**FOI 23/051**

**14th February 2023**

Dear

**Sequential to internal review of 22/012**

Following on from our correspondence of 23 January 2023, we are pleased to be able to provide answers to your list of questions regarding the parameters and data that help to characterise and control the COVID-19 Pfizer vaccine (drug substance) to a suitable standard.

Before addressing the points raised in your follow-up enquiry, it may be useful to first mention that manufacturers are required to submit the necessary quantitative and qualitative data, including batch analysis data, to support the proposed drug substance and product specifications prior to the approval of a medicinal product, such as the COVID19 vaccine. With this in mind, adequate batch information was submitted to support compliance with the 'identity' test parameter associated with the BNT162b2 COVID-19 vaccine for the initial approval of the product, which included the FASTQ files for the licensing assessment team for evaluation. Hence, the supported Certificate of Analysis (CoA) and compliance with the agreed product specifications were demonstrated. Please see below for further information.

Since BNT162b2 COVID-19 vaccine is a biological product and it is not a small molecule drug substance, molecular entities or variants of the drug substance are commonly observed for biological products. Generally, 100% fidelity is not expected in any biological system. However, any potential product-related substances formed are considered as part of the evaluation of the manufacturing process and controls. Some product-related impurities would still provide an effective product. These would have been considered clinically qualified through clinical studies. In the case of BNT162b2, satisfactory *in vivo* non-clinical and human clinical studies confirm the product is adequately controlled with the effective protein being made, in order to elicit the desirable immunological response. Hence, the high protective effects from the SARS-CoV-2 virus have been observed throughout the pandemic.

With regard to the additional 7 statements/questions included in your letter, we thank you for the option for us to provide you with a simple yes or no response. However, we felt it was necessary to provide detailed answers so that important and relevant contextual information on how a biological drug substance is usually made and controlled could be included.

We have included a copy of your follow-up enquiry below, and where appropriate to do so we have provided answers in italicised font.

***Annotated version of your follow-up enquiry***

Thank you for taking the time to respond to FOI/22/012 and addressing the correspondence I have had with the ICO.

Regarding Part 1 of my FOI and specifically my request for the original FastQ files you state:

"Here we would like to include a point of clarification that NIBSC does not carry out nucleotide sequencing of this vaccine, and therefore FastQ files are not produced in any testing by NIBSC"

May I respectfully ask,

Does the MHRA have receipt of the full genomic sequence files for each batch/lot of BNT162b2 that has been approved in the UK?

This information could come from the Innovator (Pfizer) or from one of the Innovators approved manufacturers. A simple yes/no answer would be appreciated.

The reasoning for this line of enquiry is set out below:

1. The MHRA Public Assessment Report defines the Active Substance in Section II.2 on Page 7 and quoted below:

Drug Substance (BNT162b2 RNA)

"BNT162b2 drug substance is a single-stranded, 5'-capped mRNA encoding the full-length viral S (S1S2) protein of SARS-CoV-2. The optimised codon sequence encoding the spike glycoprotein antigen of the SARS-CoV-2 virus results in a protein expressed with two proline mutations that fix the S1S2 spike protein in a pre-fusion conformation to increase potential to elicit virus neutralising antibodies. In addition, the RNA contains common structural elements optimised for mediating high RNA stability and translational efficiency (5'-cap, 5'-UTR, 3'-UTR, poly(A) – tail). Uridine is replaced by modified N1-methylpseudouridine (m1ΨTP) in the RNA synthesis which increases RNA persistence in-vivo through dampening of innate immune response to itself. The 5 prime end is capped with a structure which will not activate the innate immune system."

*We agree with the information shown in the MHRA Public Assessment Report.*

2. The mRNA sequence of the vaccine is in the public domain (FOI 21/823) and is 4,284 bases long containing multiple features as described in point 1 that are essential for the mRNA pro-drug to function as designed. A nice summary of this functionality was published in the journal Vaccines in July 2021

Vaccines | Free Full-Text | Detailed Dissection and Critical Evaluation of the Pfizer/BioNTech and Moderna mRNA Vaccines (mdpi.com)

Every single one of those 4,284 nucleotide bases of the BNT162b2 RNA active substance must be aligned in the correct sequence order starting with the very first base and ending with the final 4,284th base. This sequence is essential to guarantee in-vivo function as designed.

*This is not fully agreed.*

*Measures must be in place to avoid deviations which are likely to negatively impact on the efficacy or safety of the vaccine. This emphasises the importance of having an appropriately validated manufacturing process with suitable controls in place. This also explains the reason why a control specification which has been carefully evaluated is in place to provide reassurance that the required quality of the product must be met prior to the distribution of the product for public use.*

*In addition, as mentioned above, depending on the nature of identified errors, some product-related impurities may still confer an effective product. This is considered in the necessary manufacturing in-process controls as well as in the finished product specifications. These impurities, whether they are process- or product- related are suitably characterised and controlled to meet the necessary ICH guidelines (e.g.ICH Q6B). Consequently, the specifications do not solely rely on 'identity' of the product, but controls of other critical quality attributes that have an impact on the quality of the product are also important, which ultimately influence the safety and efficacy of the product.*

3. In April 2022 a pre-print article by Roy et al of New England Biolabs was uploaded onto biorxiv titled

"Improving the fidelity of uridine analog incorporation during in vitro transcription"

Improving the fidelity of uridine analog incorporation during in vitro transcription | bioRxiv

This paper has relevance because it assesses the in-vitro transcription (IVT) error rate for synthetic mRNA's modified with N1-methylpseudouridine (m1ΨTP). The paper enables one to estimate the error rate expected from a perfect synthesis of BNT162b2 RNA active substance. The result suggests there would be one random error in every molecule of BNT162b2. Even a single error (mutation) has potential to substantially disrupt translation of the mRNA in-vivo so this publication should be carefully considered.

*Without providing a critical appraisal of the article, we reiterate that 100% fidelity in a biological system is very rarely attained. Medicines regulators place great importance on pro-actively identifying the stage/s in a manufacturing process that would be likely to contribute to errors. Understanding how best to mitigate against risks which could contribute in a sub-standard product is an essential part of medicines control. This is evaluated accordingly by the manufacturer and regulatory authority to ensure an adequate in-process control system is in place to maximise product quality. Other control test parameters would also provide feedback on whether the manufacturing process was effective. As shown in the redacted drug substance specification, the purity and process-related impurities were also included as part of the control process.*

New England Biolabs was founded by the British biochemist Richard Roberts who won the Nobel Prize in Physiology or Medicine in 1993, so it is an institution with gravitas!

Using the aerospace industry as an analogy, a commercial jet engine has around 25,000 parts so applying the same error rate would mean each engine produced would have around six random errors, faults. Knowing that, would the public be comfortable boarding an aeroplane equipped with those engines? I doubt it. Jet engines are produced with zero errors/faults because stringent QC checks exist, furthermore, regulations mandate engines must be inspected on a regular maintenance schedule for regulators to issue airworthiness certification. Part 1 of FOI/22/012 attempted to establish exactly this point by enquiring if the active drug substance containing 4,284 "parts" is error free? This question can only be addressed by genomic sequencing every individual batch/lot of vaccine product. Demonstration of an error free high-fidelity product would deliver overwhelming public confidence in that product just like people boarding a flight knowing the engines have zero faults!

4. In the redacted Pfizer documents supplied under FOI/22/012 there are unredacted lines stating "Identity of encoded RNA sequence" using the analytical procedures of capillary gel electrophoresis and RT-PCR. However, neither of these analytical techniques can output the complete 4,284 genetic sequence of the active substance. For example, RT-PCR, is only capable of finding what you ask it to find so it will be able to confirm if certain elements of the genetic sequence are present, but it cannot distinguish if all the 4,284 bases are present and in the correct sequence order. The only technique available to accurately achieve this is next-generation sequencing (NGS).

*Validation of any proposed analytical methods must be demonstrated as part of the control testing. The routine quality control test methods of the drug substance proposed for release are considered critical to ensure the necessary quality standards are met, but they may not necessarily be the only tests performed on a drug substance. For a complex product like this vaccine, orthogonal techniques*

*and extended characterisation techniques were employed throughout the development of the product, and these were subjected to regulatory evaluation, which also provided additional information about the product with respect to its characteristics.*

*Furthermore, as shown in the redacted finished product specifications, in vitro expression assay, confirming the activity of the protein expressed is also considered important to ensure the required protein is produced from the mRNA. The correct protein cannot be translated from incorrectly assembled mRNA.*

5. It is instructive to consider that on the 10th of February 2022 the UK Health Security Agency published a press release titled "UK completes over 2 million SARS-CoV-2 whole genome sequences" stating the UK has uploaded these sequences onto the GISAID database accounting for a quarter of all SARS-CoV-2 genomes shared globally to date.

UK completes over 2 million SARS-CoV-2 whole genome sequences - GOV.UK (www.gov.uk)

Nearly 12 months later the global genome database for the virus must now contain well over 10 million sequences for which the UK is a major contributor. This painstaking and important work is carried out in the UK by COG-UK and represents an important resource for monitoring SARS-CoV-2 phylotype's, new mutations and especially variants of concern. The genomic sequence of the virus is almost ten times larger than that of the mRNA in BNT162b2 and I would suggest the total number of individual batches/lots of BNT162b2 deployed in the UK is significantly lower than two million and probably somewhere between one hundred and one thousand discrete batches. It would appear logical, given the UK has these technical resources available, that full sequencing of each batch of the vaccine could be quickly and simply carried out.

To summarise, sequencing vaccine batches that have a significantly smaller sample size and complexity than current sequencing activities COG-UK carry out on the complete viral genome should be an extremely easy to accomplish task.

*The role of the MHRA is not to perform genomic sequencing of the biological product. Consideration of the quality, safety and efficacy of the product must be made during evaluation of the marketing authorisation application.*

*In terms of quality of the product, it is important that we ensure adequate controls are in place for both the drug substance and the drug product, which is also supported by the relevant non-clinical and clinical data. By having demonstrated consistency in the manufacturing process before and post-authorisation, continuous monitoring and reporting, quality, safety and efficacy of the medicinal product can be reassured.*

6. The specification sheet for small molecule drugs always contains a section "identity" for the active pharmaceutical ingredient (API). This is where the manufacturer declares the product, they have made conforms based on a proven analytical method. For small molecule drugs methods include NMR, IR, X-Ray crystallography, chiral HPLC etc. These methods unequivocally demonstrate the API has the correct molecular structure. Furthermore, all the intermediates involved in the synthesis of the API tracking back to the Regulatory Starting Materials (RSM's) must adhere to the same exacting standards. This underpins current Good Manufacturing Practice (cGMP) and is a cornerstone for ensuring our drug products are safe. The regulators, at any time, can ask manufacturers, or their suppliers, for this exacting analytical data demonstrating the materials they have made are what they claim to have made.

The mRNA of BNT162b2 is a large molecular weight drug but it should not be exempt from the same quality standards of any other drug product. The identity/fidelity of the drug product BNT162b2 can be determined by genomic sequencing and files such as FastQ should be available for every batch produced so these can be submitted to regulators if requested. At a fundamental level this is no different from proving the identity of a small molecule API by an analytical technique such as NMR.

*The BNT162b2 COVID-19 vaccine is not exempt from the necessary quality standards of other biological drug products. The BNT162b2 vaccine is indeed considered as a large and complex biological product, which requires further characterisation in addition to those parameters tested in the routine control specifications. Characterisation includes studies on the primary and higher order structure of the BNT162b2 COVID-19 vaccine drug substance.*

*As mentioned above, the 'identity' is one of the many critical quality attributes that must be met for the drug substance and the finished drug product. Even the integrity and purity of the mRNA are controlled. The necessary quality of the drug substance is also monitored when it is formulated into the drug product, as evident by the required potency assay where the correct protein needs to be expressed.*

*Furthermore, any site manufacturing medicinal products, including COVID-19 vaccines, will have been subject to GMP inspections. Inspections will be performed either by MHRA or by the national competent authority for the country of manufacture when a mutual recognition agreement is in force for GMP inspections.*

*These inspections will include reviews of the systems in place to ensure that starting materials and finished products comply with their specifications and the requirements of GMP. This will include a review of testing processes and results, including identity testing, to ensure specifications have been met. Inspectors will review not only the processes and results but will also review the raw data used to produce the results and evaluate data integrity controls to ensure that the results can be relied upon.*

*Additionally, the Qualified Person (QP) certifying each batch has a legal responsibility to ensure all conditions of GMP and the marketing authorisation (including specifications) have been met. GMP inspections review the mechanisms by which the QP certifies batches to ensure they are fulfilling their responsibilities.*

7. The MHRA should have clear and precise knowledge that every batch/lot of BNT162b2 drug substance contains all 4,284 bases in correct sequence order as designed by the innovator, Pfizer. This sequence is the literal definition of the active substance of the drug product.

Without this information the MHRA would have approved a drug product under Regulation 174 without knowing the identity/fidelity of the active substance in that product. In plain English this would be the first time in the UK's history that a drug product has been approved by the Regulator without the Regulator confirming the active drug substance of that product is what it is claimed to be.

I am confident this cannot be the case, but I would welcome an answer to my question, yes or no. Does the MHRA have receipt of the full genomic sequence files for each batch/lot of BNT162b2 that has been approved in the UK?

*It is not a legal requirement for the company to submit to the MHRA the full genomic sequence files for each batch of the drug substance. However, once compliance to the agreed specifications of the drug substance / drug product are met and following approval of the marketing authorisation, the*

*manufacturer could be required to submit further data, for example, if there are concerns that the batches do not meet the required quality standards, including compliance with the 'identity' acceptance criteria. In situations where there is a perceived risk to public health, batch release could be suspended until data confirm that the necessary quality standards are met. Post-authorisation inspections / investigations are also considered essential to maintain regulatory oversight of manufacturing operations in order to protect public health.*

*To be clear MHRA are not in receipt of full genomic sequence files for each batch/lot of BNT162b2 that has been approved in the UK. The drug substance manufacturing process and controls, as well as batch release data for essential parameters that control the quality of the drug substance and several extended characterisation test parameters, were evaluated. These data demonstrate consistency between the drug substance described for this application and those used in the pivotal clinical study. Therefore, adequate control specifications of the drug substance and of the drug product are in place to ensure the vaccine meets the required quality standard of a vaccine. Each batch is tested against its specifications by the manufacturer and independently by NIBSC. FASTQ data are available at the batch release & QC testing sites for MHRA to inspect if requested.*

*With reference to the information provided above, it is hoped that your concerns have been adequately addressed.*

Yours sincerely,

**MHRA Customer Experience Centre**

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