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:	August 6, 2021
RE:	Disposition of AstraZeneca (AZ) AZD1222 Drug Substance (DS) Lots 21002248, 21002635, and 21002636

The purpose of this memorandum is to document the Food and Drug Administration's (FDA, the Agency, or we) determination regarding the potential export of AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 and/or drug product manufactured from these lots.

I. Background

COVID-19 vaccines made with DS produced at a facility cannot be lawfully marketed in the United States unless and until they are covered by an approved biologics license application (BLA) or emergency use authorization (EUA). AZ has not submitted an EUA request or BLA to FDA for its COVID-19 vaccine, and FDA has not issued an EUA for AZ's COVID-19 vaccine or authorized Emergent BioSolutions Inc. (Emergent)[1] to manufacture or distribute any of AZ's COVID-19 vaccine or components, nor has FDA licensed AZ's COVID-19 vaccine. Thus, AZ vaccines made from DS manufactured at the EMOB facility are unauthorized and unapproved biological products in the United States.

[1]Emergent's headquarters are located in Gaithersburg, Maryland. The Emergent Manufacturing Operations Baltimore, LLC (EMOB) Bayview facility, which is the facility discussed in this memorandum, is located in Baltimore, MD.

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AZ's COVID-19 vaccine is, however, authorized for emergency use in many other countries.[2] The Agency has received requests from AZ and these countries to make certain AZD1222 DS lots and/or vaccine manufactured from these lots available for export.

Although the Federal Food, Drug, and Cosmetic Act (FD&C Act) prohibits the introduction of an unapproved biological product into interstate commerce, section 802 of the FD&C Act contains certain exemptions that permit the export of unapproved biological products in certain circumstances. For example, section 802(a)(1)(B) of the FD&C Act allows, among other things, the export of unapproved biological products to any country in the world if the biological product complies with the laws of the importing country and has valid marketing authorization from any of the following countries: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and the countries in the European Union and the European Economic Area, and certain other requirements are met. Products exported under section 802 of the FD&C Act are required to comply with certain requirements prior to exportation, including that the product must be manufactured, processed, packaged, and held in "substantial conformity"[3] with Current Good Manufacturing Practice (cGMP) requirements (see section 802(f)(1) of the FD&C Act).

If FDA believes an entity is exporting an unapproved biological product that does not comply with applicable requirements in section 802 or another applicable exemption, FDA could work with the Department of Justice to pursue enforcement action (e.g., an injunction or seizure) to prevent the violative export. Whether FDA chooses to pursue enforcement action in such a circumstance is discretionary.

II. Discussion

Below summarizes the Agency's assessment of the quality of certain lots manufactured in Area 3 of the EMOB facility, and the Agency's determination regarding why FDA does not intend to object to the potential export of these lots and/or vaccines manufactured from these lots.

As a general matter, manufacturing of the AZD1222 drug substance commenced in July 2020. The manufacturing occurred in Area 1 and Area 3 of the EMOB facility. Since July 2020, several AZD1222 drug substance lots have been either rejected or aborted for a variety of reasons, including microbial contamination. In addition, some DS lots, including 21002248,

[2]AstraZeneca's COVID-19 vaccine (also known as Vaxzevria) has been granted conditional marketing authorization or emergency use in many other countries and jurisdictions, such as the European Union.

[3] As described in FDA's guidance entitled "Exports Under the FDA Export Reform and Enhancement Act of 1996," July 2007, FDA interprets the term "substantial conformity" under section 802(f)(1) of the Act to "mean that the firm should have passed its most recent GMP inspection (or that GMP violations have been rectified, and the firm has credible systems and personnel in place to prevent recurrence of the violation(s))."

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exhibited stalled control cell runs. While a definitive root cause was not identified, testing 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. It was noted that after these corrective measures were implemented the frequency of the control cell cross contamination with AZD1222 diminished.

Based on the conditions present in the EMOB facility, FDA has determined that the EMOB facility was not operating in a manner that was in compliance with cGMP requirements during the production of the AZ COVID-19 vaccine.

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

AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 were manufactured in Area 3 of the EMOB facility. The manufacturing initiation and completion dates for these lots were the following: September 26, 2020 to November 5, 2020 for lot 21002248; October 12, 2020 to November 21, 2020 for lot 21002635; and October 20, 2020 to November 29, 2020 for lot 21002636. In addition to the issue of control cell cross contamination with AZD1222 noted previously for lot 21002248, manufacturing of these lots included numerous deviations and included 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. Examples include release of raw materials without verification or testing, use of equipment before completion of qualification, and manufacture without implementation of proper in-process sampling procedures. Other deviations occurred repeatedly independent of the qualification status. Due to the high number of deviations associated with the DS lots manufactured at the EMOB facility, the sponsor developed a risk assessment, following ICH Q9 Risk Ranking and Filtering guidelines, to assess all major and critical deviations and the potential cumulative impact on quality and compliance.

With respect to AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 specifically, CBER has conducted a thorough review of available information concerning the manufacturing conditions of the EMOB facility during the time period in which these three DS lots were manufactured, all testing conducted for these DS lots, and all associated manufacturing

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deviations, to determine whether the overall process performance and documented manufacturing deviations had an impact on the safety and quality of the final DS.[4]

As noted above, the EMOB facility at the time that lots 21002248, 21002635, and 21002636 were manufactured was not operating in compliance with cGMP requirements. 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 product is acceptable for use for potential export, considering the current COVID-19 public health emergency.

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 21002248, 21002635, and 21002636. Based on the review of this information, the Agency concluded that the test results for lots 21002635, 21002248, and 21002636 were within the specification of these lots.[5] 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, and before the implementation of mitigating measures to mitigate the control cell stalls. 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. Information submitted by AZ and reviewed by the Agency indicated that the deviations during manufacturing of DS lots 21002248, 21002635, and 21002636 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 21002635, 21002248, and 21002636 are acceptable for use for potential export, considering the current COVID-19 public health emergency.[6]

We note that 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

[4] See FDA's review entitled "CBER Assessment of the quality of AZ AZD1222 DS Lots 21002248, 21002635, and 21002636 manufactured at Emergent BioSolutions; Baltimore, MD (EBSI) in Area 3," dated July 27, 2021.
[5] AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 were made in the EMOB facility prior to the introduction of the Janssen COVID-19 vaccine production, and consequently, the cross contamination with the Janssen adenovirus vectored vaccine was not at issue.
[6] 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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the exportation of these lots, or the exportation of vaccine made with DS from these lots by AZ or another entity[7,8] 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 memo 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 for the reasons outlined above.[9]

[7] The Agency notes that it has only determined AZ's AZD1222 DS lots 21002248, 21002635, and 21002636 and/or vaccine manufactured from these lots to be acceptable for use and not vaccine manufactured from a combination of these lots with other lots that have not been evaluated by the Agency.

[8] Additionally, FDA has reviewed information submitted by AZ to extend the expiration dating for the AZ COVID-19 vaccine made with DS from these lots and determined that the vaccine can be stored at 2-8°C for 8 months instead of 6 months. See FDA's review entitled "Evaluation of AZD1222 Drug Substance and Drug Product Stability and Drug Product Shelf-Life Extension," dated August 3, 2021.

[9] 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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