarify that the 29 680 mentioned in Mr Hauser's statement deaths refer to cases reported throughout worldwide, taking into account all vaccines authorised for Covid-19 in the EEA combined (15 October – 2024). To obtain more objective data on deaths associated with Covid-19 vaccines, it is necessary to calculate only EEA data, as this is in line with EU reporting rules which require reporting of both major and minor adverse reactions.

The EMA database EudraVigilance (EV) contains 12 688 reports of suspected adverse reactions related to Covid-19 vaccination that were fatal, registered in EEA countries until 15 October 2024 for all Covid-19 vaccines combined.

Analysing the number of reports received about suspected Covid-19 vaccine -related adverse reactions with fatal outcome can be concluded that by December 2023, when the largest number of vaccine doses were administered, there was 1 report of a suspected Covid-19 vaccine adverse reaction with fatal outcome per 100 000 vaccine doses administered in the EEA. After 2023, complete data on the coverage of Covid-19 vaccination in the EEA population are no longer available, so it is not possible to calculate the exact proportion of reports of possible adverse events related to vaccination, but the number of reports received during this period suggests that only 1.7% of the total number of reports of deaths following Covid-19 vaccination received by the EV have been recorded in the last year.

In addition, it should be noted that a huge number of people were vaccinated against Covid-19 in a very short period of time. A vaccination campaign of this magnitude is unprecedented. Therefore, deaths in people vaccinated against Covid-19 within a short period after vaccination (a day to a few weeks) due to causes unrelated to the vaccination are also more likely to have occurred, i.e. they would have died if they had not received the vaccination. It is therefore not correct to operate on data on deaths shortly after vaccination, the objective link between the causes of death and vaccination must also be analysed.

Reporting a suspected fatal side effect is not enough to confirm the cause of death. To confirm the cause of death, you need a doctor's certificate or an autopsy, as well as evidence of reasonable causation. With the exception of a few cases where the death could be related to the reported adverse event, there is no evidence to suggest that the other reported deaths could be

related to vaccination. The vaccine product information and package leaflets indicate when certain adverse events may be fatal.

The end of the Covid-19 public health emergency was announced in May 2023. Since the start of Covid-19 vaccination until 14 July 2023, 3514 reports of possible adverse reactions to Covid-19 vaccines have been received in Latvia. Until 14 July 2023, the LMA has received and evaluated 59 Covid-19 vaccine adverse reaction reports, which provide information on fatalities that occurred within days or months after vaccination. Of these, 58 cases have no confirmed association with Covid-19 vaccination, while one fatality is plausibly linked to the use of Vaxzevria (formerly known as Covid-19 vaccine AstraZeneca). After reviewing the reported case, the LMA concluded that changes identified in the post-mortem examination are likely to be causally related to the use of Vaxzevria vaccine and that a possible very rare adverse reaction to Vaxzevria vaccine, thrombosis and thrombocytopenia syndrome, has been identified in this case. The National Agency for Medicinal Products considered all available information on all reported fatalities, such as the person's medical history, information from the Emergency Medical Service, the GP, the National Health Service on medicines consumed and examinations carried out, forensic reports, including autopsy and forensic histology, and the opinion of the medical specialist (or clinical expert). The evaluation was carried out by the LMA on the basis of scientific methods and requirements that are the same across the EU, in line with the standardised criteria for assessing causality developed by the World Health Organisation (WHO) for medicines safety monitoring (or pharmacovigilance).

EMA and national medicines agencies analyse EudraVigilance data on an ongoing basis. These data ensure that unexpected signs can be identified that are consistently repeated in reports and could be indicative of very rare side effects, such as thrombotic and thrombocytopenic syndrome; myocarditis.

Anyone can submit an adverse event report to the EudraVigilance database, even if it is not clear whether the vaccine actually caused the health problem. Some EV reports may contain information that is incomplete, inaccurate or unverifiable. EudraVigilance reports cannot therefore be used to confirm or verify the cause of death. Causality can only be established after reviewing all relevant data and excluding other coincident medical events, including SARS-CoV-2 infection. Medical literature shows that infection with SARS-CoV-2 can cause serious health problems, such as heart attack and stroke, even weeks or months after infection.

In exceptional cases, where the death cannot be explained by a medical condition and a known serious side effect of the vaccine is listed as the cause of death on the death certificate, this serious side effect could have contributed to the death of the vaccinated person. So far, the EMA PRAC, which consists of pharmacovigilance experts from all EU national medicines

agencies (including the Latvian LMA), has not identified any concerns about increased mortality after vaccination in its assessment of all available data on Covid-19 vaccines.

In addition to EudraVigilance adverse reaction reports, the PRAC analyses many other types and sources of data, such as data from large clinical trials conducted before vaccines are approved, periodic safety update reports (PSURs) prepared and submitted by pharmaceutical companies, medical literature, as well as evidence from post-marketing studies and large real-world (real clinical practice) data from around the world.

Examples:

Sudden cardiac death

Sudden cardiac deaths after vaccination with Covid-19 cannot be linked to Covod-19 vaccines, as no concerns about an association have so far been raised on the basis of an assessment of the available data. Therefore, sudden cardiac death is not listed as a known adverse reaction in the summary of product characteristics.

Fatal myocarditis

Fatal myocarditis events closely related in time of onset to vaccination may be associated with the use of mRNA vaccine. However, in order to establish a vaccine link, all other possible causes, such as accidental viral infection, including Covid-19 infection, which also causes myocarditis, and other individual risk factors, must first be excluded.

Fatal cases of thrombosis and thrombocytopenia syndrome (TTS)

Fatal cases of TTS reported after vaccination with an adenovirus vector vaccine can be reasonably attributed to the vaccine, as these vaccines are the only established cause of TTS today. TTS is an extremely rare side-effect of adenovirus vector (non-mRNA) Covid-19 vaccines and, with appropriate precautions and treatment algorithm, a fatal outcome can be prevented.

4. Possible investigation

European Union legislation requires that the safety of vaccines is monitored as long as they are used in routine clinical practice. Currently, as part of the post-authorisation monitoring set out in the risk management plans for Covid-19 mRNA vaccines approved by the EMA PRAC, several actions are being taken to generate new safety data on these vaccines, such as the inclusion in the risk management plans of post-authorisation safety studies currently being conducted by the holders of the vaccine registration certificates as additional pharmacovigilance activities. Safety data are also collected and analysed in the PSUR for Covid-19 vaccines, which is regularly evaluated by the EMA PRAC. The extensive data available on Covid-19 mRNA vaccines confirm that they show a positive benefit-risk ratio and that the work

and measures taken by the competent authorities of the European Union, including Latvia, within the framework of the strict system of approval and monitoring of medicines, are sufficient to guarantee the protection of public health.

5. Call for the recall of Covid-19 mRNA vaccines

Taking into account that all Covid-19 vaccines are registered under a centralised registration procedure, the Committee for the Registration of Medicinal Products (CHMP) of the EMA, which includes representatives from the medicines regulatory authorities (medicines agencies) of all EU countries, including Latvia, can only recommend suspending marketing authorisations where evidence shows that the risks of a medicine outweigh its benefits. The currently available evidence suggests that mRNA Covid-19 vaccines provide protection against severe Covid-19 progression, which is particularly important for vulnerable people. Therefore, removing these vaccines from the market of EU Member States, unjustifiably denying their use to healthcare professionals and the general public, and without due consideration of the available safety and efficacy data, would be a major detriment to EU and public health.

The European Medicines Agency works closely with international medicines regulators, including through a dedicated ICMRA pharmacovigilance group, and no concerns have been raised about reports of deaths following global mass vaccination campaigns.

ICMRA brings together 38 medicines regulators from all regions of the world and includes WHO as an observer. Regulators recognise the importance of promoting access to safe, effective and quality products, which are essential for human health and well-being. This includes keeping abreast of the scientific progress needed to set standards and facilitate the decision-making process, and maintaining the efficiency of the regulatory process that supports the development and supply of innovative medicines, while ensuring that the benefits of these products outweigh any associated risks.

II. Is there anything that prevents the minister from initiating and prioritizing research into potential links between mRNA vaccines and cancer, infertility, or other acute, chronic and genetic diseases.

In view of all the above, we believe that there is an ongoing evaluation of the link between all vaccines, including mRNA, and cancer, infertility or other chronic diseases. We also consider that there is no reason to doubt the quality, efficacy or safety of the registered Covid-19 vaccines, which are continuously controlled and monitored by the competent authorities, as a valid marketing authorisation in the European Union for any medicinal product means that the balance of risks and benefits is favourable when used in accordance with the conditions approved in the summary of product

characteristics.

State Undersecretary for Finance Boriss Ķigins

*The document is signed with a secure electronic signature and contains a time stamp