**MEMORANDUM**

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| TO: | AstraZeneca COVID-19 Vaccine (AZD1222) IND 23522 |
| FROM: | Peter Marks, MD, PhD, Director, Center for Biologics Evaluation and Research (CBER) |
| CC: | CBER Office of Vaccines Research and Review (OVRR) and CBER Office of Compliance and Biologics Quality (OCBQ) |
| DATE: | February 16, 2022 |
| RE: | Addendum #4 (for AZ's DS lots 21003357, 21003896, 21003900 and 21003971) to the August 6, 2021 memorandum entitled "Disposition of AstraZeneca (AZ) AZD1222 Drug Substance (DS) Lots 21002248, 21002635, and 21002636" |

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The purpose of this addendum is to document the Agency's determination regarding the use for potential export of AZ's AZD1222 DS lots 21003357, 21003896, 21003900 and 21003971.

I. Disposition of AZ DS lots 21003357, 21003896, 21003900 and 21003971

AZ's AZD1222 DS lots 21003357, 21003896, 21003900 and 21003971 were manufactured in Area 3 of the EMOB facility. The manufacturing initiation and completion dates for these lots were the following: November 28, 2020 to January 10, 2021 for lot 21003357; January 7, 2021 to February 21, 2021 for lot 21003896; February 8, 2021 to March 30, 2021 for lot 21003900; and January 19, 2021 to March 2, 2021 for lot 21003971. The AZ DS lots were tested by quantitative polymerase chain reaction (qPCR) for detection of Adenovirus 26 given that this lot was manufactured in the EMOB facility at the same time as the Janssen COVID-19 vaccine. The results indicated that there was no contamination of lots 21003357, 21003896, 21003900 and 21003971 with Adenovirus 26.

Manufacturing of AZ DS lots 21003357, 21003896, 21003900 and 21003971 included numerous deviations and comprised deviations related to process and microbial control. Several of these deviations appear to be related to the start of manufacture before proper qualifications, training, and procedures were in place to ensure adherence to cGMP. Additionally, AZ DS lot 21003357 exhibited a stalled control cell run.[1] While a definitive root cause was not identified, testing

[1] AZ DS lots 21003896, 21003900, and 21003971 had a successful control cell run.



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revealed that control cells were contaminated with AZD1222 that was most likely introduced into the upstream medium and/or feed solutions during chemical component weigh dispense and/or preparation in virus positive rooms. To mitigate the control cell stalls, AZ implemented consecutive rounds of corrective measures in November 2020, December 2020, and January 2021.

FDA has conducted a thorough review of available information concerning the manufacturing conditions of the EMOB facility during the time period in which AZ's DS lots 21003357, 21003896, 21003900 and 21003971 were manufactured, all testing conducted for these DS lots, and associated manufacturing deviations, to determine whether the overall process performance and documented manufacturing deviations had an impact on the safety and quality of the final DS.[2]

Based on the conditions present in the EMOB facility at the time these lots were manufactured, FDA has determined that the EMOB facility was not operating in full compliance with cGMP requirements at the time of manufacture. However, the quality of the product produced, as illustrated by a review of facility records, a review of the results of the in-process and release testing, and an evaluation of the associated manufacturing deviations, led to FDA's determination that the AZ DS lots 21003357, 21003896, 21003900 and 21003971are acceptable for use for potential export, considering the current COVID-19 public health emergency.[3]

The Agency reviewed, among other things, information provided to FDA and collected during FDA's inspection of the EMOB facility, including the facility records, risk assessments, and deviation tables. Additionally, the Agency reviewed the in-process and release testing results for lots 21003357, 21003896, 21003900 and 21003971. Based on the review of this information, the Agency concluded that the test results for lots 21003357, 21003896, 21003900 and 21003971 were within the specification of these lots. The Agency notes, however, that AZ manufactured these lots at risk, as these lots were manufactured prior to the completion of the proper qualifications, which included equipment and process performance qualifications. Many of the deviations documented for these lots appeared to be related to AZ's decision to manufacture at risk prior to implementing the proper qualifications to ensure adherence to cGMP.

AZ evaluated certain DS attributes (e.g., potency, viral particle/infectious unit ratio) to demonstrate that these deviations did not have a negative impact on the quality of the DS.

[2] See FDA's review entitled "CBER Assessment of the quality of AZ AZD1222 DS Lots 21003357, 21003896, 21003900 and 21003971 manufactured at Emergent BioSolutions; Baltimore, MD (EBSI) in Area 3," dated February 8, 2022.
[3] This determination does not necessarily indicate that FDA finds these lots to be acceptable for use in the United States for clinical trials under IND.



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Information submitted by AZ and reviewed by the Agency indicated that the deviations during manufacturing of DS lots 21003357, 21003896, 21003900 and 21003971 did not negatively impact final DS quality. Additionally, the DS lots were tested sufficiently to conclude that the deviations did not impact their potency. As a result, FDA has determined that lots 21003357, 21003896, 21003900 and 21003971 are acceptable for use for potential export, considering the current COVID-19 public health emergency.[4]

As noted in our prior assessment, regulatory authorities in other countries should make their own judgment on the acceptability of these lots for use in their countries. However, FDA does not intend to object to the exportation of these lots, or the exportation of vaccine made with these DS lots by AZ or another entity based on the information that FDA has reviewed to date, provided that AZ includes the agreed upon information sheet with each pallet of AZ's COVID-19 vaccine that is exported in sufficient quantities to provide one copy per carton, instructions regarding the information sheet are included for those who receive the shipments, and AZ agrees to the posting of an unredacted version of this addendum on FDA's website. Although we understand that the Agency could pursue enforcement action to prevent the export in these circumstances because the exported biological product would lack premarket approval and would not meet any of the exemptions in section 802 of the FD&C Act or another applicable exemption, we do not intend to do so at this time for the reasons outlined above.[5,6]

[4] This determination is specifically regarding DS lots 21003357, 21003896, 21003900 and 21003971and does not relate to vaccine manufactured by combining these lots with different lots of drug substance that FDA has not previously determined to be acceptable for use for potential export.

[5] The Agency's decision to not pursue an enforcement action for these lots under these circumstances should not be construed as a determination that these lots are acceptable for use in the United States or would be acceptable under any other circumstances. Foreign regulatory authorities should make their own judgment on the acceptability of these lots for use in their countries.

[6] FDA expects that all records and deviations associated with the manufacture of AZD1222 DS and drug product at the EMOB facility have been reviewed by AZ and reported to the Agency. Additionally, it is the Agency's expectation that any deviation discovered to be associated with DS lots 21003357, 21003896, 21003900 and 21003971, including untimely reported deviations, will be reported to FDA expeditiously and to any relevant foreign regulatory authority, including those foreign regulatory authorities who have been in receipt or will be in receipt of product from these lots. AZ is expected to cease export until such time as the Agency has reviewed the information provided and has made a determination on the AZD1222 DS lots. In the event the export has occurred or begun on certain lots, it is the Agency's expectation that AZ will notify the relevant foreign authority regarding any additional deviation and provide the foreign authority full documentation regarding the additional deviation. FDA expects AZ to be in open and regular communication with the relevant foreign authority and to implement a process to proactively provide such information promptly.



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