Exhibit 170

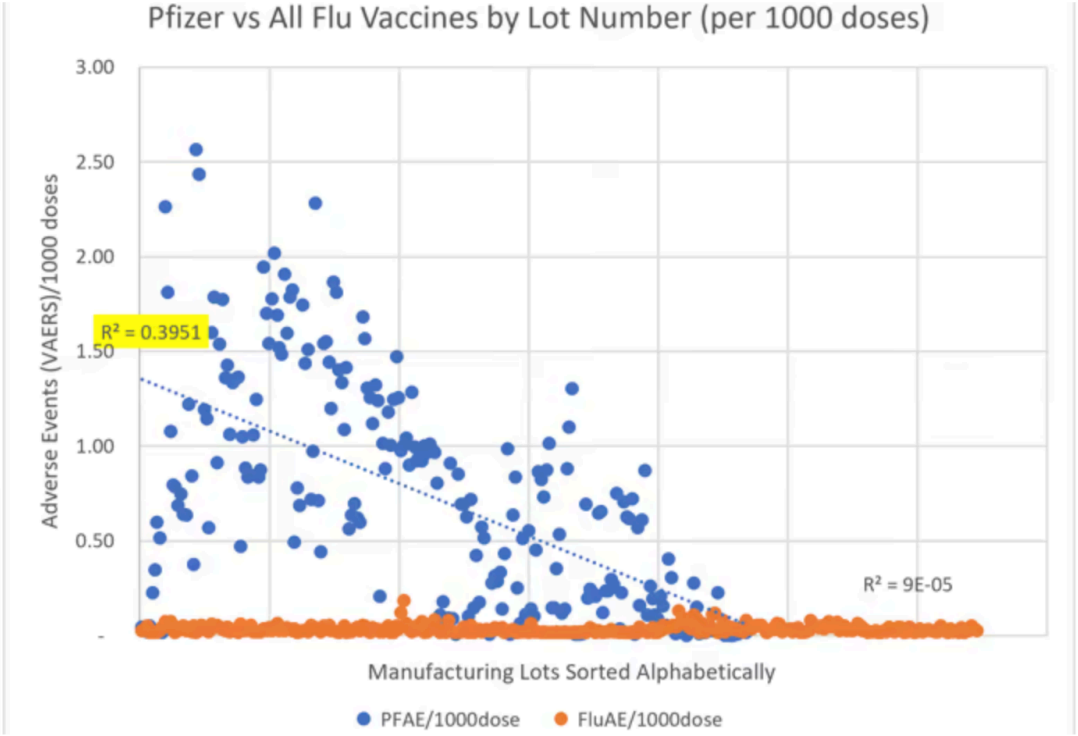
My Affidavit on Different Formulations in Pfizer Vaccine Lots

Sasha Latypova
https://www.trialsitenews.com/a/my-affidavit-on-different-formulations-in-pfizer-vaccine-lots-1b9e4ee9 - _ftnref1

COVID-19 Vaccine EMA/Rapporteur CMC Meeting 11/26/20
https://prd-tsn-main-api.s3.amazonaws.com/article/13d1ad53-0c0d-4163-941f-81c50f00f8c6.pdf

The EMA covid-19 data leak and what it tells us about mRNA instability
https://www.bmj.com/content/bmj/372/bmj.n627.full.pdf

My Affidavit on Different Formulations in Pfizer Vaccine Lots



Sasha Latypova

Writer at Independent I mRNA Fraud - Regulatory and Manufacturing Investigations
Jun. 30, 2022, 1:30 p.m.
Journalist Article

Evidence of a De-Facto Adulterated Product?

I was recently asked to provide a witness statement in regard to extensive variability of manufactured lots for Pfizer's BNT162b2 injection products. The variability is inconsistent with that expected of compendial pharmaceutical products. It can be deemed as a de-facto adulterated product. My affidavit is as follows:

The following statements are based on my review of documentation that has been publicly disclosed from Pfizer, European Medicines Agency (EMA) and Food and Drug Administration (FDA) and relates to the Chemistry, Manufacturing and Controls (CMC) sections of Pfizer's BNT162 dossier. Documents used in my review are provided in the Attachment. The documents were released due to a cyberattack on the EMA. The EMA acknowledged the release of the documents and did not dispute their authenticity. Furthermore, the British Medical Journal confirmed the contents of these documents with respect to the issues of integrity of

the active ingredient discussed herein through correspondence with the EMA, MHRA, FDA, Health Canada and Pfizer.[1]

The rates of adverse events and deaths per manufacturing batch number are derived from CDC VAERS database.

My affidavit attests to the following facts identified in the documents, with evidence information provided below:

1. The modified RNA (mRNA) which is the active substance of Pfizer's vaccine BNT162b2 is allowed to vary in its integrity by up to 50% in the finished product.
2. Product impurities in the form of truncated mRNA, untranslated DNA and other unknown nucleic acid constructs have been allowed in the finished product in unspecified quantities.
3. As a result of the reckless widening of quality acceptance criteria for the integrity of active ingredient in manufacturing batches, there is a great variation in resulting formulations of final product as dispensed in vials. Furthermore, the contents of the vials are cut by hand into multiple doses by untrained and unsupervised vaccinators who are working outside of the Good Manufacturing Practice compliance.
4. There is an excessive variation in the rates of adverse events and deaths observed post-vaccination for different manufacturing batches which far

exceeds expected batch-to-batch variations for compendial pharmaceutical products, such as for example seasonal flu vaccines.

Evidence from EMA and Pfizer Documents:

Lack of mRNA integrity and product impurities (fragmented nucleic acid chains) were found in Pfizer's product days before it was authorized for market:

mRNA integrity, and conversely, its instability, is one of the most important variables relevant to all mRNA vaccines. Pfizer and BioNTech repeatedly stated that the efficacy of the product is highly dependent on the quantity of the sufficiently intact mRNA molecule. Even a minor degradation reaction, anywhere along a mRNA strand, can severely slow or stop proper translation performance of that strand and thus result in the incomplete expression of the target antigen.

Pfizer made several major changes to its manufacturing process going from small clinical scale manufacturing (Process 1) to commercial scale (Process 2) as described in the "Rapporteurs Rolling Review Report", p. 57 (full document in Attachment).

"Process 1

[…]two changes were made within Process 1 between nonclinical toxicology and Phase 1/2/3 process: the scale of the reaction and the site. The increase in scale was required to make sufficient material for clinical trials. The location changed from a non-GMP lab into GMP facilities. This process was based on BioNTech platform knowledge from other mRNA therapeutic programs.

Process 2

[…]The DNA template changed from a PCR template to linearized plasmid DNA in order to meet commercial demands. Additionally, the magnetic bead purification was replaced with proteinase K digestion and UFDF steps. The magnetic bead purification method was not scalable, but removed small molecule impurities (e.g. spermidine, DTT), residual DNA, and enzyme impurities (e.g. T7 polymerase, DNase I). […]"

These changes were performed without re-validation of the manufacturing process or re-running the preclinical and clinical studies to confirm comparability on safety and efficacy characteristics of the product. Importantly, these changes resulted in a substantial drop in the integrity of key active ingredient – mRNA molecule as measured by the %mRNA integrity and % of fragments (Late Migrating Species, LMC) in each manufactured batch. This was identified by the regulatory reviewers at EMA and FDA, and EMA specifically recorded this as a Major Objection #2, i.e. a regulatory flag that required a resolution prior to the product approval. 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 (see Emails in Attachment). For example, a PowerPoint document from the meeting on November 26, 2020 between EMA and Pfizer/BioNTech describes the issue of mRNA integrity (see 20201126_BNT162b2_EMAmeeting14.pdf in Attachment).

In this meeting it was discussed that the batches manufactured with Process 2 had a much lower range of % intact mRNA and higher % of impurities – fragmented nucleic acid chains of various length and type (DNA and RNA). Specifically, p. 20 lists final product batches manufactured with both processes, ranging in mRNA integrity from 55% to 85% with the remaining % of volume occupied by uncharacterized fragments.

EMA regulatory concern with lack of mRNA integrity in Pfizer's product was evident. Specifically, on p. 4 the document states that:

"Significant differences between batches manufactured by DS Process 1 and 2 are observed for the CQA *[critical quality attribute]* mRNA integrity. In addition, the characterisation of BNT162b2 DS *[drug substance]* is currently not found acceptable in relation to this quality attribute. This is especially important considering that the current DS and DP *[drug product]* acceptance criteria allows (sic) for up to 50% fragmented species."

Further, on p. 5 the reviewers discussed the presence of uncharacterized fragmented nucleic chains, some long enough to translate into unknown proteins, and deemed them product impurities that required further characterization:

"Truncated and modified RNA species should be regarded as product-related impurities. Even though two methods, namely agarose gel electrophoresis and capillary gel electrophoresis (CGE), have been applied to determine RNA integrity of BNT162b2 DS *[drug substance]*, no characterisation (sic) data on truncated forms is presented. "

As a result of the manufacturing inconsistency, the clinical trial data collected using the Process 1 material was not deemed applicable to the material manufactured in Process 2. Several EMA reviewers wanted to understand the potential impact on safety and efficacy via bridging clinical studies (see Emails in Attachment). No such comparisons were done. Pfizer provided comparison of some chemical analyses from various batches, but no further characterization of the fragments of RNA and DNA or study of impact of these impurities on safety and efficacy of patients was provided.

EMA reviewers and Pfizer "resolved" this Major Objection by arbitrarily lowering the acceptance criteria for %mRNA integrity (see p.4):

“In addition, we are revising the RNA integrity specification for drug substance to >=60%, drug product release to >=55%, and drug product shelf life to >=50%. “

An extremely wide variation of the integrity of the active substance in bulk material (batch) of the product and abundant presence of uncharacterized impurities means that batches of different formulation - and thus different potency and safety profiles - are being produced. This variation is further amplified when the bulk material is filled in small quantities into vials. Each batch of Pfizer product contains approximately 300,000 vials filled with 0.45ml of drug product which may get varying quantities of intact and broken mRNA molecules. In addition, at the final step of administration, this variability is further exacerbated by dose preparation in a non-GMP environment by untrained and unsupervised staff at the vaccination centers.

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

Evidence from adverse event reports (in VAERS database) analyzed by manufacturing lot number.

Manufacturing of pharmaceutical products is regulated by laws that are established to control within tight ranges acceptable criteria for the identity, quantity, quality, purity, potency and other characteristics of the product ingredients to ensure safety and conformity to the approved product labeling. It is expected that the product lot-to-lot, or batch-to-batch, is essentially the same. Therefore, when outcomes data such as rates of adverse events reported for each manufacturing lot is examined, it is expected that only minor variations from lot-to-lot may be observed. This is true for conventional pharmaceutical products and for traditional vaccines such as seasonal flu vaccines.

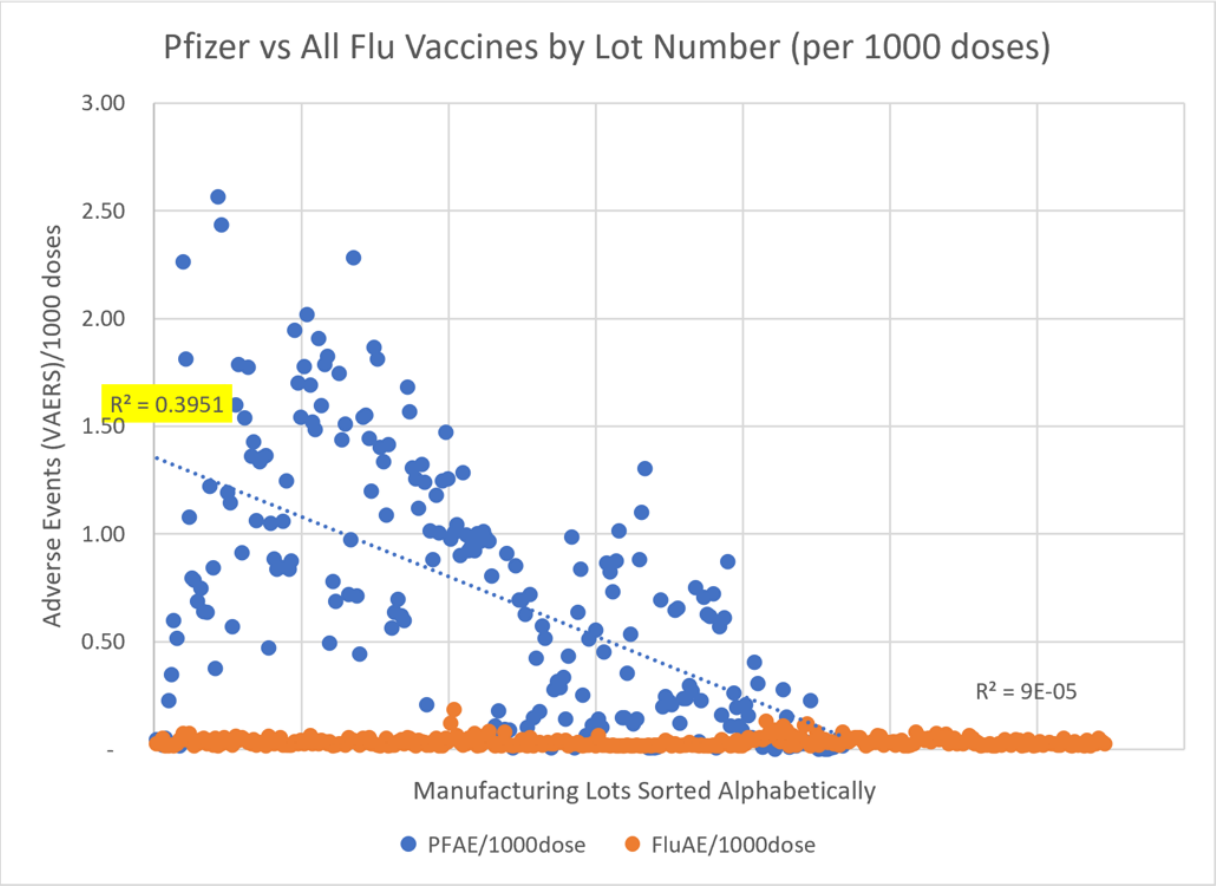
There is an excessive variation in the rates of adverse events and deaths observed post-vaccination for different manufacturing batches which far exceeds expected batch-to-batch variations for compendial pharmaceutical products, such as for example seasonal flu vaccines.

The graph below shows a comparison between the manufacturing lots of Pfizer's BNT162b2 product and manufacturing lots of all seasonal flu vaccines released in 2019-2020. The lot numbers for Pfizer were verified with CDC and dates of manufacture and expiration were obtained. The flu vaccine lot numbers were obtained by downloading data from VAERS. Rates of adverse events reported for each lot are plotted against the lot number (not shown on X-axis for clarity), sorted

alphabetically. Finally, the adverse event rates are expressed in "per 1000 doses" to normalize for the lot size.

As evident from this analysis, there is an excessive variability in the toxicity (rates of adverse events) for Pfizer product. The flu vaccine lots in comparison look very similar to each other and have overall a very low rate of adverse events. There is a large correlation between the adverse even rates for Pfizer lots with the lot number (R^2=0.4). This should not happen. There should be no difference in the safety (toxicity) of a product depending on how its manufacturing lot is numbered. This does not exist for the flu vaccine lot numbers. Overall, the rate of adverse events per lot/dose adjusted is extremely high as can be visualized on the graph below.

The difference between the two sets of products is stark and cannot be explained by normal demographic variations such as age or underlying health status of the recipient. Flu vaccines are administered to approximately 50% of population, including to old and frail people with compromised health status as well.



In conclusion, the evidence presented in my statement shows that Pfizer's manufacturing quality acceptance criteria permit for an extremely large variation of the key ingredient (up to 50%) and allow for a substantial presence of uncharacterized impurities. This can be deemed as product adulteration with de-facto different formulations produced in different batches. This leads to overall large rates of toxicities, reported adverse events and to extreme variations of product safety (toxicity) parameters in different manufactured lots.

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

References

- 20201126_BNT162b2_EMAmeeting14.pdf

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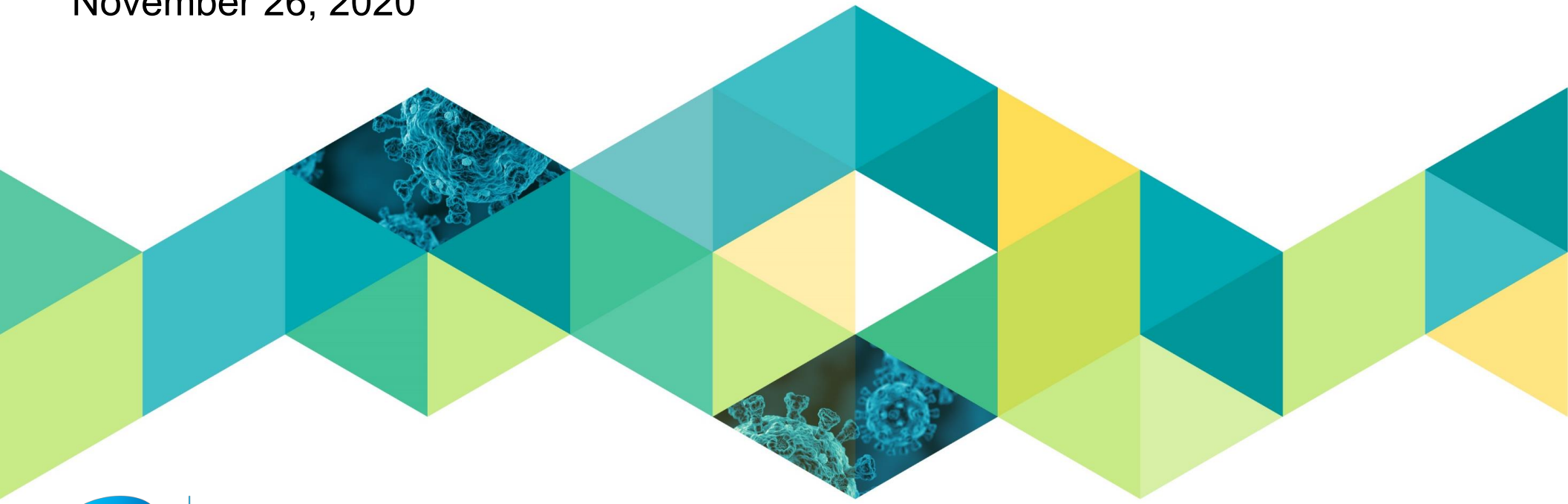
Confidential

COVID-19 Vaccine EMA/Rapporteur CMC Meeting

November 26, 2020



Agenda

1. **Intended reply strategy for draft Major Objections (25th November)**
2. Quality items in revised submission plan
3. Updated drug product specifications
4. Updated process validation strategy for drug product
5. Additional filling line and increased batch size for drug product
6. Any other business

1. Major Objection #1 (GMP status)

1) GMP status for DS and DP manufacturing sites is currently not acceptably demonstrated:

a.) A statement on GMP compliance issued by EU supervisory authority of the DS and DP manufacturing and testing sites Wyeth BioPharma Division, Andover, United States and Pfizer Inc, Chesterfield, United States should be available by adoption of the CHMP opinion.

Response for Andover and Chesterfield sites

- Ongoing inspection with EMA. Expected to be completed prior to CHMP opinion.

b.) The MIA for Pfizer Puurs is limited to the formulation and filling only. It should be clarified if authorisation will be extended to all operations listed in 3.2.P.3.1, including LNP manufacturing. Moreover, GMP certificate or a statement of GMP compliance issued by the Supervisory authority of BioNTech Manufacturing GmbH, Mainz, Germany should cover batch certification of the DP.

Response for Pfizer Puurs

- Section 3.2.P.3.3 describes all formulation activities starting from Drug Substance Thaw until the addition of cryoprotectant. All those activities are considered as part of formulation and filling processes and are licensed Manufacturing Operations for Biotechnology Products in MIA 277H.
- Pfizer Puurs confirms that a license has been obtained for all manufacturing activities as described in 3.2.P.3.1.

Response for BioNTech Mainz

- GMP certificate received yesterday and will be provided in MAA

Major Objection #2 (Comparability)

2. Comparability between clinical and commercial material has not yet been demonstrated, which raises uncertainties about consistency of product quality and hence uncertainties as regards product safety and efficacy of the commercial product. Significant differences between batches manufactured by DS Process 1 and 2 are observed for the CQA mRNA integrity. In addition, the characterisation of BNT162b2 DS is currently not found acceptable in relation to this quality attribute. This is especially important considering that the current DS and DP acceptance criteria allows for up to 50% fragmented species. Therefore, the dossier should be updated with additional characterisation data on mRNA integrity in sections 3.2.S.2.6 (comparability) and 3.2.S.3 of the dossier.

Response:
A comprehensive drug substance comparability study was performed and summarized in roll #2 of the MAA, which includes updated data in 3.2.S.2.6. In addition, we are revising the RNA integrity specification for drug substance to >=60%, drug product release to >=55%, and drug product shelf life to >=50%. The sponsor agrees to update the 3.2.S.3 section with additional characterization data concurrent with the establishment of primary/working reference material.

Major Objection #2 (Comparability)

- a.) Truncated and modified RNA species should be regarded as product-related impurities. Even though two methods, namely agarose gel electrophoresis and capillary gel electrophoresis (CGE), have been applied to determine RNA integrity of BNT162b2 DS, no characterisation data on truncated forms is presented. Results obtained on RNA integrity by CGE and agarose gels should be included in the characterisation section (3.2.S.3). The truncated forms should be sufficiently characterised, i.e. they should be described, and it should be discussed if the fragmented species are expected to be similar between batches. In addition, the possibility of translated proteins other than the intended spike protein (S1S2), resulting from truncated and/or modified mRNA species should be addressed and relevant protein characterization data for predominant species should be provided, if available.

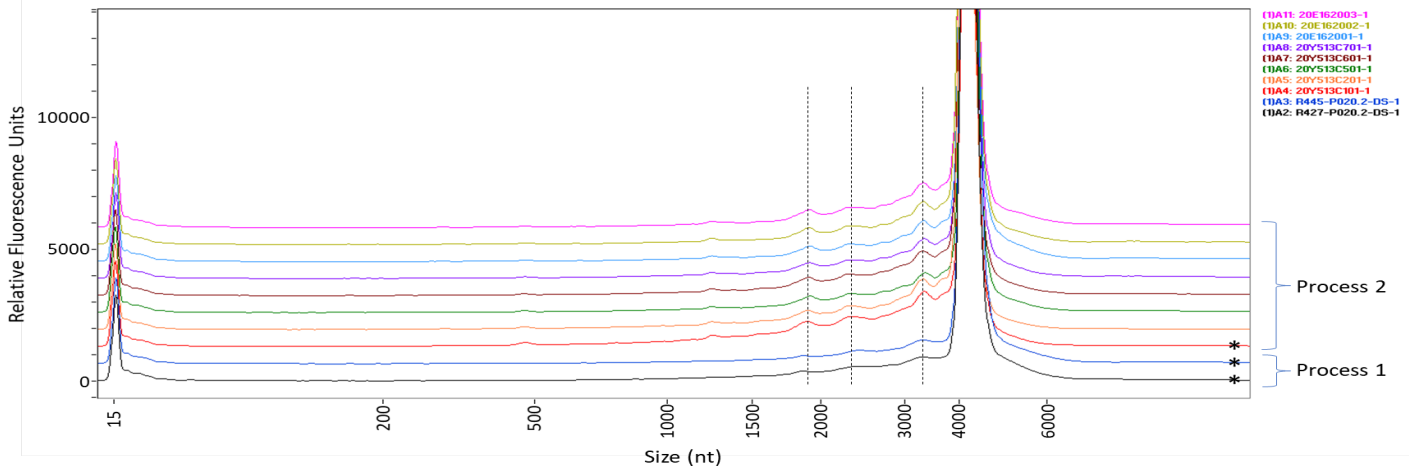
Response:

- Fragments have been observed in all toxicology, clinical, and representative commercial supply drug substance from Process 1 and Process 2
  - Expected product impurity from incomplete in vitro transcription and are confirmed to be RNA
  - Most abundant fragment species are 1500-3500 nucleotides in length
  - Extensive oligonucleotide mapping data are provided in the revised 3.2.S.2.6 comparability – no significant differences observed
- Fragmented species observed by CGE are expected to be comprised of truncated transcripts that include the 5’ region of BNT162b2 but lack the 3’ region and poly(A) tail

1. Major Objection #2 (Comparability)

- b.) Upon changing to DS Process 2, a decrease in RNA integrity was observed (only numerical values provided). Concerning this difference in RNA integrity between Process 1 and Process 2 DS batches the Applicant is requested to provide capillary electropherograms together with an evaluation of any batch differences in peak patterns. The potential safety risks associated with truncated RNA isoforms should be thoroughly discussed with reference to the batches used, clinical experience and possibly literature data. The quantitative and qualitative differences observed between Process 1 and 2 should be discussed with respect to their impact on safety and efficacy.

Response: The electropherograms comparing process 1 and process 2 drug substance batches, inclusive of clinical, emergency supply and PPQ batches, are provided. The major fragments are common between both processes. Truncated transcripts are not expected to impact safety and as they would be degraded or not translated.



1. Major Objection #2 (Comparability)

2. Comparability (continued)
   c.) For Process 2, the CTP and ATP volumes were adjusted before the manufacture of DS batch PPQ3 to align better with RNA integrity results from Process 1. Additional batch data (from PPQ4 and PPQ5) should be provided to confirm that the optimised Process 2 allows for reaching RNA integrity levels consistent with the Process 1 batches.

Applicant's Reply Strategy

- PPQ4 and PPQ5 data will be included in the 2nd CMC Roll
- 3.2.S.2.6 summary table is provided in the back-up for clinical, emergency use, and PPQ batches from Pfizer and BioNTech

BNT162b2 Drug Substance Release and Additional Testing Result Ranges				
Method	**Clinical (Process 1)**	**Emergency Supply (Process 2)**	**ACMF PPQ (Process 2)**	**BNT-REN PPQ (Process 2)**
	R427-P020.2-DS R438-P020.2-DS R443-P020.2-DS R445-P020.2-DS	20Y513C101 20Y513C201	20Y513C301 20Y513C401 20Y513C501 20Y513C601 20Y513C701	20E162001 20E162002 20E162003
RNA Integrity by capillary gel electrophoresis (%)	77 – 86	62 – 69	65 – 75	70 – 72
5'-Cap by LC-UV (%)	56 – 69	82 – 84	84 – 88	89 – 91

1. Major Objection #2 (Comparability)

2. Comparability (continued)
   d.) After contact with the applicant it was confirmed that DP batches manufactured from early Process 2 batches, with lower RNA integrity, have been recently introduced in clinical trials. However, as the cut-off date for the clinical Interim Analysis (IA) was changed, the IA doesn't include data from subjects dosed with Process 2 material, and the Company does not expect to have Process 2 included in the Final Analysis dataset. Therefore, the proposed acceptance criteria of ≥50% intact RNA for RNA integrity is considered too wide compared to clinical batch data, 69-81%. The proposed release and shelf-life acceptance criteria for the DP should therefore be tightened based on the clinical data included in the dossier or clinically qualified by other means.

Applicant's Reply Strategy

- Proposed specifications are now DS release/shelf life >=60%, DP release >=55%, DP shelf life >=50%
- Capped-intact is comparable for Process 2 DS, therefore even the slightly lower integrity not expected to affect efficacy, comparable IVE results are supportive of this as well. Additional adjustments to improve DS integrity have been implemented.
- Clinical drug product batch range from 62-86% integrity; mean - 3SD has lower limit of 47%
- Specifications will continue to be assessed following drug product PPQ

1. Major Objection #2 (Comparability)

2. Comparability (continued)
   e.) Release data provided for some of the DP batches indicates a possible decrease in mRNA integrity during the manufacturing of DP. The applicant should therefore discuss possible root causes, and present comparative results for DS and DP, on RNA integrity. A consequential need for a more stringent DS specification should be considered. Sections S.4.1 and P.5.1 in the dossier should be aligned and updated accordingly.

Response: The sponsor acknowledges a consistent drop in RNA integrity between final DS release and final DP release. Comparative results for DS and DP are provided. We have implemented a more stringent DS specification (>= 60% for release/shelf life)

DP Lot	Ingoing DS Batch	RNA Integrity (%)		Integrity Difference (%) (DP-DS)
		Drug Product	Drug Substance	
EE8492	20Y513C101	55	62	-7
EE8493	20Y513C101	55	62	-7
EJ0553	20Y513C501	68	75	-7
EJ1685	20E162001 (1071539)	66	72	-6
EJ1686	20E162001 (1071539)	69	72	-3
EK1768	20Y513C401	60	65	-5

1. Major Objection #3 (Process validation)

3. Drug product batches manufactured at the commercial facility (whole manufacturing process at the commercial site Pfizer, Puurs, at commercial scale, drug substance from process 2) were not presented. Process validation (PPQ) for commercial scale batches are already initiated and validation data should be provided. Batch results for at least 2 commercial scale batches representative of the commercial process should be presented. Comparability of commercial batches with clinical batches should be demonstrated and the data should be provided. The claimed shelf-life and storage condition are not yet acceptable since no stability data is available for batches from the commercial manufacturing site and scale and shelf-life is based on very small scale (development) batches (less than 1% of the commercial scale), not representative of the commercial batches (manufacturing site, scale, process for the drug substance). Additional stability data (6 months at long-term storage condition) should be presented.

Response:

- Batch results of at least 2 GMP batches will be submitted around the 2nd CMC Roll (precise date pending)
- Phased approach for process validation (see Agenda Topic 4)
  - Phase I, initial validation (5 PPQ lots at 5 sites including Pfizer Puurs): scheduled this week
  - Phase II, full validation (7 PPQ lots in total at Pfizer Puurs): to commence in Week 51
- Stability and shelf-life:
  - Details presented on next slide

1. Major Objection #3 (Process validation) continued

- Stability and shelf-life:
  - Stability studies have been initiated/are in progress for six additional EUA lots of DP and include storage at the intended storage condition of -90 to -60℃. These studies are representative of the commercial process/scale and information on stability protocols and data available are being provided in MAA roll #2. Additionally, MAA Roll #2 contains the draft, planned PPQ stability protocols, as well as new data available for BNT clinical lots.

  - A summary of the stability data available in MAA roll #2 is summarized below:
    - Updated stability data for 6 months at intended storage on clinical lot BCV40420-A and non-clinical lot CoVVAC/270320 support the current claimed shelf life
    - Up to 2 weeks stability data on EUA lot EE8492
    - Stability protocols and release data, where available, for EUA lots EK1768, EJ1686, EJ1685, EJ0553 and EE8493 (information on EE8493 was provided in MAA roll #1)
    - Inclusion of protocols and up to 3 months stability data for additional BNT clinical lots, including lots EE3813 (alias BCV40820-P) and ED3938 (alias BCV40720-P) which were manufactured on a scale more representative of the commercial process

2. Quality items in revised submission plan (25th November)

26th November

- Company's Responses to FDA's questions for the US EUA submitted.

30th November

- Submission of relevant quality data for EU supply chain as 'pre-read' for quality assessors:
  - 'Global EUA' dossier contains to a remarkable extent CMC data, which are not relevant for EU supply chain
  - Change in plans: Submission of a selection of M3 sections which contain either most important changes/updates or comprehensive update. A copy of sections will be taken from the ongoing process of data verification. As data verification process is not fully completed the sections are formally considered as draft although changes are very unlikely.
  - Examples: S.2 / S.4 / S.5 for New Drug Substance Site BioNTech/Rentschler, P.2 Drug Product, P.2.6 Compatibility, P.3.2 Batch Formula, P.3.3 Manufacturing Process, P.5.1 Drug Production Specification and Stability updates for DS and DP

4th December

- Submission of 2nd CMC roll package formally as part of VSI responses via eCTD: Module 3 and Module 2 abbreviated QoS.
- Abbreviated QoS includes a summary of pending information and confirmation that Quality is acceptable
- The Quality expert signature was already submitted in sequence 0002.

3. Updated specifications for drug product

Quality Attribute	**Analytical Procedure**	**Acceptance Criteria (1st CMC Roll)**	**Acceptance Criteria (2nd CMC Roll)**
Appearance (Visible Particulates)	Appearance (Particles)	Essentially free from visible particulates	May contain white to off-white opaque, amorphous particles
RNA Integrity	Capillary Gel Electrophoresis	≥ 50% intact RNA	≥ 55% intact RNA (release) ≥ 50% intact RNA (stability)

- Visible particles contain lipids and are thus intrinsic to the product
- RNA integrity:
  - ≥ 55% at release with an allowance of 5% decrease across stability
  - Late migrating species (LMS) shown to be intact RNA

- Data and discussion presented in briefing materials
  - Draft Section 3.2.P.2.2 Drug Product
  - Reply to US EUA Questions

4. Updated validation strategy for drug product

Phased approach to ensure having preliminary PV data available from individual supply nodes as soon as possible for conditional EU MAA, US EUA, and other applications

Phase I:

- Manufacturing of one batch from each global supply node
- Five PPQ lots scheduled this week at five DP manufacturing sites:
  - Node #1: EU supply (FC2 filling line, Pfizer Manufacturing Belgium NV, Puurs)
  - Nodes #4 & #5: Comparable to EU supply (Pfizer Kalamazoo, USA, filling lines 8 and 18)
  - Node #2 & #3: Supportive data (Pulymun / Pfizer Puurs and Dermapharm / Pfizer Puurs)
- Comparability assessment scheduled for all PPQ lots

Phase II:

- Global validation approach which includes EU supply
- Pfizer Manufacturing Belgium, Puurs:
  - Scheduled for Week 51/2020 – Week 02/2021
  - Additional six PPQ lots to give a total of seven PPQ lots for Pfizer Puurs
  - Matrix approach to address different DS supply sites (Andover *vs* BioNTech/Rentschler), different fill lines (FC2 *vs* VC2) and different scales (139 L *vs* 278 L)
- Comparability assessment scheduled for all PPQ lots

5. Additional filling line and increased batch size for drug product

Changes in 2nd CMC Roll for assuring sufficient EU supplies
prior to submission of variations to add further DP manufacturing sites

Additional filling line (Pfizer Manufacturing Belgium NV, Puurs)

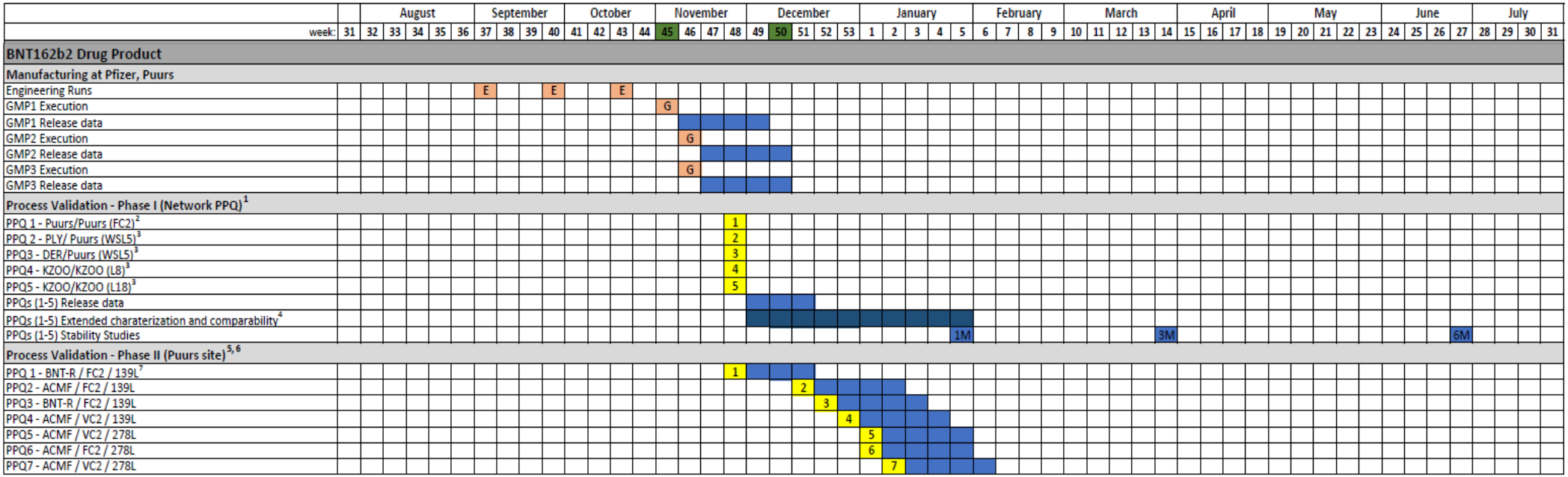
- An additional filling line (VC2) is introduced for BNT162b2 drug product and descripted is described in the respective sections in the MAA.
- Validation of the VC2 filling line is planned in Phase II of process validation

Batch size increase for DP process (Pfizer Manufacturing Belgium NV, Puurs)

- Two TFF unit operations in parallel during the DP process (Step 5 in Section 3.2.P.3.3) to increase batch size
- Batch size in Section 3.2.P.3.2 changed from 139 L to 139 L - 278 L range
- Change supported by:
  - one completed engineering lot
  - a first GMP lot scheduled to be completed this week.
- Validation of the 139 L - 278 L range is planned in Phase II of process validation

Backup

Revised manufacturing plan – DP PPQ lots



[1] Bulk DP manufacturer / F&F manufactured (Fill line)

[2] Only fill line FC2 will be used in this Phase I and VC2 fill line will be used in the Phase II PPQ

[3] Potential post-approval sites shown now as supportive data

[4] Comparability between Network PPQs, CTM, EUA and GMP

[5] DS manufacturer / F&F Fill line / Batch size

[6] Timelines shown are tentative, following the best case scenario

[7] First batch from the Phase I Netwrok PPQ (PPQ1)

E	Engineering batch	Activities executed
G	GMP batch	Activities scheduled
PLY	Polymun	Submission dates for roll 1 & 2
DER	Dermapharm	
KZOO	Kalamazoo	
BNT-R	BioNTech, Mainz incl. Rentschler, Laupheim	
ACMF	Pfizer, Andover	

1	PPQ No. 1
2	PPQ No. 2
3	PPQ No. 3
4	PPQ No. 4
5	PPQ No. 5
6	PPQ No. 6
7	PPQ No. 7

1w	Result from sample after 1 week storage
2w	Result from sample after 2 week storage
1M	Result from sample after 1 month storage
3M	Result from sample after 3 month storage
6M	Result from sample after 6 month storage

MAA Draft – Roll 2, 3.2.S.2.6

Table 3.2.S.2.6-6. BNT162b2 Drug Substance Release and Additional Testing Result Ranges

Method	Clinical (Process 1)	Emergency Supply (Process 2)	ACMF Process Performance Qualification (Process 2)	BNT-REN Process Performance Qualification (Process 2)
	R427-P020.2-DS R438-P020.2-DS R443-P020.2-DS R445-P020.2-DS	20Y513C101 20Y513C201	20Y513C301 20Y513C401 20Y513C501 20Y513C601 20Y513C701	20E162001 20E162002 20E162003
Appearance (Clarity)	Clear (≤ 3 NTU)	Clear (0 – 1 NTU)	Clear (0 – 1 NTU)	Clear (0 NTU)
Appearance (Coloration)	Colorless	Colorless (≤ B9)	Colorless (≤ B9)	Colorless
pH	7.0 – 7.2	6.9	6.9	6.9
Identity of encoded RNA sequence by RT-PCR	Complies[a]	Identity confirmed	Identity confirmed	Identity confirmed
Content (RNA concentration) by UV spectrometry (mg/mL)	1.64 – 2.26[b]	2.19 – 2.27	2.19 – 2.27	2.18 – 2.20
RNA Integrity by capillary gel electrophoresis (%)	77 – 86[c]	62 – 69	65 – 75	70 – 72
5'-Cap by LC-UV (%)[d]	56 – 69	82 – 84	84 – 88	89 – 91
Poly(A) Tail by ddPCR (%)[d]	116 – 131	88 – 104	91 – 106	85 – 106
Residual DNA Template by qPCR (ng/mg RNA)	< 200	17 – 29	10 – 211	11 – 34 pending review
dsRNA by immunoblot (pg/µg RNA)	< 120	≤ 240	≤ 240	< 40
Osmolality	52 – 143	18	17	17

a. Identity of Process 1 batches determined from the starting material (DNA template) by sequencing
b. Acceptance criterion for Content (RNA concentration) changed from 1.7 mg/mL ± 10% to 2.25 ± 10% during clinical development.
c. Value is result of a revised integration of electropherograms, consistent with the integration used for Process 2 batches. Side-by-side test results shown in Table 3.2.S.2.6-7 and Table 3.2.S.2.6-13.
d. Process 1 data taken from side-by-side assessment (Table 3.2.S.2.6-7 and Table 3.2.S.2.6-13). 5'-Cap and Poly(A) tail data were collected for Process 2 batches as an additional characterization test.

Abbreviations: ddPCR = Droplet digital polymerase chain reaction; dsRNA = Double stranded RNA; NT = Not Tested; NTU = Nephelometric turbidity unit; qPCR = Quantitative PCR; RP-HPLC = Reversed phase high performance liquid chromatography; RT-PCR = Reverse transcription PCR

Truncated transcripts

It·is·not·anticipated·that·truncated·transcripts·pose·a·safety·or·efficacy·concern.··As·the·poly(A)·tail·contributes·substantially·to·mRNA·stability·(Guhaniyogi·&·Brewer,·2001;·Nicholson·&·Pasquinelli,·2019),·truncated·BNT162b2·RNA·species·lacking·poly(A)·tails·are·expected·to·be·rapidly·targeted·for·degradation·in·the·cytoplasm.·¶

In·the·event·that·transcripts·are·truncated·at·the·5‘·end,·the·loss·of·the·5‘-cap·would·not·only·increase·5‘·degradation·of·the·unprotected·mRNA,·but·would·also·result·in·a·decrease·or·loss·of·translation·efficiency·owing·to·the·role·of·the·5‘-cap·in·recruiting·translation·intiation·factors·(Ramanathan,·Robb,·and·Chan,·2016).·¶

Statistical analysis of data sets for integrity specification

Statistical analysis of data sets for integrity specification:
Data set:
Bolded lots used in clinic to date.
Statistical analysis:

DP Lot	%Integrity
BCV40420-A	75
BCV40620-A	85
BCV40620-B	86
BCV40620-C	83
BCV40620-D	77
BCV40620-E	85
BCV40720-A	71
BCV40720-B	72
BCV40720-C	69
BCV40720-P (ED3938)	62
BCV40820-P (EE8318)	63
EE8492	55
EE8493	55
EJ0553	68
EJ1685	66
EJ1686	69
EK1768	60

Lots included	Mean	Std Dev	Mean – 3SD
All	70.6	10.1	40.3
Clinical only (all bolded)	72.5	10.4	41.3
Clinical without EE8493	74.3	9.0	47.3

DS release and additional testing ranges

BNT162b2 Drug Substance Release and Additional Testing Result Ranges				
Method	Clinical (Process 1)	Emergency Supply (Process 2)	ACMF Process Performance Qualification (Process 2)	BNT-REN Process Performance Qualification (Process 2)
	R427-P020.2-DS R438-P020.2-DS R443-P020.2-DS R445-P020.2-DS	20Y513C101 20Y513C201	20Y513C301 20Y513C401 20Y513C501 20Y513C601 20Y513C701	20E162001 20E162002 20E162003
RNA Integrity by capillary gel electrophoresis (%)	77 – 86	62 – 69	65 – 75	70 – 72
5'-Cap by LC-UV (%)[d]	56 – 69	82 – 84	84 – 88	89 – 91

Exhibit 170

My Affidavit on Different Formulations in Pfizer Vaccine Lots
Sasha Latypova
https://www.trialsitenews.com/a/my-affidavit-on-different-formulations-in-pfizer-vaccine-lots-1b9e4ee9 - _ftnref1

COVID-19 Vaccine EMA/Rapporteur CMC Meeting 11/26/20
https://prd-tsn-main-api.s3.amazonaws.com/article/13d1ad53-0c0d-4163-941f-81c50f00f8c6.pdf

The EMA covid-19 data leak and what it tells us about mRNA instability
https://www.bmj.com/content/bmj/372/bmj.n627.full.pdf

Bern, Switzerland
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INVESTIGATION

The EMA covid-19 data leak, and what it tells us about mRNA instability

Leaked documents show that some early commercial batches of Pfizer-BioNTech's covid-19 vaccine had lower than expected levels of intact mRNA, prompting wider questions about how to assess this novel vaccine platform, writes Serena Tinari

Serena Tinari *journalist*

As it conducted its analysis of the Pfizer-BioNTech covid-19 vaccine in December, the European Medicines Agency (EMA) was the victim of a cyberattack.[1] More than 40 megabytes of classified information from the agency's review were published on the dark web, and several journalists—including from *The BMJ*—and academics worldwide were sent copies of the leaks. They came from anonymous email accounts and most efforts to interact with the senders were unsuccessful. None of the senders revealed their identity, and the EMA says it is pursuing a criminal investigation.

The BMJ has reviewed the documents, which show that regulators had major concerns over unexpectedly low quantities of intact mRNA in batches of the vaccine developed for commercial production.

EMA scientists tasked with ensuring manufacturing quality—the chemistry, manufacturing, and control aspects of Pfizer's submission to the EMA—worried about "truncated and modified mRNA species present in the finished product." Among the many files leaked to *The BMJ*, an email dated 23 November by a high ranking EMA official outlined a raft of issues. In short, commercial manufacturing was not producing vaccines to the specifications expected, and regulators were unsure of the implications. EMA responded by filing two "major objections" with Pfizer, along with a host of other questions it wanted addressed.

The email identified "a significant difference in % RNA integrity/truncated species" between the clinical batches and proposed commercial batches—from around 78% to 55%. The root cause was unknown and the impact of this loss of RNA integrity on safety and efficacy of the vaccine was "yet to be defined," the email said.

Ultimately, on 21 December, EMA authorised Pfizer-BioNTech's vaccine. The agency's public assessment report, a technical document published on its website, noted, "the quality of this medicinal product, submitted in the emergency context of the current (covid-19) pandemic, is considered to be sufficiently consistent and acceptable."[2]

It's unclear how the agency's concerns were satisfied. According to one of the leaked emails dated 25 November, positive news had come from an undisclosed source in the US: "The latest lots indicate that % intact RNA are back at around 70-75%, which leaves us cautiously optimistic that additional data could address the issue," the email said.

A near miss?

It's also unclear whether the events in November constitute a near miss in the commercial manufacturing of mRNA vaccines.

EMA says the leaked information was partially doctored, explaining in a statement that "whilst individual emails are authentic, data from different users were selected and aggregated, screenshots from multiple folders and mailboxes have been created, and additional titles were added by the perpetrators."[3]

But the documents offer the broader medical community a chance to reflect on the complexities of quality assurance for novel mRNA vaccines, which include everything from the quantification and integrity of mRNA and carrier lipids to measuring the distribution of particle sizes and encapsulation efficiency. Of particular concern is RNA instability, one of the most important variables relevant to all mRNA vaccines that has thus far received scant attention in the clinical community. It is an issue relevant not just to Pfizer-BioNTech's vaccine but also to those produced by Moderna, CureVac, and others,[4] as well as a "second generation" mRNA vaccine being pursued by Imperial College London.[5]

RNA instability is one of the biggest hurdles for researchers developing nucleic acid based vaccines. It is the primary reason for the technology's stringent cold chain requirements and has been addressed by encapsulating the mRNA in lipid nanoparticles (box).

"The complete, intact mRNA molecule is essential to its potency as a vaccine," professor of biopharmaceutics Daan J.A. Crommelin and colleagues wrote in a review article in *The Journal of Pharmaceutical Sciences* late last year. "Even a minor degradation reaction, anywhere along a mRNA strand, can severely slow or stop proper translation performance of that strand and thus result in the incomplete expression of the target antigen."[6]

Crommelin and colleagues note that specific regulatory guidance for mRNA based vaccines has yet to be developed, and *The BMJ*'s attempts to clarify current standards were unsuccessful.

Transparency and confidentiality

The BMJ asked Pfizer, Moderna, and CureVac, as well as several regulators, what percentage mRNA integrity they consider acceptable for vaccines against covid-19. None offered any specifics.

The Medicines and Healthcare products Regulatory Agency, the UK's medicines regulator, acknowledged the lack of a specified percentage RNA integrity, but declined to provide further detail. "The specification limit acceptance criteria are commercially confidential," the agency said in an email.

The US Food and Drug Administration (FDA) directed *The BMJ* to read its guidance documents[7 8] and its review of Pfizer's vaccine,[9] but none of these specify the percentage RNA the agency is requiring. Asked to comment, the regulator pointed to Pfizer: "information that you seek that is not addressed in the FDA Review Memorandum should be directed to Pfizer."

In subsequent correspondence, FDA, EMA, and Canadian government department Health Canada all stated that specific information related to the acceptability criteria is confidential.

EMA did acknowledge, however, that vaccine efficacy depends on the presence of suitable amounts of intact mRNA. In the case of the commercial batches that first raised alarm bells, the agency told *The BMJ* that the levels of truncated mRNA "and the amounts of a potential protein produced by the truncated mRNA would be too low to constitute a safety risk." EMA did not comment on how truncated mRNA might affect efficacy. The issue was satisfactorily addressed, the agency underlined, when further information was supplied by the manufacturer.

Health Canada told *The BMJ* that Pfizer had conducted investigations into the root cause of reduced integrity in the commercial vaccine batches, and "changes were made in their processes to ensure that the integrity was improved and brought in line with what was seen for clinical trial batches." Health Canada said the three agencies subsequently determined that "there was no concern with the RNA integrity or any other product specifications."

Correspondence in the leaked documents suggests that FDA, Health Canada, and EMA were aligned on clinically qualified specifications of percentage mRNA integrity. Health Canada has confirmed to *The BMJ* that regulators "have worked together to align those requirements," but all agencies declined to share with *The BMJ* any specifics on grounds that such information was commercially sensitive.

Pfizer also declined to comment on what percentage mRNA integrity it is aiming for, nor would it address questions about the cause of the unexpectedly low percentage mRNA integrity in certain batches, leaving open the question of whether it could happen again. Pfizer stressed: "Each batch of vaccines is tested by the official medicinal control laboratory—the Paul Ehrlich Institute in Germany—before final product release. As a result, the quality of all vaccine doses that are placed on the market in Europe has been double tested to ensure compliance with the specifications agreed upon with the regulatory authorities."

Moderna's chief corporate affairs officer Ray Jordan declined to respond to any of *The BMJ*'s questions, stating: "At this point, Moderna will not be offering additional commentary on these topics."

CureVac, whose mRNA vaccine was submitted for EMA's "rolling review" in February,[10] told *The BMJ* that "it is too soon to give details."

The shortage of information may reflect the lack of certainty, even among regulators, about how to assess the evidence fully for this novel technology. Professor Crommelin told *The BMJ* that, "For small, low molecular weight products, the active pharmaceutical ingredient integrity is typically close to 100%."

But for mRNA vaccines? "Experience with mRNA integrity is limited."

Lipid nanoparticles—where do they go and what do they do?

Conceived three decades ago, RNA based therapeutics[11] have long inspired imaginations for their theoretical potential to transform cells of the body into "an on-demand drug factory."[12] But despite heavy investment by the biotech industry, bench-to-bedside translation was constantly hindered by the fragility of mRNA.

Over the years, researchers attempted to resolve intrinsic instability by encapsulating mRNA in nanocarriers made of polymers, lipids, or inorganic materials. Lipid nanoparticles (LNPs) were chosen by Moderna, Pfizer-BioNTech, CureVac, and Imperial College London for their covid-19 vaccines. This has attracted the attention of specialists in the field of pharmaceutical biotechnology, some of whom have raised concerns about further unknowns.

In a rapid response posted on bmj.com, JW Ulm, a gene therapy specialist who has published on tissue targeting of therapeutic vectors,[13] raised concerns about the biodistribution of LNPs: "At present, relatively little has been reported on the tissue localisation of the LNPs used to encase the SARS-CoV-2 spike protein-encoding messenger RNA, and it is vital to have more specific information on precisely where the liposomal nanoparticles are going after injection."[14]

It is an unknown that Ulm worries could have implications for vaccine safety.

Ulm told *The BMJ*: "Pfizer-BioNTech and Moderna did a remarkable job of rapidly scaling up manufacturing of such a novel system in swift fashion, which is genuinely a landmark technological achievement. However, pharmacokinetic studies, with independent laboratory confirmation, are essential to ascertain potential cytotoxicity and macroscopic toxicity, especially given the likelihood of booster injections over months or years, since the tissue trafficking patterns of the mRNA vaccine payload will determine which cells and tissues are killed by cytotoxic T-cells in each round." Given the variation in LNP formulations, it is unclear how relevant previous animal experiments are to answering this question.

Regulators and manufacturers contacted by *The BMJ* for this article did not wish to address any of the questions raised by Ulm's rapid response.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: commissioned; externally peer reviewed

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