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Evidence of violations of the Good Manufacturing Practices and lack of mRNA integrity in Pfizer batches produced between July and November 2020.

Background:

Lack of mRNA integrity and product impurities (fragmented nucleic acid chains) were found in Pfizer's product at the end of November 2020 - days before it was authorized for market[1]. mRNA integrity, and conversely, its instability, is one of the most important variables relevant to all mRNA vaccines. The efficacy of the product is highly dependent on the quantity of the sufficiently intact mRNA molecule which constitutes the active substance (or Drug Substance, DS) in the finished Drug Product (DP). Even a minor degradation, anywhere along a mRNA strand, and/or breakage of the mRNA molecule into smaller strands, can severely slow or stop proper translation performance of that strand and thus result in the incomplete expression of the target antigen, and in unpredictable off-target effects with potential consequences to the safety of the product[2].

At the time of the regulatory review, integrity of key active ingredient – mRNA molecule as measured by the %mRNA integrity and % of RNA fragments called Late Migrating Species (LMS) in each manufactured batch is highly and unacceptably variable. This was identified by the regulatory reviewers at the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The discussions around this issue are recorded in numerous documents that were released from EMA, at the end of November 2020, including email exchanges between EMA staff and management. Authenticity of the documents and emails was independently verified by the British Medical Journal[3]. The apparent "solution" to this issue negotiated between the EMA reviewers and Pfizer/BioNTech at that time was to lower the acceptance standard for the %mRNA integrity in the active substance for shelf live to just >50%, down from the previously used standard of >70%[4]. In other words, up to 50% of the nucleic acid chains and other genetic material impurities can be present in the active substance, do not need to be characterized and the product is still deemed "acceptable".

As result, an extremely wide variation of the integrity of the active substance in bulk material (batch) of the product and abundant presence of uncharacterized nucleic acid impurities means that batches of different formulation - and thus different potency and safety profiles - are being produced. This variation is further amplified when a large volume of bulk material is filled in small 0.45 ml vials and subsequently manually divided into doses by untrained and unsupervised staff at the vaccination centers.

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[1] See EMA's "Interim Opinion" document, p.21 section "Impurities" in Attachment.

[2] Kirchner B, Paul V, Riedmaier I, Pfaffl MW. mRNA and microRNA purity and integrity: the key to success in expression profiling. Methods Mol Biol. 2014;1160:43-53. doi: 10.1007/978-1-4939-0733-5_5. PMID: 24740220.

[3] https://www.bmj.com/content/372/bmj.n627

[4] See Powerpoint presentation from EMA-Pfizer meeting on Nov 26, 2020 in Attachment.

Both the regulators and Pfizer to date have not disclosed the acceptable ranges, testing methods and results for the key ingredients of the vaccine product, neither in bulk product nor in a vial (as dispensed), and claim "commercial secrets" prevent them from doing so.

Each vial of Pfizer product is labelled exactly for 225 mcg of mRNA total, and exactly 30 mcg of mRNA per dose. With variation of up to 50% in the mRNA active substance in bulk material, and further additional variation resulting from downstream manufacturing steps, filling, transportation and manual preparation of the doses, it is not possible to assure that 30 mcg of mRNA will be present in every dose. Thus, many people receiving the vaccination are receiving almost no mRNA and thus vaccination with this product is pointless, and some people may receive dangerously high amounts of mRNA, resulting in injury or even death as over-expression of spike protein would lead to major uncontrollable toxicities[5].

33 Commercial Pfizer Batches Manufactured Prior to Regulatory Review and Market Authorization in December 2020:

Records released by the EMA leak contain some manufacturing and testing details for 33 commercial scale batches made by Pfizer between July and late November 2020. Specifically, these batches and all information used in my analysis were listed in the document titled: "COVID-19 Vaccine (BNT162, PF-07302048) BB-IND 19736 Response to CBER Comments Received on 20 November 2020 Regarding Overall CMC Information." The document is dated November 25, 2020 and included in Attachment.

At the time of issue of this document, the manufacturing facilities were deemed not in acceptable compliance with the current Good Manufacturing Practices[6] by the regulatory authorities (both EMA and FDA). The non-compliance with cGMP was recorded as Major Objection #1 by the EMA reviewers, and in addition, the issue of lack of mRNA integrity and presence of significant uncharacterized impurities in the form of nucleic acid chains (LMS) was raised and recorded as Major Objection #2.

In its rolling review in November 2020, the EMA noted that a decrease in RNA integrity, which is a critical quality attribute, was observed such that RNA integrity of Process 1

[5] Seneff S, Nigh G, Kyriakopoulos AM, McCullough PA. Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs. Food Chem Toxicol. 2022 Jun;164:113008. doi: 10.1016/j.fct.2022.113008. Epub 2022 Apr 15. PMID: 35436552; PMCID: PMC9012513.

[6] CGMP a set of regulatory requirements guiding quality, purity, stability and reproducibility of mass-produced drugs and vaccines. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have. https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations

(78.1-82.8%) were much higher than the commercial scaled up Process 2 (59.7%). Furthermore, it was not possible to determine if the differences in RNA integrity were qualitative, quantitative, or both. Truncated mRNAs in Process 2 were also not defined. At the time of the Conditional Marketing Approval in EU it was not known what proteins were coded for, if any, and their clinical effect was not known. It could not be excluded that proteins different from the intact full-length spike would be expressed. Furthermore, the Pfizer vaccine-induced spike protein was different by total molecular weight from the Wuhan spike protein (180+kDa vs 141kDa, respectively) and the difference was never properly explained.

When mRNA degrades due to various factors in manufacturing, it is possible that truncated mRNA may affect translational efficacy or modify the immunostimulatory profile. Even if these truncated mRNA are not translated, they are considered genetic impurities and should minimized or eliminated as much as possible so that the same amount of intact pure mRNA is present in each batch. Micro-RNAs (miRNA) are known to have interference mechanisms in cellular genetic processes and thus can pose danger of genotoxicity and carcinogenicity on their own[7].

The lack of characterization of the expressed spike protein by the vaccine was noted as a “severe deficiency” by the EMA reviewers and the proper characterization of the expressed spike protein was included as one of the conditions of the Conditional Market Approval (CMA). However, this condition was never fulfilled by the manufacturer and was not enforced by the regulators.

There were additional numerous objections and concerns of the regulator (100+ of formal regulatory objections were found in the EMA documents from late November 2020).

Recent investigation of the 5 of the 33 batches that were shipped to Sweden revealed that these batches were illegally imported due to non-compliance with cGMP and lack of importation compliance[8].

Statistical Analysis of Relationship Between %mRNA Integrity in a Batch and the Rate of Adverse Events and Deaths Reported for the Batch in CDC VAERS Database.

The 33 Pfizer batches contained a total of approximately 6 million vials for approximately 29 million vaccine doses. Note that at the time of approval, Pfizer multi-dose vials were for 5 doses vs 6 specified on the label today. These batches were shipped commercially to locations in the US and Europe (and possibly other regions) despite the documented noncompliant manufacturing, or serious regulatory concerns.

[7] Gulyaeva, L.F., Kushlinskiy, N.E. Regulatory mechanisms of microRNA expression. *J Transl Med* **14**, 143 (2016). https://doi.org/10.1186/s12967-016-0893-x.

[8] https://www.epochtimes.se/Allvarliga-fel-i-vaccinproduktion---Lakemedelsverket-blundar-568601

Of these 33 batches, 26 batches have adverse event reports associated with them in VAERS database. To date, the following number of reports is found:

- Total Adverse Event (AE) Reports: 41,193
- Permanent Disability Reports (included in the total AE Reports): 1,614
- Life Threatening conditions Reports (included in the total AE Reports): 747
- Death Reports (included in the total AE Reports): 1,065

The table below provides details about these batches as well as the numbers of adverse events and deaths found in VAERS. It should be noted that since these batches were distributed to many regions, including US, Europe and other locations, parts of the batches or whole batches may have been sent to locations that do not submit adverse event reports to VAERS system. In addition, VAERS system is known to under-represent the true adverse event rate by 10-100 times. Therefore, the true rate of the adverse events associated with these batches is likely to be several times greater than what is shown here.

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Table 1.

Lot (batch)	# Vials	Drug Substance	Date manuf	LMS	RNA Integr	All AE	Deaths
EE8492	67,665	Pfizer Andover	5-Aug-20		55%	666	2
EE8493	68,445	Pfizer Andover	5-Aug-20		55%	608	2
EG5411	201,258	Pfizer Andover	3-Sep-20			-	-
EH9978	304,869	Pfizer Andover	23-Sep-20			-	-
EJ0553	164,580	Pfizer Andover	25-Sep-20	<QLc	68%	426	15
EJ0701	200,265	Pfizer Andover	26-Sep-20	17%	52%	-	-
EJ0724	39,195	BioNTech/ Rentc	29-Sep-20	<QLc	71%	131	5
EJ1685	159,315	BioNTech/ Rentc	5-Oct-20	9%	66%	2,776	45
EH9899	179,400	Pfizer Andover	7-Oct-20	<QLc	59%	3,470	25
EJ1686	147,615	BioNTech/ Rentc	7-Oct-20	6%	69%	1,696	64
EJ1688	150,345	BioNTech/ Rentc	12-Oct-20	10%	63%	510	31
EK4175	145,275	BioNTech/ Rentc	12-Oct-20	16%	58%	42	7
EK1768	141,960	Pfizer Andover	16-Oct-20	<QLc	60%	880	14
EK4176	131,625	BioNTech/ Rentc	16-Oct-20	10%	65%	1,344	30
EJ1691	133,575	BioNTech/ Rentc	16-Oct-20	24%	51%	-	-
EK2808	48,945	BioNTech/ Rentc	19-Oct-20			-	-
EK5730	191,295	Pfizer Andover	22-Oct-20	10%	62%	3,935	24
EL0141	156,195	BioNTech/ Rentc	29-Oct-20	5%	67%	498	13
EL0142	138,060	BioNTech/ Rentc	29-Oct-20	6%	69%	1,821	45
EL0140	155,610	BioNTech/ Rentc	29-Oct-20	6%	69%	1,865	70
EL0725	272,073	BioNTech/ Rentc	30-Oct-20	9%	63%	925	50
EL0739	294,239	BioNTech/ Rentc	3-Nov-20	6%	67%	1,051	19
EK9231	230,685	Pfizer Andover	4-Nov-20			3,827	51
EL1484	277,608	BioNTech/ Rentc	4-Nov-20			1,488	37
EK4244	*na*	BioNTech/ Rentc	5-Nov-20			606	3
EK4243	*na*	BioNTech/ Rentc	5-Nov-20			589	13
EK4237	140,985	BioNTech/ Rentc	5-Nov-20	9%	64%	125	2
EL1283	245,895	Pfizer Andover	11-Nov-20			2,578	69
EJ6795	282,645	Pfizer Andover	12-Nov-20			1,079	145
EJ6796	293,828	Pfizer Andover	13-Nov-20			1,070	117
EL1284	214,305	Pfizer Andover	17-Nov-20			2,775	47
EJ6797	293,526	Pfizer Andover	17-Nov-20			2,005	73
EL3246	204,360	Pfizer Andover	19-Nov-20			2,407	47
Total vials	**5,675,641**					**41,193**	**1,065**
Doses	**28,378,205**						

EMA and FDA documents contained some detailed batch analyses for 18 batches, including the %mRNA integrity metric. I compared this parameter to deaths, permanent disabilities, and total adverse events (including non-serious) reported for the batch number in the CDC Vaccine Adverse Events Reporting database (VAERS). The regression analysis demonstrated significant statistical relationship between %mRNA

integrity and deaths and permanent disabilities reported per batch. The deaths, disabilities and total adverse even rates were adjusted for the number of vials produced in a batch. No trend was found for total adverse events that included non-serious events. Figures 1-3 summarize the results.

Figure 1.

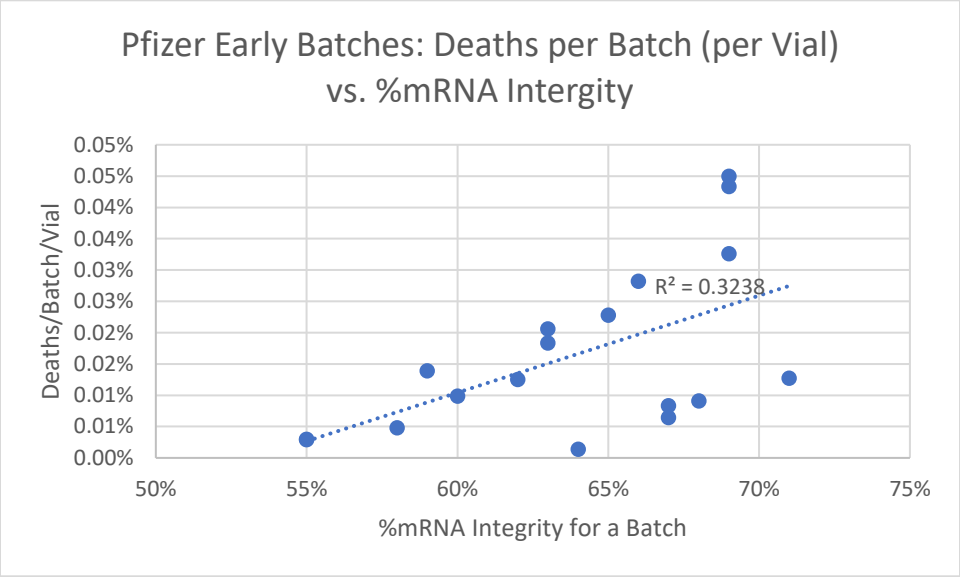

Figure 1 demonstrates significant association (R^2 = 0.33) between %mRNA integrity and death reported per batch, adjusted for the number of vials produced – higher integrity in the early batches leads to more lethal events reported for the batch in VAERS.

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Figure 2.

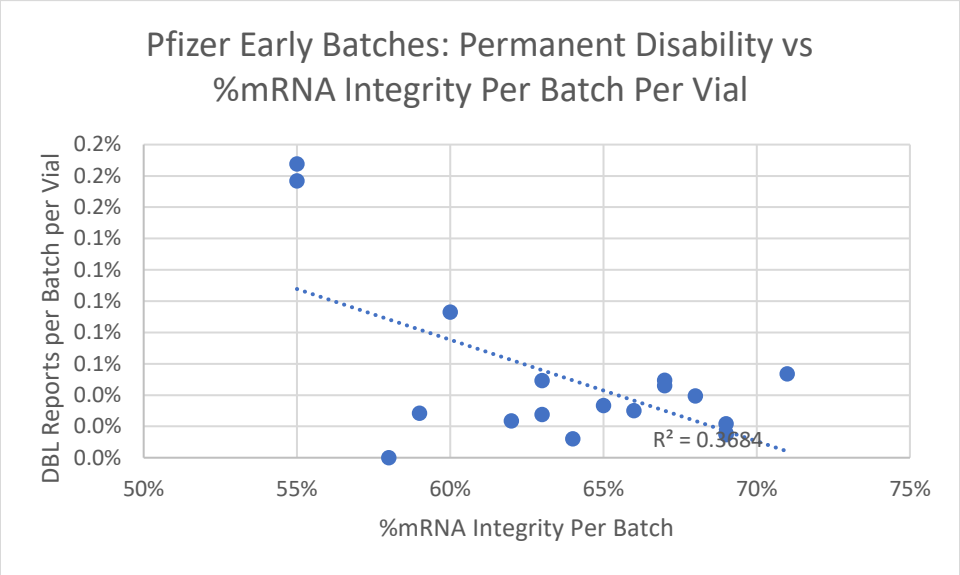

Figure 2 demonstrates the significant inverse association ($R^2 = 0.37$) between %mRNA integrity and permanent disabilities reported per batch, adjusted for the number of vials produced – higher integrity in the early batches leads to relatively fewer permanent disability events reported for the batch in VAERS. This trend almost perfectly mirrors the deaths associated with higher %mRNA integrity.

Figure 3.

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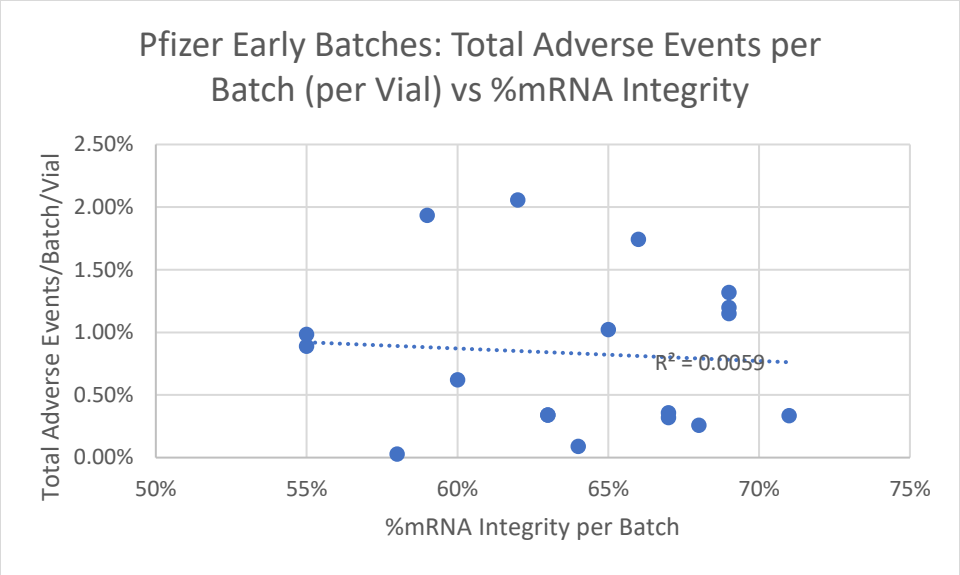

Figure 3 demonstrates that no statistical trend was found for total adverse events reported per batch vs. %mRNA integrity metric.

Discussion:

At the time of Conditional Marketing Authorization in the EU, it appears Pfizer's product would not normally meet the most basic quality controls expected of an injectable pharmaceutical. The basic pharmacology was unknown, the quantity and structure of the produced spike was unknown, and the quality and reproducibility of the production of the commercial batches were extremely poor and non-compliant with cGMP.

My current dataset exhibits alarming trends – extremely large ranges of adverse events, deaths, and disabilities as well as strong statistical association between %mRNA integrity metric with deaths and permanent disabilities. mRNA integrity is only one of dozens of critical quality attributes of this product. The manufacturer has never made the batches available for an independent testing and characterization, sequencing, or assessment of the mRNA or other nucleic acid fragments and impurities present in them. The vials in the United States are US Government property until they are injected into a person, and any independent research with these vials is prohibited. Outside of the United States, vaccine purchasing contracts expressly prohibit the purchasers from testing the product on importation. These prohibitions from independent verification of the conformity of the product to the label cannot possibly aid the transparency and public trust in these products. Thus, millions of people injected with these substances can never know what exact sequence(s) of nucleic acids were present in these injections, and what proteins may be expressed and what health impact they may have. Sadly, at least 1000 people lost their lives to these "unknown" effects by a poorly

made product shrouded in “commercial secrecy”. Without the knowledge of exact nature of the composition of various batches it is not possible to make definitive conclusions or offer good treatment options to the survivors of these injections.

The current Pfizer product does not meet the robust quality requirements of a pharmaceutical grade product as it contains large amounts of genetic material impurities. The manufacturer and regulators actively avoid transparency, disclosure, or correction of these issues. It is likely that the Pfizer product should be considered an adulterated drug as per FDA and other regulatory guidance and would normally have been withdrawn or suspended pending quality control assessment.

Alexandra Latypova (CV in Attachment)