CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s024

PRODUCT QUALITY REVIEW(S)

Memorandum of Review
(Environmental Assessment)

Date: September 18, 2017

To: File for STN: 125514 SUPPL-24 (SD #1094)

From: Mark Paciga, Ph.D., Product Quality Reviewer, DBRR1/OBP

Through: Jennifer Swisher, Ph.D., Team Leader, DBRR1/OBP

Subject: 125514/SUPPL-24 Immunogenicity assay updates, environmental assessment, and acceptability of drug product used in the clinical study

Applicant: Merck Sharp & Dohme Corp.

Product: Keytruda® (pembrolizumab)

Indication: Treatment of patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (b) (4)

Received: March 22, 2017
Action Due Date: September 22, 2017

Review Recommendation: The claim of categorical exclusion from the environmental assessment is accepted. The qualification of new negative and positive controls for the screening/confirmatory assay to detect anti-drug-antibodies is acceptable, as well as the validation of the new, more sensitive assay to detect neutralizing antibodies against pembrolizumab. Appropriate pembrolizumab drug product supplies were used in these studies.

1. FDA Regional Information
1.12. Other Correspondence
1.12.14. Environmental Analysis

Merck requests a categorical exclusion from the preparation of an environmental assessment pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, as provided in 21 CFR 25.31(c) for an action on a supplemental Biologics License Application. Under this regulation, exclusion is provided if the substance comprises naturally occurring elements but has a sequence different from that of a naturally occurring substance, and when approval of the application does not significantly alter the concentration or

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

distribution of the substance, its metabolites or degradation products in the environment.

Reviewer comment: *There is no information in this supplement indicating that any additional environmental information is warranted, and the claim of categorical exemption is accepted.*

Clinical Supplies Dispensed to Patients

In the Phase Ib study in patients with advanced solid tumors (Protocol KEYNOTE-012) the clinical material used was (b) (4) MK-3475, 50 mg/vial. In the Phase II study in patients with recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma (Protocol KEYNOTE-059) the clinical material used was (b) (4) MK-3475, 100 mg/vial.

Reviewer comment: *Pembrolizumab used for these trials was sourced from commercial material.*

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Reviewer comment: *There are no new immunogenicity data presented in this efficacy supplement for the indications studied. However, the updates to the screening/confirmatory assay for anti-pembrolizumab antibodies and the assay to detect neutralizing antibodies are reviewed below and are found to be acceptable.*

Reports (b) (4) 201 Version 1.01 Validation Report Addenda 4 and 5

New negative control (addendum 5) and positive control (addendum 4) samples were created and qualified for this previously validated MSD-based ADA assay for pembrolizumab. Previously, the negative control was created from a pool of human sera from (b) (4) individuals purchased from (b) (4) (lot (b) (4)). This time, (b) (4) separate lots were ordered from the same vendor as the original pool with the intent to create a much larger negative control pool for future use. Prior to their combination, the aliquots of all (b) (4) lots were analyzed for comparability to the original NC pool. All pools except for one (NC pool 7) generated relative light unit (RLU) values and signal-to-noise ratios (SNR) that were within (b) (4)% of the original pool. Because NC pool 7 produced values that were 18% higher than the current NC pool (p-value < 0.05), it was excluded.

New low- and high- positive control samples (LPC and HPC) were created using this new NC pool as a matrix at levels defined for this method (7 ng/mL and 500 ng/mL, respectively.) They were not found to be comparable and were re-prepared, as the error was found to be most likely due to a measurement error of the samples. To this end, a new preparation was created at the same target concentrations and when tested, passed all acceptance criteria. These new NC, LPC, and HPC will be banked and used for the assay.

Report (b) (4) 202 Version 2.00 Validation Report ((b) (4) Project Code (b) (4))

This report details the validation of a new assay to detect neutralizing antibodies against pembrolizumab. The previous assay assessed the neutralizing capacity of samples (b) (4)

(b) (4)

(b) (4)

In the new the assay, patient samples

The overall results of the validation are provided in the table below.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Bioanalytical Method Validation Summary
Anti-MK-3475 Neutralizing Antibodies in Human Serum

(b) (4) **Project Code**	(b) (4)		
(b) (4) **Method ID**	(b) (4) 202 Version 2.00		
Analyte	Anti-MK-3475 neutralizing antibodies		
MRD	No MRD		
Matrix	Human Serum		
Method Description	Electrochemiluminescent		
Sample Volume (µL)	50-µL aliquot		
Sample Storage Temperature	-80 °C ± 10 °C		
Assay Cut Point	0.900 signal-to-noise ratio		
Mean Sensitivity	15.6 ng/mL		
PC Characteristics	CDR-enriched purified rabbit polyclonal anti-MK-3475 Ab added to a negative control pool		
PC Concentrations	28.8 and 500 ng/mL		
Control Intra-assay Statistics (%)	Level Low PC High PC	Conc. (ng/mL) 28.8 500	Precision (S/N) 5.52% 5.13%
Control Inter-assay Statistics (%)	Level NC Low PC High PC	Conc. (ng/mL) N/A 28.8 500	Precision (S/N) 4.35% 4.91% 14.9%
Thawed Matrix Stability (hours)	24 hours at room temperature		
Freeze/thaw Stability (cycles)	Six cycles thawed at room temperature		
Drug Tolerance	Results are summarized in Table 15C		
Matrix Interference and Selectivity (Healthy Matrix)	Acceptable with ten out of ten sample lots meeting the acceptance criteria		
Matrix Interference and Selectivity (Disease State Matrix)	Acceptable in non-small cell lung cancer, melanoma, and solid tumor with five out of five sample lots meeting the acceptance criteria. Acceptable in hematologic malignancy with thirteen out of fifteen sample lots meeting the acceptance criteria. Unacceptable in renal cell carcinoma with twelve out of fifteen sample lots meeting the acceptance criteria.		
Hook Effect	No apparent hook effect observed at ADA concentrations up to 100,000 ng/mL		
Hemolysis	No apparent effect from hemolysis on the detection of anti-MK-3475 neutralizing antibodies		
Lipemia	No apparent effect from lipemia on the detection of anti-MK-3475 neutralizing antibodies		
Concomitant Analyte Interference	No apparent effect from the presence of Ipilimumab, Sylatron, PF-05082566, MK-4166, MK-1248, Avastin, orMK-4280 on the detection of anti-MK-3475 neutralizing antibodies		

Reviewer comments: *The new assay has improved sensitivity (15.6 ng/mL vs. 685 ng/mL for the previous NAb assay) and no minimum dilution is required. The precision of the assay is also the same as or better than the previous assay.*

\Cut Point

The assay cut point was determined using the analysis of 50 individual drug-naïve human serum sample lots using three independent assays performed by two analysts over two days. Two samples were excluded due to unacceptable variability (CV> (b)(4)%) and two samples were excluded as outliers, leaving 146 sample values for the calculation. The cut point, determined in order to yield a false positive rate of 1%, was determined to be at a signal to noise ratio of 0.900. Samples at or above the cut point are reported as positive. Population-specific cut points may be determined for this assay in the future.

Sensitivity

The positive control is the same as is used for the screening/confirmatory assay, described above. Six independent serial dilution curves were generated from the positive control at a starting concentration of 500 ng/mL and tested by two analysts at 2-, 4-, 8-, 16-, 32-, and 64-fold dilutions. Assay sensitivity was reported as the average interpolated concentration of the positive control at the cut point using a linear regression between the two points on the curve that bracket the cut point. The sensitivity of the assay was calculated as 15.6 ng/mL and used to establish the new low positive control concentration for this assay by multiplying it by 3.365 x SD, resulting in a new low PC concentration of 28.8 ng/mL.

Matrix Interference and Selectivity.

Matrix interference and selectivity in disease state serum was tested using serum samples from five individuals from each of the following disease populations: non-small cell lung cancer, melanoma, solid tumor (gastric cancer and head and neck cancer), hematologic malignancy, and renal cell carcinoma at blank (SP) and anti-drug antibody concentrations (SPFs) at the low positive control level (LPC, 28.8 ng/mL) and high positive control level (HPC, 500 ng/mL). The matrix interference and selectivity data at the blank and high-level PC concentrations met all acceptance criteria for all tested disease states. However, the selectivity results for samples tested using the low-level PC concentration were unacceptable for two out of five samples prepared in hematologic malignancy serum and two out of five samples prepared in renal cell carcinoma serum, as the LPC did not measure above the cut point. Additional samples were prepared in hematologic malignancy and renal cell carcinoma from ten individuals with the negative control and with anti-drug antibody concentrations at the low and high positive control levels (28.8 and 500 ng/mL) and met the acceptance criteria for all ten hematologic malignancy sera and nine out of ten renal cell carcinoma sera. The selectivity acceptance criteria in each matrix pool are (b)(4)

Reviewer comment: *This level of sensitivity, selectivity, and lack of interference is acceptable in all disease population sera. The sponsor is considering* (b)(4) *which would be a reasonable potential approach to use in analyzing samples from this disease population.*

Precision

Intra-assay precision was measured using six independent measurements each of LPC and HPC and the %CV was found to be 5.12 for the LPC and 5.53 for the HPC. Inter-assay precision was calculated from the control values from the first six validation runs containing positive controls performed by multiple analysts. Six other validation runs were excluded due to variability in the negative control responses, which at times were below the cut point, suggesting a positive result. The variability was diminished by restriction of the wells used to the first eight columns of the (b) (4), and the acceptance criteria of the method were (b) (4).

Stability

LPC and HPC were subjected to six freeze/thaw cycles (at -80 °C ± 10 °C and thawed at room temperature) prior to their use in the assay and the %CV were 1.50 and 5.34, respectively, demonstrating the stability of the low and high ADA controls for use in the assay after multiple freeze/thaw cycles.

Interference from Hemolysis, Lipemia, or Concomitant Medications (biologics)

NC, LPC, and HPC samples were prepared respectively in five individual hemolyzed human serum lots (~1000 mg/dL), five lipemic human serum lots (>300 mg/dL triglycerides), or in the presence of eight different biologics at the following concentration: 50, 150, and 450 µg/mL ipilimumab, 1.5, 4.4, and 13.2 ng/mL PEG-IFNα 2b, 60, 200, and 600 µg/mL PF-05082566, 30, 100, and 300 µg/mL MK-4166, 30, 100, and 300 µg/mL MK-1248, 130, 400, and 1200 µg/mL avastin, 100, 300, and 900 µg/mL MK-4280, and 30, 100, and 300 µg/mL MK-3475 (pembrolizumab).

In the hemolyzed and lipemic human sera, no significant effect of the serum matrix was found in either group and CVs were within acceptable ranges. In the presence of the above-mentioned concentrations of biologics, no inhibitory effect was shown on the detection of anti-pembrolizumab neutralizing antibodies by any compound except MK-3475 (pembrolizumab itself) in a manner consistent with the drug tolerance (reviewed below.)

Drug Tolerance

To evaluate the levels of drug present in patient samples that would be inhibitory in this assay, six levels of the positive control (15.6 ng/mL to 500 ng/mL) and a blank were mixed with six levels of drug (blank and 31.3 µg/mL to 500 µg/mL) and pre-incubated at room temperature for at least one hour prior to analysis. The average drug concentration corresponding to the assay cut point for each anti-drug antibody concentration was considered to be the drug tolerance level. Drug tolerance at 125 ng/mL anti-MK-3475 ADA was calculated as 5.92 µg/mL drug, at 250 ng/mL anti-MK-3475 ADA as 45.5 µg/mL drug, and at 500 ng/mL anti-MK-3475 ADA as 68.9 µg/mL drug.

Reviewer comments: *In summary, the qualification of the new lots of negative and positive controls for the screening/confirmatory assay for anti-pembrolizumab antibodies is acceptable. The new assay for the detection of neutralizing antibodies against pembrolizumab was assessed for sensitivity, specificity, precision, robustness, accuracy and precision of titration, drug tolerance, and stability of QC samples at room temperature and following freeze-thaw. All validation criteria were met, confirming the ability of the assay to sensitively detect neutralizing antibody responses against pembrolizumab.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK PACIGA
09/22/2017

JENNIFER F SWISHER
09/22/2017