What the Leaked EMA Emails & Docs Reveal: Major Concerns with Pfizer C-19 Vaccine Batch Integrity and The Race to Authorize

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Opinion Article

Trial Site News recently were able to review leaked internal emails from the European Medicines Agency (EMA) and meeting report between the agency and Pfizer. The EMA oversees the evaluation and supervision of medicinal products for the European Union. Like other regulatory health bodies, its main responsibility is to protect and promote public health. Snapshots of internal EMA email correspondence; a November 26, 2020, PowerPoint presentation from a pivotal meeting between Pfizer and the agency, as well as a confidential 43-page Pfizer report were provided by an anonymous source because of their trust in *Trial Site's* commitment to transparency, accessibility, and accountability in furtherance of a highly ethical, quality-focused and public health-centric biomedical research industry.

Regulatory agencies, like the EMA, the Food and Drug Administration (FDA) in the U.S. and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) are chartered to make decisions based to better the public. External influences such as political or media pressure are not meant to be a driving factor in their decision-making, however, when it came to pandemic conditions and the fast-tracked conditional marketing authorization of the Covid-19 vaccines (particularly for the mRNA-based vaccines produced by Pfizer-BioNTech and Moderna), it appears the latter won the day.

The time period of the email correspondence in question stretches from November 10 – 25, 2020, just weeks before the EMA granted CMA (conditional marketing authorization) for the Pfizer-BioNTech Covdid-19 vaccine on December 21, 2020. The FDA granted EUA (emergency use authorization) for this vaccine on December 11 with the MHRA making it first to the finish line on December 2. Here this author uses the term 'finish line,' as the emails do reveal an intense, almost competitive-like rush to authorize the Covid-19 vaccines, as quickly as possible. Understandably, the world was gripped by a pandemic at the time, where there was immense impetus to authorize a vaccine to protect people from the novel coronavirus.

The Rush into EUA

In an email from Marco Cavaleri, at the time the EMA's Head of Biological Health Threats and Vaccines Strategy, communicated with urgency how the U.S. FDA "are going to rush into EUA."


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Cavaleri Marco

Mon 11/16/2020 12:34 PM

Inbox

FDA has a call with MHRA in 3 hours to discuss Biontech CMC aspects. They are going to rush into EUA. FDA still unclear and not so easy for them to be faster than Xmas, but pushed hard by Azar and US GOV

Marco

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Cavaleri refers to this '*rush*' being '*pushed hard by Azar and US GOV.*' Under the Trump administration, Alex Azar, former pharmaceutical executive was the United States Secretary of Health and Human Services (HHS) from 2018-2021. The FDA is an agency that falls directly under the HHS.

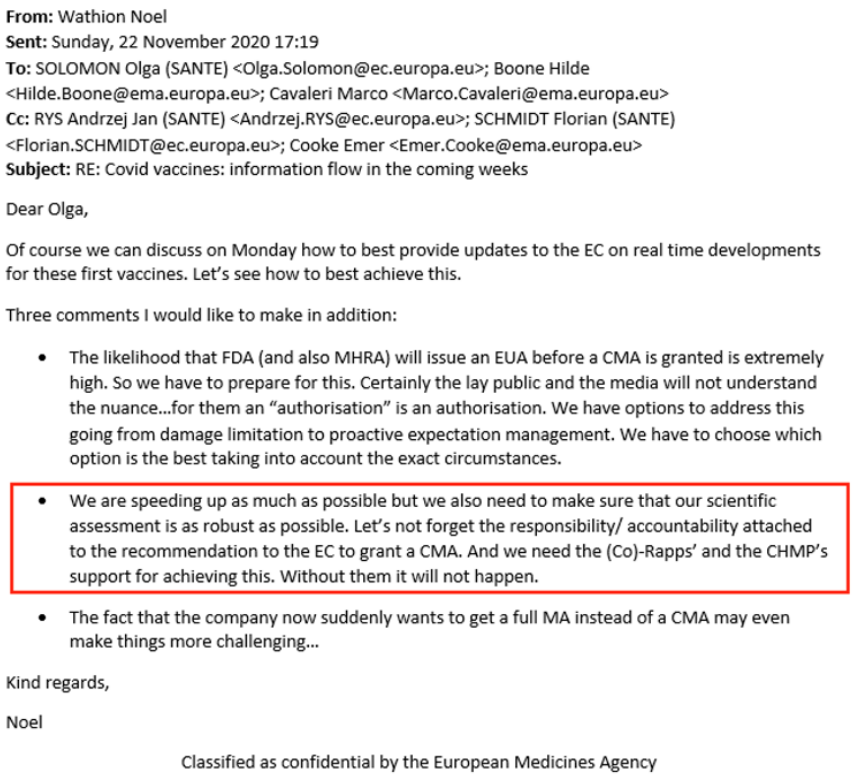
It's worth noting that when Azar was former president of Lilly USA LLC, a division of Eli Lilly, drug prices skyrocketed under his leadership. The pharmaceutical company was also embroiled in a class-action lawsuit under his tenure where it was accused of exploiting the drug pricing system to increase profits for its insulin drug. Of course, this doesn't necessarily mean this executive was complicit in any way, but the timing is noteworthy.

Cavaleri's email speaks to the extent of how politics (and the US government) was driving the FDA's regulatory process, making sure it was going at 'warp speed'. And of course, on that note Trump's Operation Warp Speed was to ensure all vaccine development records would be shattered. The intentions were undoubtedly good given the outbreak of the worst pandemic in a century.

However, across the Atlantic in Europe's regulatory agency tension mounted as the pressure to accelerate deadlines made the air and general mood tense—the

pressure and anxiety was palpable in the reviewed email exchanges.

Persons of high integrity and clarity as to their roles and commitments as stewards of public health emerged. For example, one individual demonstrated palpable concern over accelerated timelines to ensure they would meet the 'deadline' for vaccine authorization at the expense of a robust assessment. He was Noel Wathion, at the time the EMA's deputy executive director, but who has since retired. This EMA official importantly pointed out, *'We are speeding up as much as possible, but we also need to make sure that our scientific assessment is as robust as possible. Let's not forget the responsibility/accountability attached to the recommendation to the EC to grant a CMA.'*



From: Wathion Noel
Sent: Sunday, 22 November 2020 17:19
To: SOLOMON Olga (SANTE) <Olga.Solomon@ec.europa.eu>; Boone Hilde <Hilde.Boone@ema.europa.eu>; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>
Cc: RYS Andrzej Jan (SANTE) <Andrzej.RYS@ec.europa.eu>; SCHMIDT Florian (SANTE) <Florian.SCHMIDT@ec.europa.eu>; Cooke Emer <Emer.Cooke@ema.europa.eu>
Subject: RE: Covid vaccines: information flow in the coming weeks

Dear Olga,

Of course we can discuss on Monday how to best provide updates to the EC on real time developments for these first vaccines. Let's see how to best achieve this.

Three comments I would like to make in addition:

- The likelihood that FDA (and also MHRA) will issue an EUA before a CMA is granted is extremely high. So we have to prepare for this. Certainly the lay public and the media will not understand the nuance...for them an "authorisation" is an authorisation. We have options to address this going from damage limitation to proactive expectation management. We have to choose which option is the best taking into account the exact circumstances.
- We are speeding up as much as possible but we also need to make sure that our scientific assessment is as robust as possible. Let's not forget the responsibility/ accountability attached to the recommendation to the EC to grant a CMA. And we need the (Co)-Rapps' and the CHMP's support for achieving this. Without them it will not happen.
- The fact that the company now suddenly wants to get a full MA instead of a CMA may even make things more challenging...

Kind regards,

Noel

Classified as confidential by the European Medicines Agency

Wathion assumes the FDA (and the MHRA's) EUA would be issued before the EMA granted its own CMA, which turned out to be correct. What's interesting is his concern

to address the '*damage limitation*' resulting from the probable outcome of the EMA finishing last in this regulatory race and his fear that this would result in public opinion and the media turning against the agency.

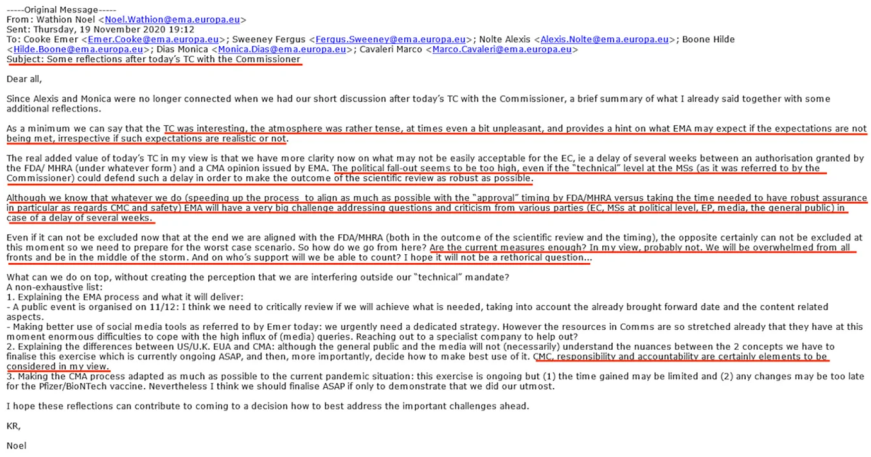
Speed seemingly superseded concerns of quality based on a careful review of these emails.

In a November 19 email, Wathion reveals a '*rather tense*' TC (teleconference call) with the European Commissioner (Ursula von der Leyen) which was '*at times even a bit unpleasant.*' This reflects the mounting pressure which the EMA staff were under to issue CMA quickly following an EUA granted by the FDA/MHRA for the Pfizer-BioNTech vaccine. Von der Leyen is implicated in potentially being responsible for this tense environment with '*a delay of several weeks...not easily acceptable for the EC [European Commission]*'.

In early 2022, Trial Sites News reported how von der Leyen was embroiled in scandal when a group of independent MEPs demanded her immediate resignation and full disclosure of a series of private text messages between her and Pfizer's CEO, Albert Bourla. Only a small portion of these texts were ever disclosed. Of the ones that were, they revealed her negotiating portions of a European-wide vaccine deal, unilaterally with Bourla via a series of texts! Clearly standard protocols in Europe were thrown out the window in favor of expediency and this seemingly was tied to a unified competitive pressure on all three regulatory agencies.

Wathion lays bare his reflections after this particular TC, and shockingly writes how '*the political fall-out seems to*

be too high even if the "technical" level at the MSs [Member States] could defend such a delay in order to make the outcome of the scientific review as robust as possible'. Put another way the continuous broadcast of science first appeared as a cover for politics first.



-----Original Message-----
From: Wathion Noel <Noel.Wathion@ema.europa.eu>
Sent: Thursday, 19 November 2020 19:12
To: Cooke Emer <Emer.Cooke@ema.europa.eu>; Sweeney Fergus <Fergus.Sweeney@ema.europa.eu>; Nolte Alexis <Alexis.Nolte@ema.europa.eu>; Boone Hilde <Hilde.Boone@ema.europa.eu>; Dias Monica <Monica.Dias@ema.europa.eu>; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>
Subject: Some reflections after today's TC with the Commissioner

Dear all,

Since Alexis and Monica were no longer connected when we had our short discussion after today's TC with the Commissioner, a brief summary of what I already said together with some additional reflections.

As a minimum we can say that the TC was interesting, the atmosphere was rather tense, at times even a bit unpleasant, and provides a hint on what EMA may expect if the expectations are not being met, irrespective if such expectations are realistic or not.

The real added value of today's TC in my view is that we have more clarity now on what may not be easily acceptable for the EC, ie a delay of several weeks between an authorisation granted by the FDA/ MHRA (under whatever form) and a CMA opinion issued by EMA. The political fall-out seems to be too high, even if the "technical" level at the MSs (as it was referred to by the Commissioner) could defend such a delay in order to make the outcome of the scientific review as robust as possible.

Although we know that whatever we do (speeding up the process to align as much as possible with the "approval" timing by FDA/MHRA versus taking the time needed to have robust assurance in particular as regards CMC and safety) EMA will have a very big challenge addressing questions and criticism from various parties (EC, MSs at political level, EP, media, the general public) in case of a delay of several weeks.

Even if it can not be excluded now that at the end we are aligned with the FDA/MHRA (both in the outcome of the scientific review and the timing), the opposite certainly can not be excluded at this moment so we need to prepare for the worst case scenario. So how do we go from here? Are the current measures enough? In my view, probably not. We will be overwhelmed from all fronts and be in the middle of the storm. And on who's support will we be able to count? I hope it will not be a rethorical question...

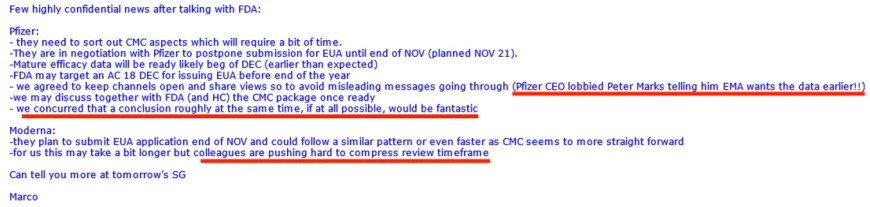
What can we do on top, without creating the perception that we are interfering outside our "technical" mandate?
A non-exhaustive list:
1. Explaining the EMA process and what it will deliver:
- A public event is organised on 11/12: I think we need to critically review if we will achieve what is needed, taking into account the already brought forward date and the content related aspects.
- Making better use of social media tools as referred to by Emer today: we urgently need a dedicated strategy. However the resources in Comms are so stretched already that they have at this moment enormous difficulties to cope with the high influx of (media) queries. Reaching out to a specialist company to help out?
2. Explaining the differences between US/U.K. EUA and CMA: although the general public and the media will not (necessarily) understand the nuances between the 2 concepts we have to finalise this exercise which is currently ongoing ASAP, and then, more importantly, decide how to make best use of it. CMC, responsibility and accountability are certainly elements to be considered in my view.
3. Making the CMA process adapted as much as possible to the current pandemic situation: this exercise is ongoing but (1) the time gained may be limited and (2) any changes may be too late for the Pfizer/BioNTech vaccine. Nevertheless I think we should finalise ASAP if only to demonstrate that we did our utmost.

I hope these reflections can contribute to coming to a decision how to best address the important challenges ahead.

KR,

Noel

Wathion points out that a potential delay of several weeks to secure '*robust assurance in particular as regards CMC and safety*' will be met with '*criticism from various parties,*' including media, EC (European Commission) and EP (European Parliament). Wathion speaks of his fear that if the deadline '*to align as much as possible with the "approval" timing by FDA/MHRA*' cannot be met- '*we will be overwhelmed from all fronts and be in the middle of the storm.*' However, this potential delay appeared to be necessary *'in order to make the outcome of the scientific review as robust as possible.'* This implies that speed at the expense of safety was the order of the day to avoid *'political fallout.'* Clearly, politics was dictating Covid-19 vaccine authorisation protocol, not the science.



Few highly confidential news after talking with FDA:

Pfizer:
- they need to sort out CMC aspects which will require a bit of time.
-They are in negotiation with Pfizer to postpone submission for EUA until end of NOV (planned NOV 21).
-Mature efficacy data will be ready likely beg of DEC (earlier than expected)
-FDA may target an AC 18 DEC for issuing EUA before end of the year
- we agreed to keep channels open and share views so to avoid misleading messages going through (Pfizer CEO lobbied Peter Marks telling him EMA wants the data earlier!!)
-we may discuss together with FDA (and HC) the CMC package once ready
- we concurred that a conclusion roughly at the same time, if at all possible, would be fantastic

Moderna:
-they plan to submit EUA application end of NOV and could follow a similar pattern or even faster as CMC seems to more straight forward
-for us this may take a bit longer but colleagues are pushing hard to compress review timeframe

Can tell you more at tomorrow's SG

Marco

In the above email from Marco, the EMA official reveals that Pfizer's CEO Albert Bourla 'lobbied' Peter Marks, and this could be interpreted as highly controversial, given Marks is the director of the Center for Biologics Evaluation and Research (CBER) at the FDA. Pfizer's apparent access into the federal watchdog raises significant questions at the least, if not introduces the possibility for disturbing entanglements between industry and a purportedly independent, scientific federal agency.

Major concerns with the integrity between vaccine batches

An email from Cavaleri (see below) reveals at that time the FDA knew of '*some issues*' associated with the CMC which needed to be sorted out and may '*end up being the difficult bit*'. CMC refers to the Chemistry, Manufacturing and Controls, also referred to as pharmaceutical quality, which covers various procedures used to assess and ensure the safety and consistency between pharmaceutical product batches.


Cavaleri Marco
Tue 10/11/2020 14:00
Deleted Items
Thanks Irene
I just learned from FDA that there are some issues on CMC to be sorted out so I guess that if we can try to catch up would be good. I fear CMC will end up being the difficult bit
FDA may conclude on EUA by Xmas (not earlier); any chances we can issue CMA at the same time?
Marco
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An email from Evdokia Korakianiti (an EMA scientific administrator) explains in more detail what these "issues" were and how they were in fact major concerns to do

with the Pfizer- BioNTech vaccine.

Korakianiti Evdokia

Mon 23/11/2020 10:38

Inbox

Dear Colleagues,

This email is for awareness and to flag an important comparability issue with the BioNTech vaccine that needs to be addressed prior to approval.

Issue: A significant difference in %RNA integrity / truncated species has been observed between the clinical batches (~ 78% mRNA integrity) based on which the Interim analysis was performed and the proposed commercial batches (~ 55%).

The company claims that the efficacy of the drug product is dependent on the expression of the delivered RNA, which requires a **sufficiently intact RNA molecule.** The root cause for for the lower %RNA integrity at commercial batches has not yet been identified

Impact: The potential implications of this RNA integrity loss in commercial batches compared to clinical ones in terms of both safety and efficacy are yet to be defined. Whether or not the observed comparability issues could be a blocking point will depend on the relevance of these observations to safety and efficacy and the company will be requested to fully justify the lower %RNA integrity (and other differences noted).

Point for discussion will be whether the comparability issues can be solved only by Quality data (additional functional/ in vitro biological data + available non-clinical) or that further clinical data (bridging studies are/will be performed) will be needed. It is difficult to make any projections on this.

Way forward: This issue and other MO (but in our view not blocking to a potential approval) have been raised at ETF and are being discussed at BWP this week and in a TC with FDA on Wednesday

With many thanks to Ton who's is the Quality specialist for this vaccine together with Brian looking after the chemical elements

Best regards

Evdokia

Alarmingly, significant differences in the levels of mRNA integrity between Pfizer-BioNTech's commercial (large scale) and clinical vaccine batches (small scale) were observed. '*~78% mRNA integrity*' in the clinical ones and '*~ 55% in the proposed commercial batches*' with the '*root cause*' not yet identified. Safety and efficacy implications due to this concern were also noted in the email *'as yet to be defined.'*

In a confidential Pfizer report, which was also leaked along with the EMA emails, the company states that according to Acuitas Therapeutics' (the biotech company who developed the lipid nanoparticle platform for the Pfizer and Moderna vaccine) own general experience, *'a minimum threshold is approximately 70%.'* (See screenshot below)

RNA molecules that are not fully encapsulated and protected by the LNP are considered inactive, as they are exposed to nucleases and further degradation after administration. RNA

inactive, as they are exposed to nucleases and further degradation after administration. RNA must be sufficiently intact to be successfully translated to the target protein, hence a minimum level of encapsulation efficiency needs to be achieved for a candidate RNA-LNP system. This minimum threshold is approximately 70% based on Acuitas Therapeutics general experience.

Then on page 30 it states: *'The efficacy of the product is dependent on expression of the delivered RNA,* ***which requires a sufficiently intact RNA molecule.'*** *(See screenshot below)*

3.2.P.2.2.3.4.1. RNA Integrity

The RNA integrity of BNT162b2 drug product samples is assessed using a capillary gel electrophoresis-based (CGE) method, also called the Fragment Analyzer (FA) method, to separate components based on the differential migration of RNA of different molecular size in an applied electric field. In contrast to drug substance sample analysis, RNA from drug product is analyzed following disruption of the LNP in detergent and ethanol. Under fully denaturing conditions, the RNA is expected to unfold and migrate through the gel matrix, as a function of length and size, toward the anode. An intercalating dye binds to RNA and associated fragments during migration allowing for fluorescence detection. All other peaks that migrate prior to or after the main peak are integrated separately and will lower the overall RNA integrity percent, ie. intact RNA. The efficacy of the product is dependent on expression of the delivered RNA, which requires a sufficiently intact RNA molecule.

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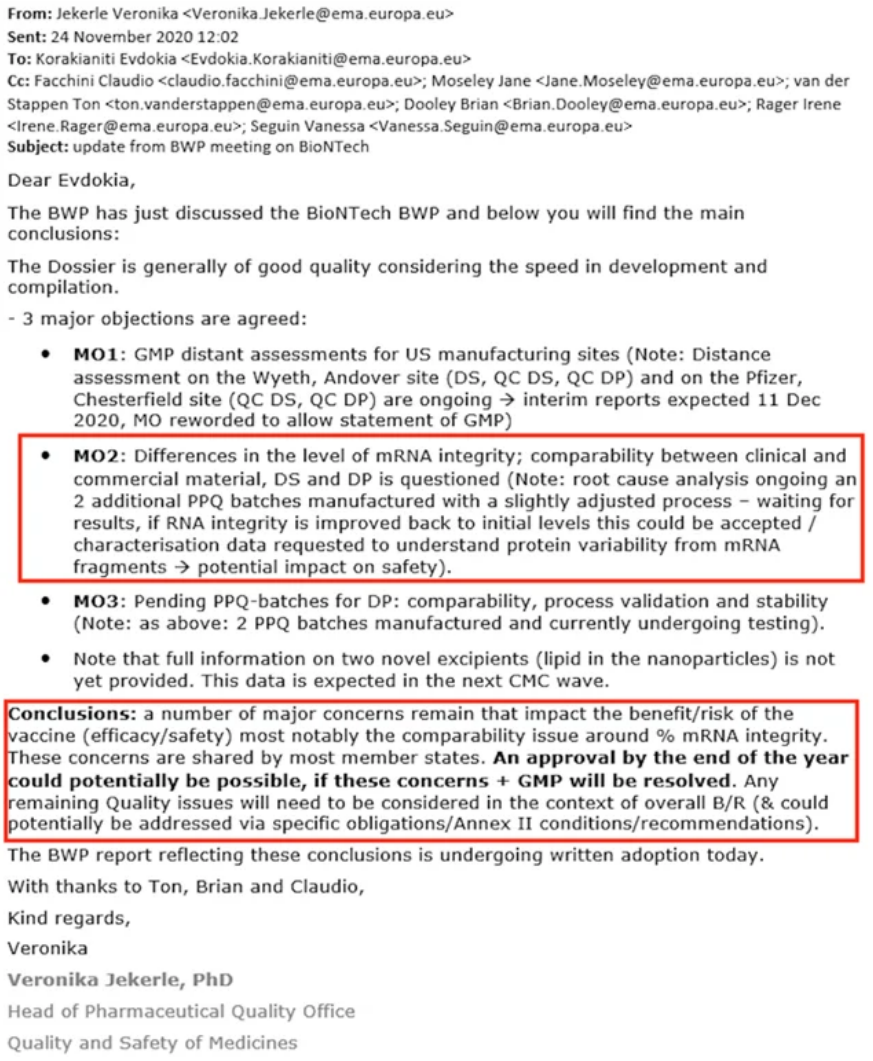
This exact phrase *'requires a sufficiently intact RNA molecule'* was used in the email from EMA staffer, Evdokia Korakianiti, which I included above, sent on November 23, 2020- now we likely know where Korakianiti referenced it from.

For the commercial batches (which were going to be rolled out across the globe) to have such a significantly lower level of mRNA integrity (intact RNA molecule) is greatly concerning given its intrinsic tie to the efficacy and potential safety of the product.

The next day Veronika Jekerle, Head of Pharmacy Quality Office, writes to Evdokia (see below).



From: Jekerle Veronika <Veronika.Jekerle@ema.europa.eu>
Sent: 24 November 2020 12:02
To: Korakianiti Evdokia <Evdokia.Korakianiti@ema.europa.eu>
Cc: Facchini Claudio <claudio.facchini@ema.europa.eu>; Moseley Jane <Jane.Moseley@ema.europa.eu>; van der Stappen Ton <ton.vanderstappen@ema.europa.eu>; Dooley Brian <Brian.Dooley@ema.europa.eu>; Rager Irene <Irene.Rager@ema.europa.eu>; Seguin Vanessa <Vanessa.Seguin@ema.europa.eu>
Subject: update from BWP meeting on BioNTech

Dear Evdokia,

The BWP has just discussed the BioNTech BWP and below you will find the main conclusions:

The Dossier is generally of good quality considering the speed in development and compilation.

- 3 major objections are agreed:

- **MO1**: GMP distant assessments for US manufacturing sites (Note: Distance assessment on the Wyeth, Andover site (DS, QC DS, QC DP) and on the Pfizer, Chesterfield site (QC DS, QC DP) are ongoing → interim reports expected 11 Dec 2020, MO reworded to allow statement of GMP)
- **MO2**: Differences in the level of mRNA integrity; comparability between clinical and commercial material, DS and DP is questioned (Note: root cause analysis ongoing an 2 additional PPQ batches manufactured with a slightly adjusted process – waiting for results, if RNA integrity is improved back to initial levels this could be accepted / characterisation data requested to understand protein variability from mRNA fragments → potential impact on safety).
- **MO3**: Pending PPQ-batches for DP: comparability, process validation and stability (Note: as above: 2 PPQ batches manufactured and currently undergoing testing).
- Note that full information on two novel excipients (lipid in the nanoparticles) is not yet provided. This data is expected in the next CMC wave.

Conclusions: a number of major concerns remain that impact the benefit/risk of the vaccine (efficacy/safety) most notably the comparability issue around % mRNA integrity. These concerns are shared by most member states. **An approval by the end of the year could potentially be possible, if these concerns + GMP will be resolved.** Any remaining Quality issues will need to be considered in the context of overall B/R (& could potentially be addressed via specific obligations/Annex II conditions/recommendations).

The BWP report reflecting these conclusions is undergoing written adoption today.

With thanks to Ton, Brian and Claudio,

Kind regards,

Veronika

Veronika Jekerle, PhD
Head of Pharmaceutical Quality Office
Quality and Safety of Medicines

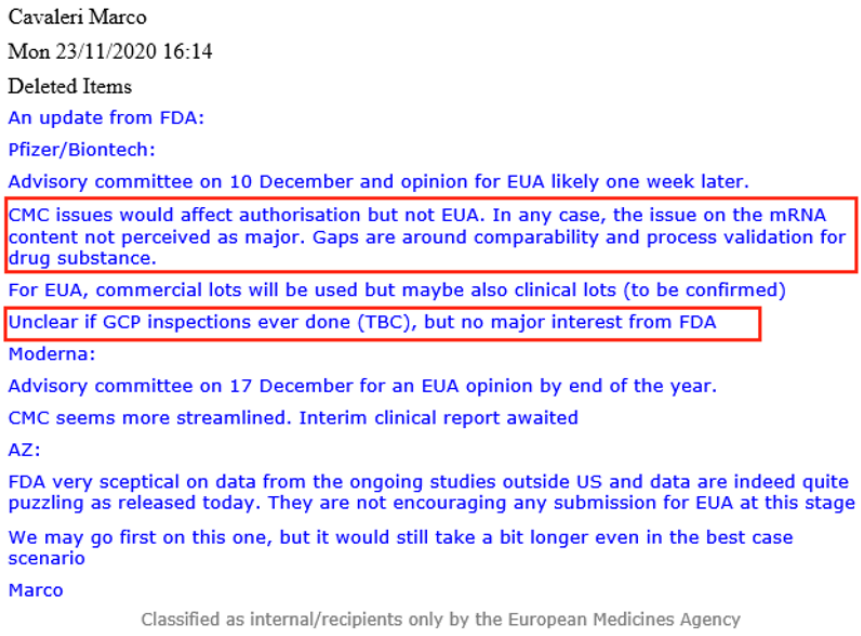
The difference in the level of mRNA integrity was again noted as a major concern '*shared by most member states*' and its '*potential impact on safety.*' Jekerle highlights in bold, ***"An approval by the end of the year could potentially be possible, if these concerns + GMP will be resolved."***

This gives rise to the critical question- how were all these concerns resolved when CMA was granted only a few weeks later, on December 21? A possible way it was resolved is explained later in this report.

In contrast to the concerns of some of the other EMA officials, Marco Cavaleri writes around the same time in

the following email (see below) that the mRNA content is not a major concern, according to the FDA- '*the issue on the mRNA content not perceived as major.*' He also shockingly states, '*unclear if GCP inspections ever done*'. This revelation is highly concerning given that GCP refers to Good Clinical Practise, which is *'an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.'*

What's even more alarming is his following statement- '*no major interest from FDA*'. This looks to reveal the regulatory agency's apparent lack of concern or even interest on whether GCP inspections were completed, in the context of Pfizer's clinical trials, which was relied on by the FDA to grant EUA for the Pfizer-BioNTech vaccine. In one of this author's previous investigative reports for Trial Site News, we noted that the FDA only inspected 1% of Pfizer's trial sites.



Cavaleri Marco
Mon 23/11/2020 16:14
Deleted Items
An update from FDA:
Pfizer/Biontech:
Advisory committee on 10 December and opinion for EUA likely one week later.
CMC issues would affect authorisation but not EUA. In any case, the issue on the mRNA content not perceived as major. Gaps are around comparability and process validation for drug substance.
For EUA, commercial lots will be used but maybe also clinical lots (to be confirmed)
Unclear if GCP inspections ever done (TBC), but no major interest from FDA
Moderna:
Advisory committee on 17 December for an EUA opinion by end of the year.
CMC seems more streamlined. Interim clinical report awaited
AZ:
FDA very sceptical on data from the ongoing studies outside US and data are indeed quite puzzling as released today. They are not encouraging any submission for EUA at this stage
We may go first on this one, but it would still take a bit longer even in the best case scenario
Marco
Classified as internal/recipients only by the European Medicines Agency

Further damming information is revealed (see screenshot below) when multiple regulatory agencies: Health Canada

below) with multiple regulatory agencies. Health Canada (HC), EMA, MHRA and FDA are all aware of the issue with % mRNA integrity, yet FDA and Health Canada make an unsubstantiated claim that *'safety concerns associated. Are more of a theoretical concern.'*

From: Jekerle Veronika <Veronika.Jekerle@ema.europa.eu>
Sent: 25 November 2020 16:28
To: Korakianiti Evdokia <Evdokia.Korakianiti@ema.europa.eu>; Prilla Stefanie< Stefanie.Prilla@ema.europa.eu>; Nolte Alexis <Alexis.Nolte@ema.europa.eu>
Subject: RE: Ad-hoc MLT minutes for comment by 16:30 today

Dear Evdokia,

Please see the additional points resulting from the TC with FDA we just had:

FDA shared with us the following information:

- FDA have received 7 commercial DS and 6 additional DP lots (2 additional GMP lots which EU hasn't received yet). 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

- FDA and Health Canada indicated that the safety concerns associated with variable species of mRNA/protein are more of a theoretical concern as 5' caped intact species appear to stay comparable (which equates to fully functional mRNA)

- FDA/HC/EMA agreed that alignment on specifications % mRNA integrity are key in order to avoid that one regions gets all the suboptimal material (in particular a concern by Health Canada), specifications should be clinically qualified

- FDA mentioned an amendment of the CT protocol to compare immunogenicity of process 1 and 2 material; however unclear whether patients have received these doses yet; this info would be valuable to bring clinical bridge in the range of the specs for % of mRNA integrity; very likely to not be available though before end of the year

- FDA indicated that for a full BLA they would require 3 PPQ lots each for DP and DS

- Applicant has shared with FDA and us/MHRA only today an issue with visible particles in the DP (appears to be lipid nanoparticle components). FDA has posed questions to applicant, we will also FU on this issue.

Kind regards,

Veronika

Health Canada then appears to contradict itself because its later described as showing particular concern about one region receiving *'all the suboptimal material.'* Obviously, it didn't want to be that region.

Shockingly, the end of the email reveals the *'Applicant [Pfizer] has shared with FDA and us [EMA]/MHRA* ***only today*** *and issue with* ***visible particles in the DP*** *[drug product] appears to be lipid nanoparticle components.)'*

This is highly concerning due to this significant issue being made known to the three key regulatory agencies on November 25, only a few weeks away before the EMA granted CMA and the FDA granted EUA for the Pfizer vaccine. Alarmingly, it was just days before the MHRA granted authorization in the UK on December 2, 2020

granted authorization in the UK on December 2, 2020. Veronika's assumption that the '*visible particles*' could be

LNPs (lipid nanoparticles) is hard to accept given nanoparticles are not visible to the naked eye. Other anomalies were apparent, yet this was probably still a historical effort in terms of speed of vaccine development. It seems clear however some more time was needed.

How % mRNA integrity was apparently resolved

The discrepancy between batches appears to have may been resolved when it's mentioned that the *'latest lots [received by the FDA] indicate the % intact RNA are back around 70-75%.'*

However, in a leaked report of a meeting with Pfizer and the EMA on November 26, 2020, a day after Veronika's email, it shockingly reveals that the RNA integrity specification was revised down to >=50% for drug product shelf life, significantly lower than the minimum threshold of 70% that Acuitas Therapeutics had stipulated and the average 78% of the clinical batches. Was this the EMA's (and potentially FDA/MHRA/HC) way of 'resolving' the issue to ensure *'an approval by the end of the year'*?

Major Objection #2 (Comparability)

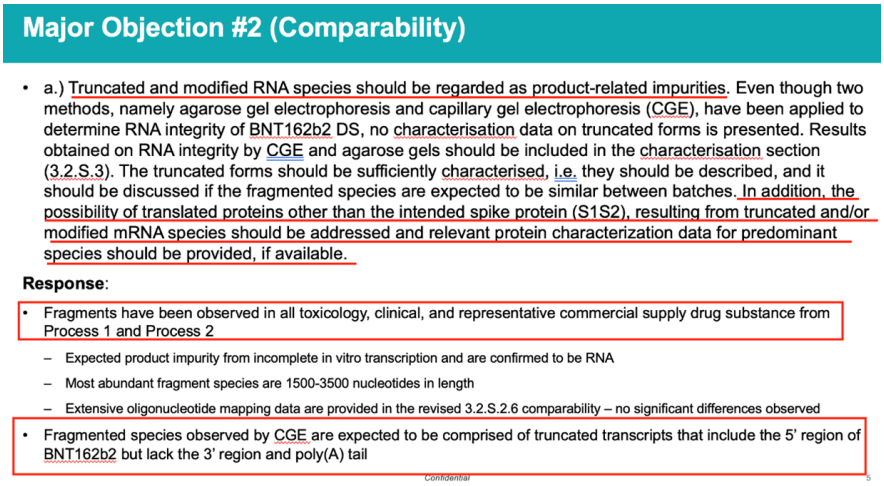
2. Comparability between clinical and commercial material has not yet been demonstrated, which raises uncertainties about consistency of product quality and hence uncertainties as regards product safety and efficacy of the commercial product. Significant differences between batches manufactured by DS 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.

Confidential 4

Mention is made of '*uncertainties about consistency of product quality and hence* ***uncertainty as regards product safety and efficacy of the commercial product.***' Yet, it's baffling how lowering the RNA integrity specification would remedy that major objection.

In another slide the artifact states, *'Truncated [shortened] and modified RNA species should be regarded as product-related impurities.'* This confirms that these shortened mRNA species which lowered the level of %mRNA integrity were classed as impurities. Another alarming concern arising from these impurities is flagged '*the* ***possibility of translated proteins other than intended spike protein (S1 S2)*** *resulted from truncated and/or modified mRNA species should be addressed.'* (See screenshot below)



The evidence in this report confirms that regulatory bodies like the FDA, MHRA, EMA and Health Canada knew of the differences in batches, regarding % mRNA integrity and because of that the effect on '*safety and efficacy'* was unknown. The leaked Pfizer/EMA meeting

report raises material concerns assuming the issue was resolved by simply lowering the RNA integrity specification. In other words, perhaps it was never resolved.

A particular website that has drawn a lot of attention recently, which speaks to the difference between batches is howbadismybatch.com. It's a comprehensive database with analysis on 'batch codes and associated deaths, disabilities and illnesses for Covid 19 Vaccines.' By entering a batch number of any of the Covid-19 vaccines, it tells you the frequency of adverse events reported associated with that batch.

I spoke with Sasha Latypova, who has run clinical trials for over 25 years and owns her own biotech company, to ask her expert opinion on the leaked documents. She said, *"The lack of mRNA integrity and presence of uncharacterized fragments of RNA in batches of Pfizer's product was identified as a "Major Objection" - a formal regulatory red flag, deemed a product impurity and would have been a showstopper in any normal drug approval process. At a minimum, it required an additional "bridging" clinical trial to evaluate the clinical effects which would have taken months to design and conduct properly. Panic overruled scientific integrity, and an arbitrarily lowered batch acceptance standard was adopted for the sake of meeting a politically motivated deadline. To date, this issue remains unresolved and could be the underlying cause for the enormous variation in the rates of adverse events and deaths observed for different manufacturing batch numbers in the CDC VAERS and other databases.'*

Latypova made an apt reference to the fate of the Titanic, by drawing a comparison in the way regulatory bodies conducted their 'warp speed' process of authorising the Covid-19 vaccines. The Titanic's captain, Edward J. Smith, was aiming to better the crossing time of another vessel, which meant the ship was travelling way too fast, in waters known to have ice. This set it on a fatal collision with an iceberg and the rest is history.

In light of the evidence included in this report and the fact that the Pfizer-BioNTech Covid-19 vaccine is one of the most lucrative products in history (last year Pfizer made $37 billion in sales with predictions for 2022 being $32 billion), this author strives to open a discussion with some vital questions which must be addressed by the regulatory agencies involved, Pfizer and those in the scientific/medical community:

What are the safety and efficacy implications of a significantly lowered mRNA integrity (arising from truncated and modified mRNA) in the commercial batches of this vaccine?

Exactly what are the visible particles observed in the DP (drug product) that Pfizer shared last minute with the EMA, FDA and MHRA and what are its safety and efficacy implications?

Answers to these questions are of major public importance.

Trial Site News recently were able to review leaked internal emails from the European Medicines Agency (EMA) and meeting report between the agency and Pfizer. The EMA oversees the evaluation and supervision

of medicinal products for the European Union. Like other regulatory health bodies, its main responsibility is to protect and promote public health. Snapshots of internal EMA email correspondence; a November 26, 2020, PowerPoint presentation from a pivotal meeting between Pfizer and the agency, as well as a confidential 43-page Pfizer report were provided by an anonymous source because of their trust in *Trial Site's* commitment to transparency, accessibility, and accountability in furtherance of a highly ethical, quality-focused and public health-centric biomedical research industry.

Regulatory agencies, like the EMA, the Food and Drug Administration (FDA) in the U.S. and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) are chartered to make decisions based to better the public. External influences such as political or media pressure are not meant to be a driving factor in their decision-making, however, when it came to pandemic conditions and the fast-tracked conditional marketing authorization of the Covid-19 vaccines (particularly for the mRNA-based vaccines produced by Pfizer-BioNTech and Moderna), it appears the latter won the day.