U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

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 Vaccine Research and Review (OVRR) and CBER Office of Compliance and Biologics Quality (OCBQ)
DATE:	September 21, 2021
RE:	Addendum #1 to the August 6, 2021 memorandum entitled "Disposition of AstraZeneca (AZ) AZD1222 Drug Substance (DS) Lots 21002248, 21002635, and 21002636"

The purpose of this addendum is to document the Agency's updated assessment of AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 for potential export. The Agency was informed by AZ of additional deviations potentially impacting AZD1222 DS lots after the Agency's preceding memorandum dated August 6, 2021 noting that these batches were acceptable for use for potential export.

I. FDA's updated assessment of AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 for potential export by AZ or another entity

On August 12, 2021, AZ notified FDA that Emergent had identified another major deviation linked to all AZD1222 lots. This deviation resulted from the use of a sample matrix that was not qualified to perform bioburden testing on nine different raw materials including several excipients. Additionally, on August 20, 2021, FDA was notified of another deviation that impacted all lots manufactured in Area 3 of the EMOB facility. This deviation was related to upstream in-line testing where the system did not perform as expected, including missed auto quality control testing. AZ conducted an investigation of the impact of these deviations on the quality and safety of AZD1222 DS lots, and the deviation investigation reports were submitted to the Agency on August 20, 2021.

On September 10, 2021, AZ notified FDA of a third major deviation impacting lots in Area 3. This deviation was related to the use of certain unqualified temperature control units in Area 3 for AZD1222 DS downstream manufacturing process. Specifically, these unqualified units were

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used to control the downstream process intermediate temperature in the single-use mixer bags to ensure that the maximum process intermediate hold times were not exceeded. An investigation of the impact of this deviation on the quality and safety of the AZD1222 DS lots was conducted, and the deviation investigation report was submitted to the Agency on September 13, 2021.

As noted in our prior memo dated August 6, 2021, the EMOB facility at the time that lots 21002248, 21002635, and 21002636 were manufactured was not operating in compliance with cGMP requirements. Several of the deviations noted for the AZD1222 DS lots are related to the start of manufacture before proper qualifications, training, and procedures were in place to ensure adherence to cGMP.

With respect to these additional deviations, CBER has conducted a thorough review of the information provided by AZ concerning their assessment of the impact of these deviations on the AZD1222 DS lots to determine whether these manufacturing deviations had an impact on the safety and quality of the final DS.[1] FDA has determined that the quality of the product produced is acceptable for use for potential export, considering the current COVID-19 public health emergency.[2] This determination is consistent with our initial assessment of AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 for export.

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 DS from these lots by AZ or another entity based on the information that FDA has reviewed to date, provided that 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.[3]

[1] See FDA's review entitled "Update to CBER Assessment of the quality of AZD1222 Drug Substance Lots 21002248, 21002635, and 21002636 manufactured at Emergent Manufacturing Operations Baltimore, LLC (EMOB) in Area 3," dated September 3, 2021; see also FDA's review entitled "Deviation 001161: Use of Unqualified Mokon Temperature Control Unit," dated September 20, 2021.

[2] 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.

[3] 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.

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FDA expects that all records and deviations associated with the manufacture of AZD1222 DS 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 21002248, 21002635, and 21002636, 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 with 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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