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

Astra-Zeneca (AZ) Covid-19 Vaccines:

- The manufacturing process is divided into cell culture and downstream processing.
- The recombinant viral DNA is amplified and produced in bacteria using bioreactors.
- After the bacterial cells are lysed, their chromosomal DNA is degraded using nucleases, and the recombinant viral DNA (active substance) is isolated and purified to remove process-related impurities.
- Finally, the recombinant DNA is sterile filtered to remove any remaining bacteria via a 0.2mm filtration step.
- The DNA is stored at -90°C to -55°C. As soon as the DNA is available, it is transfected into T-Rex cells, which then express the viral proteins from it.
- Some of these proteins combine with the DNA to form the finished virus particles, which are then released by the cells into the growth medium. The produced viruses are finally isolated from the medium.

Examining the level of RCA in each lot of adenovirus vector products is important. In addition, examining for the presence of RCA in patients who have been administered adenovirus vectors is mandatory to test for viral shedding during the clinical study. **The latter was not done**.

These tests are vital for human health, and it is not acceptable to skip them.
At the time of approval, the protocols did not specify any limits for process-related impurities.
The applicant is unable to provide this information because the limits have not yet been validated. to reduce the number of animal tests.

Comparison of different processes/batches:
Four different processes were used in the development of the vaccine. According to EMA, processes 1, 2, and 3, which were used to produce the material used in the clinical trials, are comparable.

A comparison between these three processes and the commercial process 4 was also provided to EMA, **but the acceptance ranges for several attributes were considered to be too large** and should be tightened as more manufacturing experience becomes available to ensure batch comparability between the processes. However, **the data package needed to assess comparability is not yet complete. It is not acceptable that such essential data should only be required after the approval**.

For a new vaccine to be launched, in addition to efficacy and safety, batch-to-batch consistency must also be demonstrated to confirm the reliability of the manufacturing process. This has become a mandatory step in vaccine development and should not be neglected. **Until the final results of such studies are available, the commercial batches should not be considered equivalent.**

Reference standard:
There are two different reference standards, one from process 3 and another from process 4, which were prepared from different virus and cell banks. The two reference standards were characterized using different tests, so that **the comparability of the two**

processes cannot be determined. The applicant must now **generate a new reference standard** from a good manufactory practice (GMP) vaccine batch prepared by the commercial process 4.

In addition, the applicant should perform a full characterization of the new reference standard including tests to analyse virus identity, virus protein fingerprint, transgene expression stability, and level of aggregated particles in the reference standard qualification protocol.

Due to the very high variability of the biological systems used to produce the vaccines, vaccine manufacturers must take special care to ensure that the different batches of a vaccine are of appropriate consistency and that the immunogenic activity of each batch is equivalent to that of the vaccine preparation whose efficacy in the target species was originally demonstrated. Consistency can be demonstrated by regularly comparing the different batches with a reference standard that serves as a fixed point of reference in the manufacture and quality control of a vaccine.

Since with AZD1222 there is no well-characterized reference standard, it is not possible to compare the different batches of the vaccine with the reference standard and to check their suitability. Inefficient vaccine batches might then be produced.

Shelf-life specification and infectiousness of the virus:
The final product has a 4-6-fold lower shelf-life specification for the concentration of infectious virus particles than the test product used during clinical trials.

Until conditional approval was granted, there was **no data produced to demonstrate the efficacy of the current vaccine doses or the acceptable immunogenicity of the commercial batches at the end of their shelf life. The clinical consequences of the use of different doses have not been conclusively determined and the applicant has been asked to investigate this further**.

How can it be that a vaccine has already been licensed, while the efficacy of the commercial batches in terms of adequate immune response has yet to be established with certainty?

It is irresponsible to accept uncertainties in shelf life, since EMA cannot know for how long each batch will be used. Extended storage obviously might reduce the amount of infectious virus particles to an extent that vaccination would result in little or no immune response.

Non-clinical aspects
No studies on secondary pharmacodynamics have been performed.

Some safety pharmacology investigations have been performed.

No studies on pharmacodynamic drug interactions have been performed (changes due to diseases, genetic mutations, aging or the influence of other drugs).

Primary pharmacodynamic studies on different animal models:
In conclusion, many studies showed none or only a slight protective effect of vaccination against an experimental SARS-CoV-2 challenge based on pathological analyses (rhesus macaques, ferrets).

Also, the immunological response in the form of antibody formation and cytokine release between the vaccinated groups and unvaccinated groups showed either no or only partial differences.

Further, there is a shortage of data on the cellular immune response. Data on Th1/2-biased response and T cell subtyping after vaccination and challenge was rather limited and, in some studies, completely absent.

Since the clinical data are the predominant source of uncertainty, it cannot be concluded from these studies that the vaccine AZD1222 has a protective effect against SARS-CoV-2 pathology in animals.

It must be noted that the animals in these studies were young and healthy. Infection with SARS-CoV-2 is only possible by application of a high viral load directly into the respiratory tract (trachea). Translating this to humans, it is important to remember that the most vulnerable groups are older and have underlying diseases that make them more susceptible to severe forms of COVID-19.

If this vaccine is unable to protect even these young healthy animals from COVID-19 disease, then this raises grave doubts about its efficacy in humans with many comorbidities.

A vaccine which uses 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:
At the time of approval, these data were not yet available, and there thus was no information on which tissues the vaccine enters or which organs the viruses affects, how long they remain in the body, and how they are degraded.

Toxicology:
The assessment report does not provide any detailed information about what exactly has been investigated.
Based on current knowledge, it is irresponsible to already administer adenovirus-based vaccines such as AZD1222 to healthy people – particularly on such a large scale as has been done since immediately after the approval.

Thrombocytopenia
This experiment clearly demonstrates that thrombus frequently occurs in atherosclerotic arteries after adenovirus-mediated gene transfer.

The novel method of introducing genetic material into human cells via adenoviruses or adeno-associated viruses appears to cause dangerous side effects, the causes of which are not at all clear.

While such risks might be acceptable in otherwise incurable conditions such as spinal muscular atrophy, it is absolutely irresponsible to impose them on healthy people who have little or no risk to ever experience a severe course of COVID19.

Spread of antibiotic resistance genes:
Due to the manufacturer's lack of transparency, it is not clear to the public whether the DNA vector of AZD1222 contains an expression cassette for an antibiotic selection marker.

If AZD1222 has an antibiotic resistance gene, this gene will be spread among the vaccinated population; it may then be transmitted to pathogenic bacteria and render them resistant to the antibiotic in question.

Interference of adenovirus cross-immunity with vaccination:
Our understanding of the global adenovirus serum epidemiology is incomplete, particularly with respect to African countries, which are often primary targets for vaccination campaigns.

In summary, immunity to the vector severely limits the useful effect that can be expected from repeated administrations of vaccine AZD1222 to the same patient.

Genotoxicology:
No studies on genotoxicology have been performed.

EMA maintains that such studies are not relevant to viral vaccines since no adjuvants or novel excipients are used in this product.

The EMA's decision not to demand genotoxicity studies is irresponsible and incomprehensible. It has been known for over 30 years that foreign (viral) DNA can integrate into the genome of mammalian host cells. The site of viral integration into host cell DNA cannot be controlled.

It should be emphasized that all integration sites in the host cell genome are shown to be transcriptionally active.

The resulting genotoxic effect:

- **Gene inactivation**
- **Gene activation**
- **Gene regulation**
- **Chromosomal damage**
- **Autoimmune-like disease**

Long-term investigations concerning possible genotoxic effects by chromosomal integration in the pre-clinical and clinical trial stages are necessary for a proper and valid benefit-risk analysis of gene transfer vectors like the vaccine AZD1222.

It is irresponsible to use an adenovirus vector as a vaccine on humans when so little scientific data is available. **It is dangerous to assume that adenovectors will never integrate into the cellular genome; there are no studies to prove this point.**

On the contrary, in previous ***in vivo*** studies it was shown that injection of hamsters with **wild-type adenovirus type 12 (Ad12) resulted in tumour formation due to chromosomal integration of the virus DNA and the expression of cancer-promoting proteins.**

Carcinogenicity
No studies on carcinogenesis have been performed.

EMA claims that such studies are not relevant for viral vaccines since no adjuvants or novel excipients are used in this product.

However, as discussed above (see section: genotoxicity), the EMA's decision not to demand carcinogenicity studies is not acceptable and must be categorically rejected.

Ecotoxicity /environment risk assessment
No studies on ecotoxicity /environment risk assessment have been performed.

High risk of antibody-dependent enhancement:
Thus, further studies are urgently needed to clarify the possible causation of ADE by antibodies against SARS-CoV-2 spike protein induced by vaccination.

Risk of inefficacy due to dual use of the same adenovector:
Clinical trial for AZD1222, which also showed no increased T-cell response after the second vaccination with the same vector.

These are only two examples **to highlight the importance of carrying out long-term clinical trials, since not only side effects but also the efficacy of a vaccine can only be clearly determined over time.**

The duration of the AZD1222 clinical trials were far too short to judge long-term efficacy; and furthermore, only very few COVID cases were detected in both the vaccinated and the control groups, so that the reported efficacy is very questionable and varies between studies.

Risk of coagulopathies due to an autoimmune attack:
In sum, the "vaccine" must be feared to vigorously promote vascular injury and clot formation in small vessels and veins throughout the body via multiple pathways. The severity of these events must be expected to vary substantially between individuals, depending on the level of their previous immunity to SARS-CoV-2, but also on happenstance – if the needle slices a blood vessel during intramuscular injection, a much larger than usual amount of the vaccine may enter the circulation directly, with proportionally more intense expression of the spike protein within the circulation.

Not a single possible pathway leading to the potentially devastating event has been examined, let alone excluded, in any preclinical animal experiments. However, since the approval of the "vaccine", numerous cases of thromboembolic events and DIC have been observed in vaccinated individuals, which motivated the transient suspension of its use in as many as 15 countries, many of them EU members.

Clinical studies in human trials:
A detailed investigation of the optimal vaccine dose for AZD1222 in humans, the required number of vaccine doses, and the time interval for administration of these doses was not performed.

During the course of the studies important parameters were changed. **The extension of the time interval before the second vaccine dose was based on logistics problems in the production of the vaccine in all 4 studies.** The time interval between the two doses is important for the interpretation of the immune response. Further, the antibody titres were not measured before and after the second dose was administered, **so that no statement can be made concerning the efficacy of or the need for a second dose.**

In conclusion, at the time of approval, no evidence was available to support the need for a booster dose or the induction of protective immunity in old people by the vaccine. Moreover, evidence was lacking regarding the activity against emerging SARS-CoV-2 variants.

In a new study in February 2021, dual dosing of ChAdOx1-nCoV19 was shown to confer no protection against mild and moderate Covid-19 due to the B.1.351 variant.

Whether the vaccine protects against severe disease caused by this variant could not be determined in this trial. Likewise, no firm conclusions can be drawn about vaccine efficacy in terms of dose amount and timing of administration.

The risk-to-benefit ratio of the vaccine

The ratio of benefit to risk will decline with time, and the decline will likely be significantly within even a few short months. The risk-benefit relation must therefore be reassessed, and the conditional approval of the vaccines be reevaluated, at intervals shorter than the currently effective approval period of one year.