

MEMORANDUM

DATE: March 5, 2019
FROM: Judy Beeler, MD DVP 72/1332
TO: Yu Do, Ph.D., OTAT
The File
RE: STN 122590 amendment 0022 ADMA Biologics IGIV and (b) (4)
assay.

Background: ADMA is seeking to license an IGIV, human, product and has proposed to label the product to highlight the potency of (b) (4). They are seeking an indication for the prevention and possibly also for the treatment of (b) (4) in individuals with PIDD.

The BLA review team asked me to address the following question:

The (b) (4) assay was performed by (b) (4) for clinical lots. For this BLA, the assay was transferred from (b) (4). Two SOPs (QM4920 and PDR-ATM-AHX.0001) and their corresponding validation reports (KCM205-0416-ANA and TTP-AHX-M0004MT) by (b) (4) were submitted. Do you think the (b) (4) assay has been adequately validated?

Response: It is this reviewer's opinion that the sponsor has made a good attempt to validate the (b) (4) assay, however, there are a few questions about the assay that still need to be addressed particularly if the sponsor intends to use this test for lot release. If the sponsor intends to use this test for lot release, a biostatistician should review the validation data as well.

This product is a human immune globulin manufactured using plasma derived from donors (b) (4) IgG binding antibodies using an (b) (4) test. [The (b) (4) method was not described in any of the documents I received for review.] Manufactured lots of ADMA IGIV, human are then tested for (b) (4) using a (b) (4) assay with an (b) (4) endpoint performed by a contractor, (b) (4). The method was developed and validated by (b) (4) [Validation of the (b) (4) assay is in report KCM2015-0416-ANA]. The method was then transferred to the (b) (4) using a qualification study conducted in 2018 [TTP-AHX-M0004] to demonstrate comparability of the assays performed at both sites [i.e. system suitability and precision testing by (b) (4) analysts.]

A similar product, (b) (4), was manufactured by (b) (4) following licensure of product tested in human clinical trials (b) (4)

For this product, individual donors were screened for high levels of (b) (4) using a (b) (4) method; the IGIV product manufactured from their plasma was similarly tested for (b) (4) using the (b) (4) assay (b) (4) also conducted studies to

demonstrate that the product could be used to treat (b) (4) infected infants with underlying cardiac and lung disease, however these clinical trials were not successful. Following the licensure of a (b) (4) (b) (4) withdrew (b) (4) from the market without prejudice.

ADMA has attempted to fill the gap created by the absence of (b) (4) by manufacturing IGIV human (b) (4) IgG antibodies for the (b) (4) in patients with PIDD. Their efforts so far are summarized below:

- ❖ ADMA has not conducted any clinical studies to demonstrate that their product **prevents** serious (b) (4) lower respiratory tract infection in subjects with PIDD or at high risk for serious (b) (4)
- ❖ ADMA has not conducted any clinical studies to demonstrate that this product is effective in **treating** (b) (4) lower respiratory tract disease in subjects with PIDD.
- ❖ ADMA has not conducted any clinical trials using ADMA lots to show that the dose administered is associated with serum levels of (b) (4) that are at or above the level associated with protection against lower respiratory tract disease due to (b) (4) [as reported in the (b) (4) clinical trials and (b) (4) package insert].
- ❖ ADMA has not demonstrated that they are able to consistently manufacture product with (b) (4) at or above the mean concentration seen in archived lots of (b) (4) when ADMA lots and (b) (4) lots are tested (b) (4) in the same (b) (4) assay [see my consult review from 2016].
- ❖ The potency of (b) (4) in some ADMA IGIV lots falls below the mean concentration of (b) (4) measured in (b) (4) lots.

RPM Yu Do provided the following documents by e-mail on 15 February 2019:

- ❖ Letter to ADMA summarizing the June 27, 2016 meeting with CBER
- ❖ STN 125590 Section 3.2.P.5 Control of the Drug Product
Subsection 2 Analytical Procedures
2.4 (b) (4) [QM4920 and PDR ATM AHX.0001] [7 pages]
- ❖ STN 125590 Section 3.2.P.5 Control of Drug Product
Subsection 3 Validation of Analytical Procedures
3.4 (b) (4) Assay [4 pages]
- ❖ PDR ATM AHX-0001 (b) (4) Assay for (b) (4) Version 2.0 dated 4SEPT2018 Contract Lab (b) (4) [35 pages] SOP for this method.
- ❖ Document QM 4920.01 (b) (4) Assay for (b) (4) July 2015
- ❖ (b) (4) Validation of Method QM4920 (b) (4) /July 2015
- ❖ Method Transfer and Assay Control Sample [ACS] Qualification of a (b) (4) assay for (b) (4) Protocol TTP-AHX-M0004, Method Transfer, April 23, 2018

Review strategy: The focus of this review was on the (b) (4) method, Version 2.0, described in SOP PDR ATM AHX-0001 dated 4SEPT2018 since this was the latest version of the (b) (4) method submitted to the BLA. I briefly reviewed the Validation Report [KCM2015-0416-ANA] and the Method Transfer Qualification Report [TTP-AHX-M0004]. I provide comments on mainly on the assay method, with a summary of the validation studies and qualification report. Please have a biostatistician look at the data in the Validation Report and Method Transfer Qualification Report if this test will be used for product release.

(b) (4) **Method QM 4920 Version 2.0:** Briefly, the (b) (4) assay was developed by (b) (4) 48017.CD]. The method is similar to that described by (b) (4) test for (b) (4) based on an (b) (4) and modified as described by (b) (4).

The (b) (4) assay was then transferred to (b) (4) and optimized [PDR-ATM-AHX.0001]. The Reference Standard for the new validated (b) (4) assay is RI-002 Lot (b) (4). The Reference Standards used during testing at (b) (4) were RI-001 lot (b) (4) [tested (b) (4) with (b) (4) lots] and RI-001 Lot (b) (4) tested side-by-side with other RI clinical lots but **not** tested side-by-side with (b) (4) lots.

The validated (b) (4) assay provides quantitative results and reports potency as the (b) (4) in µg/mL or as a relative potency [relative to the performance of the Reference Standard in the same test], rather than a (b) (4). The (b) (4) for the test sample is compared to the (b) (4) for the Reference Standard and, if parallel, the ratio of (b) (4) values are calculated to yield a % relative potency. The proposed release potency on the Batch analysis reports describes (b) (4) the relative potency as (b) (4) of the Reference Standard.

The assay method: (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

System Suitability checks appear appropriate for a virus (b) (4) assay with the following exceptions:

1. The vendor did not provide the (b) (4) of the (b) (4) stock nor the amount of (b) (4) used for the (b) (4) assay. Ideally, the vendor should evaluate the robustness of the assay to variations in the (b) (4) input. It is also good practice to verify the amount of (b) (4) in the (b) (4) on a (b) (4) on the day of the assay to verify that the amount of (b) (4) added was appropriate.
2. Additionally, it should be shown that the signal in (b) (4) [in the absence of the test sample] is substantially above the signal seen in (b) (4) [for example, the mean signal in (b) (4) is at least (b) (4) above the mean signal seen in (b) (4)]
3. Please state the acceptable range for the mean (b) (4) signal in the ACS control (b) (4). The robustness testing suggested under item 1 above [varying the (b) (4) input] should also help to set the minimum expected (b) (4) values for the lower asymptote for the ACS for a valid test.

Methods documentation templates were attached as appendices to the SOP and were reviewed.

(b) (4) template: reviewed and no comments at this time.

(b) (4) template: reviewed.

(b) (4) Template: notes that (b) (4) should not be used beyond (b) (4).

(b) (4) Template: reviewed.

(b) (4) Template: reviewed

(b) (4) Template: reviewed

-Assay Template: reviewed;

-See page 29/33, (b) (4) stock should state the potency of the (b) (4) per mL and the expected potency of (b) (4) stock after it is diluted (b) (4).

-The sponsor should perform a (b) (4) to determine the potency of the stock and diluted (b) (4) used in each assay

Assay Validation: described under 3.2.P.5 Control of Drug Product Validation of Analytical Procedures for RI-002 ADMA Biologics, Subsection 3.4 (b) (4) assay. In this section ADMA notes that two versions of the (b) (4) assay were validated:

- 1) the (b) (4) method 48017.CD, Validation 5251, RPT 09-002 and
- 2 (b) (4) Method QM4920, Validation Report [KCM205-0416-ANA] and qualification of Method transfer [TTP-AHX-M0004MT].

ADMA states that they have shown equivalence of the (b) (4) methods using (b) (4) assay results as well as (b) (4) potency values obtained from each assay method and using results generated from testing of the RI-002 reference material lots and the Analytical Control Sample. The results of these analyses were summarized in TEC-15-004-RPT. [N.B. Reviewed in consult memo dated 18MAY2016]

A comparison of the main features of each assay method and the results of the validation and qualification studies are summarized in Table 1 below.

1 page determined to be not releasable: (b)(4)

(b) (4)

Reviewer's summary: The (b) (4) assay performed by (b) (4) appears to be similar to that developed by (b) (4), and modified and used by (b) (4), for the development and testing of (b) (4) licensed previously by (b) (4).

However, it is unclear from the documents reviewed if (b) (4) has sufficient checks in place to assure that the assay is valid in all respects. For example, with regards (b) (4) controls and the (b) (4) there are a few comments to address:

1. Does the test include (b) (4) [no (b) (4) or test sample] as well as (b) (4) but no (b) (4) /test sample]?
2. Does the test determine the mean signal in (b) (4) [in the absence of test sample] is substantially above the mean signal obtained in (b) (4) as evidence of (b) (4) For example, is the mean signal in (b) (4) at least (b) (4) above the mean signal in (b) (4)
3. If the maximum signal for the (b) (4) is obtained using data generated from (b) (4) containing (b) (4) concentrations of IgG using data obtained from (b) (4) containing the (b) (4) Assay Control Sample, please state the acceptable minimum mean (b) (4) signal for the ACS control infected with (b) (4) and indicate how this value was determined.
4. Please provide the (b) (4) of the (b) (4) stock used as the (b) (4) for the (b) (4) assay. Please also state the (b) (4) added per (b) (4) following dilution of the stock (b) (4).
5. Evaluate the robustness of the assay to variations in (b) (4) input over a broad range. This testing should also help to set the minimum expected (b) (4) value for the asymptote at (b) (4) concentrations of IgG.
6. For each (b) (4) assay run, verify that the amount of (b) (4) in the (b) (4) was acceptable by performing a (b) (4) of the diluted (b) (4) on a susceptible (b) (4) [such as (b) (4) on the day of the assay to verify that the amount of (b) (4) added was appropriate.

With regards to the (b) (4) validation study, (b) (4) validated the (b) (4) assay that was developed in their laboratory; subsequently, (b) (4) executed a very similar (b) (4) and validated a subset of the testing in their laboratory. A few comments on the validation studies include the following:

1. Please have a biostatistician review the data from the validation and qualification reports if the sponsor will use this (b) (4) test to release their product.
2. In the (b) (4) labs, specificity was shown by varying the (b) (4) to include either (b) (4) . Other labs have demonstrated specificity of (b) (4) assays by (b) (4)

Since it is difficult to identify (b) (4)

assay. Alternatively, please justify the use of Lot (b) (4) as the control for the assay.

3. For the (b) (4) assay, please state the linear range for the test sample [in ug/mL] over which the concentration of (b) (4) can be determined with acceptable precision and accuracy.
4. Similarly, for the lower limit of quantitation, [LLOQ], please state the lowest concentration of test sample that can be measure (b) (4) with acceptable accuracy and precision.

With regards to the Method Transfer Qualification Report: This evaluation included a system suitability check using two test samples, the ACS and the Reference Standard as well tests to evaluate inter-assay precision/repeatability and intra-assay precision by (b) (4) analysts testing (b) (4) replicates in each of (b) (4) tests. For the most part, the testing was successful. However, the Method Transfer was noted to have (b) (4) system suitability failures [summarized on table 3 of the Qualification Report TTP-AHX-M004].

In summary, it is this reviewer's opinion that the sponsor has made a good attempt to validate the (b) (4) assay however, there are a few questions about the assay that still need to be addressed particularly if the sponsor intends to use this test for lot release. If the sponsor intends to use this test for lot release, a biostatistician should review the validation data as well.