COMMISSION ON HUMAN MEDICINES (CHM)

COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP - Quality ad hoc Group

Minutes of the meeting held on **Saturday 28th November 2020** at **10:00** via videoconference

Participants Present

Members

Professor K M G Taylor (Chair)
Mr VI G Fenton-May
Mr R Lowe
Professor Y Perrie
Dr R Thorpe
Dr S Walsh[1]

Observer - CHM

Professor S Ralston (Chair of CHM)

BioNTech/Pfizer Representatives

[redacted] - BioNTech
[redacted] - Pfizer
[redacted] - BioNTech
[redacted] - Pfizer
[redacted] - Pfizer
[redacted] - Pfizer
[redacted] - Pfizer
[redacted]
[redacted] – BioNTech
[redacted] - Pfizer
[redacted]

Secretariat

[redacted]
[redacted]

[1] Joined during item 3

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD

Supporting specific items

[redacted] - LD

MHRA Observers

Dr S Atkinson - Dir
Dr M Bailey - MHRA-NIBSC
[redacted] - MHRA-NIBSC
[redacted] - LD
[redacted] - LD
[redacted] - LD
Dr SP Lam - LD
Mr K McDonald - LD
[redacted] - IE&S
[redacted] - Government Legal Team
Dr J Raine - MHRA-CEO
Dr N Rose - MHRA-NIBSC
[redacted] – IE&S
Dr C Schneider - MHRA-NIBSC
[redacted] - LD
[redacted] - IE&S
[redacted] - LD

[redacted]

18th January 2021

Key
LD = Licensing Division
NIBSC = National Institute for Biological Standards & Control
VRMM = Vigilance & Risk Management of Medicines
CTBV = Clinical Trials, Biologicals & Vaccines EAG
CPS = Chemistry, Pharmacy & Standards EAG
PHE = Public Health England
CHM = Commission on Human Medicines
DMO = Deputy Medical Officer
Dir = Director of Operational Transformation
MHRA CEO = Chief Executive
IE&S = Inspection, Enforcement & Standards

1. Introduction and Announcement

1.1 The Chair reminded Members that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 The following members, invited experts and observers declared the following interests and other relevant interests for this meeting:

Professor Yvonne Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Ralston (Observer) – NPNS – Sanofi, Pfizer, Janssen, AstraZeneca & Other relevant interests in NHS Lothian and Oxford University. Professor Ralston has an honorary consultant contract with NHS Lothian but has not been involved in any trials relating to COVID-19. He also has agreed to be an external examiner for Oxford University clinical trials MSc; however, this has not yet started.

1.4 The Chair welcomed:

Company representative from BioNTech / Pfizer at 11am.

Observer, Professor Ralston, Chair of the Commission on Human Medicines (CHM)

2. Quality Assessment Report

2.1 The EWG quality sub-group heard that there had been a last-minute change to the batches relevant for the UK for a potential Regulation 174 opinion as of the evening of Friday 27th November. The immediate concerns of comparability as associated with the original two batches under review were no longer a priority whereas a discussion of the particulate 'defect' became more urgent as this impacted on the batch being considered as of this date. The EWG quality sub-group also heard that two further batches are also identified as being the next two batches intended for UK supply. One of these batches was associated with an investigation of a late migrating RNA species by capillary electrophoresis which was also characterised as a priority concern.

2.2 The preliminary assessment report on EJ0553, EJ0724 and EJ1688 was sent to the EWG quality sub-group members during the discussion. This report was based on the submission received the day before (27.11.2020). An accompanying paper highlighted the comparability

between the drug substance (RNA), as well as the drug product (manufacturing process) used in clinical trials, emergency and commercial use.

2.3 The company joined the meeting to address questions on the concerned batches, which prioritised the following issues: i) particulate matter found in EJ0553; ii) "late migrating species" in Batch EJ1688); iii) RNA integrity in early Process 2 batches; iv) stability data available for the proposed deployment model (e.g. -90 °C vs -60 °C).

2.4 The EWG quality sub-group discussed the particulate matter found in the batch of immediate interest (EJ0553). It was highlighted that vials containing particulates were removed from the batch based on 100% visual inspection. With regards to the visual inspection, it was highlighted that this particular batch failed to meet its own AQL for major defects on inspection. Discussions considered the nature of these particles, and when they are formed in the process, and that < 1.5% of the total batch was removed due to the appearance of white-coloured particulate matter. On examination the company explained that these "lipid-associated particles" are around 500-600 µm in length and not spherical. Initially, the company commented that these particles only consisted of lipids, but later indicated that these particles also contain RNA. However, no studies have been performed to determine the ratio of lipids or RNA in these particles. The particles were described as "flaky" in appearance. The company said that the particles were process filling line-associated (after sterile filtration) and not a stability-indicating phenomenon. It was also not the first time that this particular filling line was used for the manufacture of this product. A higher occurrence of subvisible particles was also seen when peristaltic pumps were used for the manufacture of LNPs, which is not currently used for the upscale batches. The company also confirmed that there does not appear to be a correlation between subvisible and visible particulate matter. The appearance of these lipid-associated particles increases at the end of the filling line. However, the company also acknowledged that no IPCs or visual inspection is performed during manufacturing process until after filling.

2.5 The company further explained that these particles did not alter the concentration of the drug product and they did not think this would have an impact on safety and efficacy of the product. However, as these were rejected vials, they did not perform a potency test on these rejected vials. It was confirmed by the company that this was an occurrence in more than one batch, including a clinical trial batch. However, no other batches were reported by the company at the meeting to have failed the AQL for major defects on inspection. The occurrence is said to be dependent on the batch size manufactured, which implied that the process could be optimised to ensure freedom from particles.

2.6 The company also indicated these particles 'disappear' after the product is diluted with normal saline and they do not recommend shaking the vials. The company said that it is recommended that the administrator should inspect the vial before administration for all parenteral products, not just for this product. However, the assessment team commented that pulling out vials from a batch that were deemed defective is not considered good practice and the reliance on HCPs to decide if there were particles present in the vials following dilution is also not ideal. The information for HCPs indicates that diluted vaccine should be discarded if particulates are present.

2.7 Since the product is sterilised by filtration through a 0.2 µm pore filter, and that these particles are generally found after filtration, during the filling stage, the EWG quality sub-group did not consider that these are aggregating particles, although no micrographs have been presented to confirm this. The reflections of the EWG quality sub-group were that the particulate matter for this batch was an OOS (out of specification) observation; the particles were described as intrinsic in nature; whilst not typically expected were not understood to be associated with a change in concentration of RNA containing LNPs, all of which provided some reassurance

that efficacy is not adversely impacted. An evaluation had been conducted and these were requested as supplementary information to be sent following this meeting. The company is also working on improving the number of rejects due to particulate matter.

2.8 Additional documentation is anticipated to help address residual safety concerns. It was thought that information on the batch generated by NIBSC may provide additional interpretation of these particles.

2.9 With regard to the potency assay, a discussion on its reliability and specification was also made and it was confirmed that assay utilising 150 µg does show a more comparable and acceptable read out than the assay utilising 100 µg. It was also confirmed with the company that 150 µg was to be used for future studies.

2.10 The EWG quality sub-group considered the late migrating RNA species (LMS) found in a drug product batch and not found in drug substance. The EWG quality sub-group were satisfied that the use of orthogonal methods to characterise this species as (likely) conformationally folded or reversibly aggregated RNA that is not denatured in the sample preparation of the CGE method supports the claim that this is actually an artefact of sample handling required to perform the RNA integrity test which requires extraction and denaturing of the RNA from the LNP before being assayed. This is not required for drug substance analysis where this species is not observed.

2.11 The comparability of the drug substance source used for the proposed batch (EJ0553) and the tested clinical batches was discussed at length, particularly considering the critical parameters such as particle size, RNA integrity, and 5' capped RNA. It was reassuring that the RNA integrity for the newer batches are relatively higher than the previously assigned batches (EE) for release in the UK. The EWG quality sub-group considered that the drug product is deemed comparable as the potency assay is variable which makes interpretation of the available data difficult, while other key parameters such as particle size, polydispersity, and RNA integrity can be compared, as long as the potency does not drop below 50 %. A concern was raised that if the product has less than 50 % RNA integrity, it may suggest that half of the product is not what it was laid out to be. Nevertheless, it seems more reassuring to the EWG quality sub-group that the later developmental batches have a higher level of RNA integrity that is more comparable with the earlier clinical batches. It was important to determine where the uncertainty in the RNA integrity came from.

2.12 The EWG was informed about difficult to interpret results regarding the length of the polyA tail found in the CoA for batch EJ0553. They considered this concern mitigated by the potency results for this batch, which appeared to be within the clinically qualified ranges.

2.13 The EWG sub-group considered that whilst the new batch under consideration was considered more acceptably comparable to previous clinical trial batches whereas the original two batches had not been, this was only through comparison with this single batch.

2.14 A concern about the continuity of supply of the vaccine was raised. It was considered important for deployment of the product in mass vaccination programme.

2.15 The EWG quality sub-group considered stability of the drug product in relation to the deployment model as it is understood. It was confirmed that there are no stability data available for the batch concerned and there was in fact no interpretable stability data from any so-called emergency use batches manufactured through process 2. It was confirmed to the sub-group that all stability statements were based on reliance of extrapolating stability data found on process 1 small scale clinical trial batches. Where total reliance was difficult to accept for the original batches under consideration this seemed more feasible to the sub-

group for the batch under consideration since this was, for release testing results, more closely comparable in terms of physicochemical aspects to clinical trial batches than the originally proposed batches had been. The EWG sub-group considered that a comparison of stability profiles is normally a contributory analysis when establishing comparability. In this instance reliance has to be made on comparability at Time 0, without confirmation from measured stability data. It was confirmed that two independent transport episodes of 6 hours each in a truck at refrigerated temperatures had been validated on an unconfirmed single batch. It is thought that this is not likely to be sufficient to support long primary care network distribution pathways. The company do not intend to submit any further stability data that would qualify additional transportation nodes in the deployment of vaccine. Stability data confirming temporary excursions to -90°C. The Tg (glass transition temperature) of higher than -60°C was reassuring.

2.16 The company agreed to provide further data on rubber stopper fragmentation studies qualifying multiple punctures of the rubber stopper after exposure to ultra low temperatures.

2.17 Overall, the EWG quality sub-group was positive in their opinion on the quality of the drug product batch under consideration but felt that the issue of intrinsic particle formation will need to be addressed further by the company. QP release certification and investigation of particles documentation should be required of the company.

3. Future Steps / Any Other Business

3.1 None.

4. Date and time of next meeting

N/A

The Meeting started at 10:05 and ended at 15:21.

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Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.