This is based on an Expert Report on the EMA's Open Assessment Report on the data supplied for license, by Dr Vanessa Kruger-Schmidt.
https://www.ema.europa.eu/en/documents/assessment-report/spikevax-previously-covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf

Moderna Covid-19 Vaccines:

It should be kept in mind that this is a gene therapy product that alters human cells.
https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

Content of the vaccine:

a) **active substance:**
   - mRNA: single-stranded, 5´capped mRNA, 5´UTR, 3´UTR, 3´PolyA
   - two mutations for prefusion-stabilized spike protein; K986P and V987P
   - **substitution of uridine by N1-methylpseudouridine**

b) **Lipid nanoparticle (LNP):**
   - **SM-102: new lipid, not approved by EMA; cationic lipid**
   - **PEG2000-DMG: new lipid, not approved by EMA; lipid contains PEG**
   - Cholesterol
   - Helper lipid: DSPC (zwitterionic helper)

c) **Substances for keeping the pH and osmotic pressure:**
   tromethamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose and water

Dose of vaccination
2 x **100µg** (on **day 1** and **day 28**), 0.5ml/dose (n=10 per vial)

The applicant assures that all specimens of clinic phase 3 trail will be followed up 24 months after the second vaccination.
Long-term damage from the vaccination cannot be determined due to the massively shortened observation time of the clinical phase study. It is known that **side effects of a vaccination can also occur far in the future**.

Manufacturing process of mRNA:
The mRNA manufacturing process started with a small-scale process which were increased with more demand: small-scale to Scale A, to Initial Scale B, and then to Final Scale B.

Importantly, Scale A batches were used in the Phase III clinical trial.

The main change was the transition from the small-scale process to the Scale A process, including the addition of two process steps for the Scale A process.
After a process change, **the integrity of the vaccine components, the final vaccine and the activity must be retested and re-evaluated**. Moderna was requested to submit the full comparability data (phys-chem data as well as data about biological evaluation like pharmacology and toxicology) for the initial Scale B to Lonza Visp* as soon as the data are available.
* = Visp Switzerland

The validation data for the consistency of the manufacturing process of the initial process B at Lonza are not available at the time of admission.

Moderna submitted plans for an upscale process in the original dossier that were not supported by validation data. If Moderna wishes to include this upscaled process (final Scale B) in the marketing authorization, **an amendment with all data to substantiate the consistency of both different preparations should be submitted**. This should include appropriate validation data for the new scale which is applied for the running people´s vaccination.

Product impurities:

1. **Abbreviated mRNA products:**

There are truncated mRNA products due to premature termination of mRNA synthesis during *in vitro* transcription. Most of the truncated mRNA molecules do not have a proper polyA attachment at the end. The applicant uses a chromatography purification technique to remove those truncated mRNA molecules. It is not clear what proportion of the truncated mRNA molecules are still in the final vaccine product. Truncated mRNA products are unstable in the cell and are rapidly degraded, increasing the risk that the desired amounts of proteins will not be produced, **which could result in a lack of immune response**.

2. **Impurities of the mRNA:**

The first batches of the vaccine, which included the early clinical trial batches, had higher purity than the proposed limits and from some batches of the current vaccine administered to clinical trial III participants. The lower RNA purity values measured in some batches are not acceptable to the EMA.

Currently, too little batch analysis data is available from the commercial manufacturing process to provide more accurate information on the effect of the lower RNA purity vaccine. Once this information is available, the specifications and limits will still be adjusted after approval by Moderna.

In the Phase II study, comparable neutralizing antibody responses were observed in subjects receiving effective doses of 40 µg and 79 µg. In addition, the non-clinical setting showed that lower purity batches were as effective as higher purity batches. Considering the totality of the data, the EMA justifies the proposed lower purity limit.

If doses of 40 µg and 79 µg are effective, why inject 100 µg of RNA twice. More RNA needs more lipids and solvents leading to higher toxicity and harm of the body.

3. **Multiple protein bands:**

There were multiple protein bands produced from the mRNA. These additional protein bands should be compared with respective positive and negative controls. EMA is not sure if other proteins/peptides are formed in addition to the spike protein. If this occurs, a protein sequence analysis must be performed to exclude possible homologies with other peptides that could lead to molecular mimicry (**protein mimicry leads to autoimmune diseases**). Moderna must analyse the additional bands and data must be submitted to EMA.

4. **Impurities through dsRNA:**

It must be ensured that the contamination with double-stranded dsRNA always remains at a low level, since **dsRNA has an immunostimulatory effect. What is the control strategy and what is the level of dsRNA contamination in the final product?**

5. **Robustness of the methods:**

It is important that the methods are well established and validated in each production plant to ensure consistent quantity and quality of the product. **This data could not be provided for the Lonza AG site so far**; it is currently being generated. This method validation data from the EU trial facility should be made available as soon as possible.

6. Impurities of lipid SM-102 were detected.
It is likely that these impurities are also found in the final product. The nature of the impurities has not clearly been described, so that one cannot make any statement about what damage to the body might occur. Moderna describes the impurities as product-related substances and process-related impurities (elemental impurities, solvent residues, peroxides, water content, and inorganic impurities).

Although vaccination is already underway**, there is a lack of data to assess the risk of hazardousness for the body. All impurities should be evaluated with different toxicological risk assessments.** In addition, the applicant will perform an assessment of mutagenic impurities based on ICH M7.

Moderna should test intermediates and the final product for impurity of benzene, which may be present e.g., in toluene or acetone. The applicant undertook to submit a risk assessment for the presence of benzene in SM-102. **Benzene is one of the substances proven to cause cancer in humans**. Epidemiological studies have shown clear links between occupational exposure to benzene and the occurrence of leukemias and lymphomas. In animal studies, benzene also leads to the development of tumors in other tissues and organs.

7. Impurities in lipid PEG2000-DMG:
During the synthesis of PEG2000-DMG, **polydispersity as a form of impurity was detected**.

To measure polydispersity by gel-permeation-chromatography as a measure of the width of molecular weight distributions is very important for the correct interpretation and comparison of different, during synthesis obtained, molecular weight distributions of polymers. The provided information of the results of the gel-permeation-chromatography **was not sufficient** since the reporting of impurities in the batch analysis data does not match the current characterization data.

The possible presence of **mutagenic impurities** in PEG2000-DMG should be evaluated and the results should not be **submitted after approval, because mutagenicity is a dangerous toxicological risk for people**. Polydispersity and numerical limits should be included in the post-approval specification for PEG2000-DMG. **The current reporting of impurities is not acceptable.** Also, characterization data for impurities that are currently under "**content unknown**" should be provided **only after** approval.

8. Possible contamination of nitrosamines:
There is no quantitative risk assessment for nitrosamines in the nanoparticle or in the final product. Nitrosamines are **strong carcinogens** that may produce cancer in diverse organs and tissues including lung, brain, liver, kidney, bladder, stomach, oesophagus, and nasal sinus.

9. Determination of Limits:
There are **no numerical limits of impurities** of the components of the vaccine. The applicant has yet to determine these. These limits may be further revised when data from batch analysis become available. However, **batch analysis has been done insufficiently to date**. In principle, the vaccine could have hazardous impurities that exceed official human health limits.

10. Contamination of DNA:
EMA allows a waiver of in-process control testing for plasmid DNA residues and plasmid DNA copy number. The percentage of covalently closed circular DNA is routinely monitored after chromatography. However, this method has not yet been validated and requires

further monitoring. In particular, **residues of linearized plasmid DNA have not been satisfactorily tested because analytical data from sufficient batches are lacking. The risk of integration of linear DNA residues into the host cell genome and thus the development of cancer cells is not discussed.**

Storage and stability of the vaccine:

1. **Storage of the active substance:**

There is no stability test of the container closure system of the Mobius-containers with which the RNA is transported by Lonza. The transport therefore takes place in an untested container. The suitability of the container must be verified.

2. **Stability of the final product:**

The initial shelf-life claim at -20°C ± 5°C is not considered acceptable by EMA based on the provided data. Both RNA purity and quantity decrease with increasing temperatures. Process-related impurities and the particle size increase. According to EMA, storage of the final product at -20°C is still acceptable because very little RNA is degraded although optimal storage temperature of the final product is -70°C.

Here are inconsistencies which temperature is acceptable and which not?

Also, the thawed RNA/LNP-complex is sensitive to stress like filling, mixing and shaking. Studies must be performed to rule out **degradation events during transport of the vaccine**.

3. **Optical test:**

The applicant agrees to develop an optical test for the finished product to detect visible particles that may precipitate in the solution. Visible particles like aggregates in the solution indicates degeneration of the different substances. **On the one hand, this renders the vaccine ineffective and unusable; on the other hand aggregates enhances the risk of thrombosis in the blood stream.**

Comparison of process A vs process B:

1. **Batch comparison:**

Analytical comparison data from different batches from different processes were generated and compared. **No definitive conclusions can be made regarding the comparability of the processes for Scale A (clinic) and Scale B (commercial).**

The final validation report including an assessment of comparability will be requested. Differences are based on description and justification of process changes including locations, scales, raw materials, process equipment, and evaluation of process performance in terms of critical process parameters and IPCs, as well as statistical evaluation of comparability of release test results.

The EMA did not verify that the characterization data of the commercial batches manufactured by Lonza are identical to the batches from the clinical trial. The comparability studies have yet to be performed.

The final specifications for lipid nanoparticles and the final product have not yet been analysed and implemented. Moderna must first collect analysis data from the batches now being produced for folk vaccination.

People are being vaccinated with substances where it is not yet possible to say whether the vaccine from commercial production is identical to the vaccine from the clinical phase.

Non-clinical aspects

No studies on secondary pharmacodynamics (how the drug effects the organism) have been performed.

No studies on safety pharmacology have been performed.

-physiological functions in relation to exposure in the therapeutic range

No studies on pharmacodynamic drug interactions have been performed.

-no studies showing physiological changes due to diseases, genetic mutations, aging or influence of other drugs.

Primary pharmacodynamics

Challenge studies in animals:

- EMA concludes that it is not possible to determine a specific vaccine dose from these studies which provides full or only partial protection.
- In conclusion, no real challenge study was performed with this preparation. It is shown in BioNTech authorization that monkeys as well as rats are not the appropriate animal model for Corona disease.

Pharmacokinetic studies:

- **No ADME** (Absorption, Distribution, Metabolism, Excretion) studies have been performed.
- It is not acceptable that EMA claimed that ADMA studies are not relevant to investigate the development and licensure of a new vaccine.

A vaccine with completely new technology needs to be closely monitored in every direction, including how the components of the vaccine are absorbed, metabolized and broken down by the body and whether any residues are excreted which can contaminate the environment and pollute supplies such as drinking water.

Distribution study:

The distribution study was not performed with the original vaccine but with another RNA, mRNA-1647, in a non-GLP way (GLP = good laboratory practice) as 100µg single-dose IM injection in Sprague Dawley rats.

The mRNA-1647 contains six different mRNAs but the same composition of (LNP). Although the composition of the LNP determines the tissues which they penetrate, the amount and length of the six mRNAs dictate the particle size and thereby also the intake quantity and toxicity of the LNP/mRNA-complex by the cells which will be different from the original vaccine mRNA-1273.

Study in rats: 5 rats were sacrificed for each timepoint (2, 8, 24, 48, 72 and 120 hours after injection). Presence of mRNAs in the blood and in most organs (except kidney) found **after the shortest timepoint of 2 hours (peak between 2-24 hrs); mRNA was found at the injection site of the muscle, the plasma, lymph nodes, heart, lung, male sex organ, liver, spleen, eye, and brain.**

Due to the toxic effect of the LNP/mRNA-complexes on cells (see below) there will be massive damage on multiple organs especially the heart and the brain which are quite

sensitive tissues. Importantly, here is the evidence that the vaccine can cross the blood-brain barrier.

There is no information available how long the vaccine is present in the body since investigations were stopped at 120hr post-injection. Such substances normally decompose exponentially in the body and residues remain in the body for a relatively long time. To make a better comparison with the current vaccination, it would have been necessary to inject twice. The components of the vaccination then linger much longer in the body and, accordingly, greater damage could also be recorded.

No distribution, metabolism, and pharmacokinetics were performed on the novel toxic lipid component SM-102.
Due to structural similarity between SM-86 and SM-102, Moderna just hypothesised that SM-102 distributes similarly and is efficiently and rapidly metabolized and eliminated via the bile and kidneys. A hypothesis is not evidence. This was given as iv injection.

It is hypothesised (BioNTech vaccine) that the cationic lipid ALC-0315 has a half-life of 20-30 days and needs 4-5 months for 95% elimination. This very long terminal half-life leads to a high risk for permanent organ damage and development of autoimmune diseases.

Toxicology

- It is not clear which organs were analysed for adverse effects.
- Moderna refers to adverse effects in the spleen in toxicological studies in rats.
- No adverse effects were observed in the brain/CNS and eye.
- Long-term damage was not investigated at all.

Importantly, according to EMA, the study with the original vaccine was not conducted in compliance with GLP (good laboratory practice) and has significant procedural & methodological limitations. EMA overrides these guidelines and accepts the results of this study.

In general, all nanoparticles are toxic to cells. The toxicity of nanomaterials is directly related to the size, surface area, surface activity, shape, and composition (Cassee et al. 2002; Yang et al. 2009).

- The small size of nanomaterials makes it possible to cross the cell membrane and organelles such as mitochondria and increase the chance of escape from the cellular clean-up system.
- The small size also causes more interactions with cells and biomolecules that are similar in size with the nanomaterials.
- Ratio of RNA : Lipids ~ too much leads to cell death; too little has little / no effect.
- Each cell type tolerates different

This kind of technique is used in cancer patients to destroy the cancer cells with help of oxidative cell stress through cationic lipids in the LNPs. The benefit-risk-balance is completely different in cancer patients to what is done now on healthy people during vaccination.

Furthermore, cationic lipids also change protein function by oxidizing amino acids in proteins. These modifications lead to a change of protein folding with loss of function of these proteins and enzymes. The damaged cell reacts with massively release of cytokines.

The nanoparticles reach the blood system and come in direct contact with blood cells, endothelial cells, and plasma proteins, where they can change the structure and critical functions of these blood components.

Plasma proteins can surround the surface of nanoparticles to form a protein/LNP complex and may even lead to increase cellular activation and thrombotic complications through nanoparticle-induced coagulopathy.
Therefore, it is very important that Moderna should make every effort to conduct thorough hemocompatibility studies on newly engineered nanoparticles that evaluate the interactions between the LNPs and all three cellular constituents of blood.

These studies were NOT done, especially not in humans. It is possible to analyse those parameters.

On page 21 of this review, EMA concluded that the mRNA differences in the injected substances are not important. Now, they claim that the immunological response may come from the different antigens. Here they contradict themselves.

Adverse Events

- Some of the adverse effects were reversible.
- All experiments were done on healthy and young rats. What happens in the pre-damaged humans and elderly?
- There were no critical considerations of clinical relevance in humans, and such analyses performed in animals are not envisioned in participants (with or without risk factors) in phase 3 clinical trial.
- The consequences of overcoming the blood-brain barrier were not discussed.
- Nerve cells are very sensitive and die immediately after exposure to LNPs.
- LNPs in the brain is a reasonable explanation for the occurrence of facial nerve paresis in vaccinated individuals.
- LNPs in the eye was not discussed. Damage of retina or eye nerve can lead to severe eye diseases and blindness.

Genotoxicology

1. Genotoxic potential was performed using an in vitro reverse mutation assay in Salmonella typhimurium and Escherichia coli (both bacteria), which resulted in no genotoxic activity in the bacteria.

   I am also not aware that bacteria could take up these lipid nanoparticles at all, since bacteria (unlike human cells) do not have lipoprotein receptors that take up cholesterol containing LNP from the environment. There is no evidence that the above bacteria produce cholesterol or take up and need any. This test makes no sense and should not get in this account.

2. According to EMA, an injection of the luciferase mRNA in LNP as single dose in small amounts up to 3.21µg/kg mRNA with 60µg/kg SM-102 in rats observed no genotoxicity. However, a reduction of polychromatic erythrocytes was seen at the lowest dose already after 2 days.
   When a reduction of polychromatic erythrocytes is visible in a micronucleus test then this is an indicator of bone marrow toxicity induced by mutagens.

3. Increases in micro-nucleated erythrocytes means that the nucleus is not alone as one, but that one or more small parts of the nucleus are also present separately. **This is an indication of DNA damage at the chromosome level after cell division.** The EMA report points out that this observation may also have other causes. However, this has not been tested in any way.

CONCLUSION: Basically, genotoxicology has not been studied well enough, as evidence of DNA damage *in vivo* is available but has not been followed up. It is reasonable to assume that this preparation is genotoxic and mutagen.

Carcinogenicity
No studies on carcinogenesis have been performed.

There are several studies showing that LNPs can enter all organs and the cationic lipids cause oxidative stress. There have been numerous studies for over 20 years explaining in detail that oxidative stress leads to DNA damage, and this is causative in development of cancer.

Reproduction test (DART)
No vaccine dose was administered during early organogenesis to account for direct embryotoxic effects of the components of the vaccine formulation. According to EMA, such a risk is considered low in humans because mRNA-1273 is a non-living organism and the risk of genotoxic effects of SM-102-containing LNP in humans is low.

This interpretation is not correct, because **the vaccine is also contaminated with DNA, which can integrate into the DNA of the host cell. Such an integration can lead to cancer cells**. Likewise, it has been scientifically proven by multiple publications that cationic lipids (Moderna uses SM-102) cause massive oxidative stress in cells, which leads **to high degree of DNA damage**.

Ecotoxicity /environment risk assessment
Moderna **has not investigated** whether the vaccine or any part of the vaccine is excreted into the environment. No urine or stool has been tested for vaccine components that cause a **problem for important municipal providers** e.g. for drinking water.

Autoimmune diseases:
There was no discussion about the possibility to develop an autoimmune disease after vaccination.

a) There are hints that the spike protein can cause molecular mimicry in the body.
b) There is an increased of autoantigen production due to massive cell damage by cationic lipids and the elimination of spike proteins from the cells by the immune system.

If the levels of autoantibodies are not decreasing and the tissues cannot recover an autoimmune disease can develop.

Hypersensitivity against PEGylated lipid PEG2000-DMG:

Moderna uses a new PEGylated lipid which is not approved yet.

PEG triggers hypersensitivity and allergic reaction up to anaphylactic shock. Subjects with previous formed antibodies against PEG display a hypersensitive reaction after receiving the vaccine. The antibodies cause a rapid elimination of LNP in the blood and the vaccination has failed.

Determination of vaccine dose in human clinical study 2a:
Two vaccine doses (50µg and 100 µg) were tested in adults aged 18 years and older (2 age cohorts: 18-54yrs and ≥55yrs) in clinical study 2a (*Study mRNA-1273-P201*). Every participant received 2 doses separated by 28 days.

Results:
All groups developed both binding and neutralising antibodies against SARS-CoV-2, **regardless of dose level**. **Antibody response between 50µg and 100µg is close to**

negligible. **Higher dose levels mean also higher levels of adverse events and increased risk for severe damage to the body.**

S**ome important analyses were not performed**. **Analysis plans for phase 2a and phase 3 do not outline any further investigations on this important aspect likely contributing to protection against SARS-CoV-2.**

There is still a theoretical risk of vaccine dependent enhancement of disease (VAED). Immunokinetics over time and the correlation of protection/risk could not be characterised.