An Independent Analysis of the Manufacturing and Quality Issues of the BNT162b BioNTech/Pfizer Quasi-vaccine based on the European Medicines Agency's Public Assessment Report (EPAR)

by

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This article summarizes the main findings of a more detailed technical assessment concerning the development and manufacturing of the BioNTech/Pfizer's COVID-19 quasi-vaccine BNT162b. A number of deficiencies in the product's development were identified by regulatory agencies and appear to have either been ignored or glossed over. Vaccine approval for the declared COVID-19 pandemic was given 'fast-track 'conditional approval to address "a seriously debilitating, rare or life-threatening disease devoid of a viable treatment" and approval was granted on the condition that additional information would be forthcoming after the vaccine was rolled out. *This data has not been fully provided to date.*

Data for this review was primarily obtained from the European Medicines Agency European Public Assessment Report (EPAR)[1] for the BioNTech/Pfizer vaccine. Additional information was obtained through email leaks from *December, 2020* that were released to journalists and to the British Medical Journal.[2,3]

The COVID-19 quasi-vaccine contains synthetic mRNA. The mRNA is "humanized" so it can be translated into the SARS-CoV-2 spike protein by ribosomes in our cells. These chemical modifications, or codon optimization, include replacing one of the nucleosides (*i.e.*, uracil) with another one (*i.e.,* pseudo-uracil) that is not present in human mRNA, but which results in increased stability and improves the efficiency of spike protein production compared to using viral mRNA.[4] Other changes made to the mRNA 'recipe' include a set of two proline amino acid residues to lock the spike protein into a pre-fusion state and changes in the "stop codons" that are used to instruct the ribosomes to stop translating the protein. While this genetic engineering of the viral mRNA results in high levels of spike protein production, it is now known that this modified mRNA can persist for days or weeks in humans,[5] as can the spike protein itself.[6]

The genetic engineering of the mRNA may result in aberrant proteins production. The various modifications made to the mRNA may be prone to errors when translated in our cells and this may generate variations in the resulting spike proteins when compared to the Wuhan spike

[1] European Medicines Agency. Comirnaty European Public Assessment Report. Dec. 21, 2020. https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf Accessed August 24, 2022.

[2] Tinari J (2021). The EMA covid-19 data leak, and what it tells us about mRNA instability. *BMJ* 372:n627. https://www.bmj.com/content/bmj/372/bmj.n627.full.pdf

[3] Rappaport Rolling Review Report overview LoQ-COVID-19 mRNA vaccine BioNTech. https://www.covidtruths.co.uk/2021/04/ema-leaked-papers/ Accessed August 24, 2022.

[4] Kim SC, Sehorn SS, Shin WR, Ahn G, *et al.* (2022). Modifications of mRNA vaccine structural elements for improving mRNA stability and translation efficiency. *Molecular and Cellular Toxicology* 18(1): 1-8. https://link.springer.com/content/pdf/10.1007/s13273-021-00171-4.pdf

[5] Röltgen K, Nielsen S, Silva O, Younes SF, *et al.* (2022). Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell* 185(6), 1025–1040.e14. https://doi.org/10.1016/j.cell.2022.01.018

[6] Bansal S, Perincheri S, Fleming T, Poulson C, *et al.* (2021). Cutting Edge: Circulating exosomes with COVID spike protein are induced by BNT162b2 (Pfizer-BioNTech) vaccination prior to development of antibodies: a novel mechanism for immune activation by mRNA vaccines. *J Immunology* 207 (10);2405-2410. https://www.jimmunol.org/content/jimmunol/207/10/2405.full.pdf

protein. Differences in folding of the spike protein[7] and generation of other antibodies with unknown effects may occur.[8] Abnormal spike protein and fragments following vaccination have been documented.[9,10] It is not yet known if these mutant proteins may be associated with unwanted and adverse events as has been demonstrated with other codon-optimized proteins.

The exact features of the spike protein produced by the synthetic mRNA are unknown. It is not known how the spike protein translated from the modified mRNA fully compares to the original Wuhan virus version. It is assumed the genetic engineering of the nucleotide sequence as undertaken with the COVID-19 vaccines would not alter the spike protein amino acid sequence. However, there is a lack of clarity regarding the spike protein characterization despite several requests for such data from the EMA. A full comparison of the spike protein made by the mRNA in the vaccine to the natural virus has not been performed to date. Although the amino acid sequence of the spike protein produced by the modified mRNA in the quasi-vaccine is currently unknown, thousands of distinct gene sequences for the SARS-CoV-2 spike protein and its variants are publicly available. These concerns are further compounded for the most recent 'bivalent' modified mRNA injectable formulations released this Fall 2022 that encode two distinct spike proteins, namely the original ancestral Wuhan strain and a combination of BA.4/BA.5 Omicron sub-variants. This allows for formation of unnatural trimeric complexes with novel mixes of spike proteins from both versions of the SARS-CoV-2 virus.

We cannot assume the results of the clinical trials apply to the products used in the general population. To rapidly produce sufficient doses and to decrease production costs, the manufacturing process used for the commercial roll-out of the vaccines is quite different than the manufacturing process used for the clinical trials. In its rolling review in November 2020, the EMA notes that there was a decrease in the purity of the mRNA. In the clinical trial batches, the intact mRNA was 78-83% pure, which was much higher than in the commercial batches at 60%.[3] This difference is may be large enough to normally require confirmatory clinical trials. These impurities included fragmented mRNA, and it is not yet known what effects these smaller mRNA fragments (impurities) have in the body, since shorter spike protein fragments may be produced, which may be release more readily into the circulation from vaccine transfected cells. Such truncated fragments may lack the transmembrane domain at the back end of the spike protein, which would normally anchor them to the cell membrane. At the time of conditional approval, the allowable limits for fragmented mRNA was up to 50% in the final product.[3]

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[7] McKernan K, Kyriakopoulos AM, McCullough P (2021, November 25). Differences in vaccine and SARS-CoV2 replication derived mRNA. Implications for cell biology and future diseases. *OSF Preprints*. https://doi.org/10.31219/osf.io/bcsa6

[8] Seneff S, Nigh G, Kyriakopoulos, AM, McCullough P (2022). Innate immune suppression by SARS-CoV2 mRNA vaccinations: the role of g-quadruplexes, exosomes, and microRNAs. *Food and Chemical Toxicology* 164: 113008. https://www.sciencedirect.com/science/article/pii/S027869152200206X

[9] Patterson BK, F. E., Yogendra R, Long E, *et al.* (2022, July 12). "SARS-CoV-2 S1 protein persistence in SARS-CoV-2 negative post-vaccination individuals with Long Covid/PASC-like symptoms." *Research Square (Preprint)*. https://www.researchsquare.com/article/rs-1844677/latest

[10] Magen E, Mukherjee S, Bhattacharya M, Detroja R, *et al.* (2022). Clinical and molecular characterization of a rare case of BNT162b2 mRNA COVID-19 vaccine associated myositis. *Vaccines* 10(&): 1135. https://www.mdpi.com/2076-393X/10/7/1135

We have little data on whether these fragmented mRNA result in harmful proteins or peptides (small proteins) or if they induce autoimmunity (cause the body to attack itself). For example, there can be as much as a 30% amino acids similarity between the spike protein and a human protein called Syncytin-1, and although cross-reactivity of spike protein antibodies produced in vaccinated individuals have not yet been directed towards Syncytin-1,[11,12] autoimmunity often takes years before they manifest in people.

Although improvements have been noted in many of the identified manufacturing deficiencies over time, quality issues are likely still present and more rigorous characterization of the spike protein produced by the synthetic mRNA remains to be done.

The lipid nanoparticles (LNPs) are novel for use in humans and have not undergone rigorous safety assessments. The LNPs are semi-spheres made of fat (lipids) that protect the mRNA from decaying (degrading) and also carry the mRNA into our cells. They contain PEGylated lipid (ALC-0159) and the cationic lipid (ALC-0315), *neither of which have been used in humans before*. Normally, approval for such novel components would require a full independent review for pharmacology and toxicity. These safety studies appear to be incomplete.

Cationic lipids are known to cause inflammation (both with and without mRNA cargo inside them), and can be directly toxic to cells.[13] PEGylated lipids can cause significant allergic reactions.[14] There is limited data both on the metabolism and distribution of these lipids, and it is not known how much ends up in each organ. *There is no clinical data to support the safety of repeated exposures to the LNPs in humans.*

No one knows the potency, the quantity, or the duration of the spike protein produced in different organs and the endothelium (*i.e.,* lining of blood vessel walls) given widespread biodistribution. There is no control of the amount of or length of time spike protein is produced by our cells. Tens of trillions of lipid nanoparticles are injected with each vaccination. It is not known if age, sex, weight or other characteristics affect the potency of the vaccine. *We do not know how much spike protein is made in each organ* in humans that takes up the synthetic mRNA. Evidence appears to indicate that small amounts of LNPs may result in large amounts of spike

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[11] Prasad M, Lin JL, Gu Y, Gupta R, Macary P, Schwartz H (2021). No crossreactivity of anti-SARS-CoV-2 spike protein antibodies with Syncytin-1. *Cell Mol Immunol* 18:2566-2568. https://doi.org/10.1038/s41423-021-00773-x

[12] Mattar CNA, Koh W, SeowY, Hoon A, Venkatesh A*, et al.* (2021). Addressing anti-syncytin antibody levels, and fertility and breastfeeding concerns, following BNT162b2 COVI-19 mRNA vaccination. *medRxiv* 2021.05.23.21257686. https://doi.org/10.1101/2021.05.23.2125768

[13] Ndeupen S, Qin Z, Jacobsen S, Bouteau A, Estanbouli H, Igyártó BZ (2021). The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. *iScience* 24(12), 103479. https://doi.org/10.1016/j.isci.2021.103479

[14] Moghimi SM (2021). Allergic reactions and anaphylaxis to LNP-based COVID-19 vaccines. *Mol Ther* 29(3), 898-900. https://doi.org/10.1016/j.ymthe.2021.01.030

protein being produced in a particular organ.[15] Basic pharmacological data of the optimal dose, its ranges, and its upper toxicity thresholds are lacking.

The quasi-vaccine quality is questionable and variable. There may be substantial differences in the mRNA vaccines between batches and even between vials. This may be due to variations in handling, freezing/thawing/dilution requirements, the short half-life of the mRNA, and manufacturing variability. Stainless steel particles seen with the naked eye in some Moderna vials[16] should have forced a product review- but this was not done. A very wide range of limits for purity and quality was permitted in the commercial production of the vaccines. Large manufacturing variability between batches plus patient-to-patient variability will likely result in different levels of spike production and response to the quasi-vaccine.

In a December 2020 draft document on regulatory evaluation,[17] the World Health Organization admitted that detailed information was not available for the production of the COVID-19 mRNA vaccines. The WHO confirmed that controls for safety and efficacy of gene-based mRNA vaccine biologic products were not standardized. Certain details of vaccine components remain proprietary and were not publicly disclosed. In light of these unknowns, the WHO conceded that it was not feasible to develop specific international regulatory guidelines or recommendations, and strict adherence to normal regulatory guidance may not be possible. Has this flexibility resulted in products with critical flaws that may result in harm to those administered the product?

It appears that there is insufficient evidence that this vaccine product meets the quality required of a pharmaceutical product, raising concerns about its safety and efficacy. Regulatory assessment using current vaccine guidance is likely inadequate to determine safety and efficacy for a genetic product. **Assessment using a stricter gene therapy guidance may have been more appropriate but currently is *not required* if the *use* of the product is for prevention of infectious diseases such as a vaccine.**[18] Real-world data falsifies the original claim that mRNA based COVID-19 biologics function as an authentic vaccine for preventing viral infection and transmission rather than as a short-term gene-based therapeutic agent that might alleviate at best symptom severity. With this in mind, the authorization for these products should be suspended until the concerns in this review have been resolved and publicly verified by the regulatory authorities.

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[15] Di J, Du Z, Wu K, Jin S, *et al.* (2022). Biodistribution and non-linear gene expression of mRNA LNPs affected by delivery route and particle size. *Pharm Res* 39(1): 105-114.

[16] Takeda Inc. (October 2021). Moderna COVID-19 vaccine recall investigation report. https://www.takeda.com/4a7623/siteassets/ja-jp/home/announcements/2021/report/moderna-covid-19-vaccine-recall-investigation-report--october-2021.pdf Accessed August 25, 2022.

[17] World Health Organization. Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: Regulatory considerations. Draft December 20, 2020. https://www.who.int/docs/default-source/biologicals/ecbs/reg-considerations-on-rna-vaccines_1st-draft_pc_tz_22122020.pdf?sfvrsn=c13e1e20_3 Accessed August 25, 2022.

[18] Food and Drug Administration Center for Biologics Evaluation and Research (2020, January). Human therapy for rare diseases. Guidance for industry. https://www.fda.gov/media/113807/download Accessed August 24, 2022.

Abbreviations:

EMA: European Medicines Agency
FDA: Food and Drug Administration
LNP: lipid nanoparticles
mRNA: messenger ribonucleic acid
Translation: the process in a cell by which a protein is produced from mRNA (messenger ribonucleic acid)
WHO: World Health Organization

The authors declare no conflicts of interest with respect to the information in this report.