Summary Basis for Regulatory Action

From: Meihong Liu, Chair of the Review Committee

BLA STN#: 125684/0

Applicant Name: Millipore (UK) Limited

Date of Submission: May 24, 2018

MDUFA Goal Date: June 1, 2019

Proprietary Name: Blood Grouping Reagent, Anti-k (Monoclonal) (IgG) (For Further Manufacturing Use)

Established Name: Not Applicable

Intended Use:

"The product is a monoclonal IgG Anti-k reagent for further manufacturing use (FFMU). Its intended use is as a standardized raw material for the manufacture of finished Anti-k blood typing reagents/devices for *in vitro* use. This FFMU reacts with the k antigen."

Recommended Action:

The Review Committee recommends approval of this product.

Review Office Signatory Authority: Nicole Verdun, MD, Director, Office of Blood Research and Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
Clinical Review(s) and Non-clinical data	Not Applicable for this submission
Statistical Review	Not applicable for this submission
CMC Reviews • *CMC (Product Office)* • Bioburden (*OCBQ/DBSQC*) • *Facility Review* (*OCBQ/DMPQ*)	Meihong Liu, OBRR/DBCD/DRB Kimberly Bigler, OBRR/DBCD/DRB Elias Paz Alonzo, OBRR/DBCD/DRB Review Memo- December 3, 2018 Review Memo-August 6, 2018 Approval Memo-March 26, 2019 Simleen Kaur, OCBQ/DBSQC/LMIVTS Review Memo (Approval), September 6, 2018 Ashley Burn, OCBQ/DMPQ/MRBII Priscilla M. Pastrana, OCBQ/DMPQ/MRBII Inspection Waiver memo- July 17, 2018 Review Memo (Approval)-November 29, 2018

Labeling Review(s) • *Product Office*	Meihong Liu, OBRR/DBCD/DRB Kimberly Bigler, OBRR/DBCD/DRB Elias Paz Alonzo, OBRR/DBCD/DRB Review Memo- December 3, 2018 Review Memo-August 6, 2018 Approval Memo-March 26, 2019
Lot Release Protocols/Testing Plans	Not applicable for this submission
Establishment Inspection Report	Not applicable for this submission
Bioresearch Monitoring Review	Not applicable for this submission

1. Introduction

Millipore (UK) Ltd. (Millipore), located in Livingston, United Kingdom, submitted this Biologics License Application (BLA) requesting approval of Blood Grouping Reagent, Anti-k (Monoclonal) (IgG) (For Further Manufacturing Use) [FFMU] manufactured from the cell line P3A118OL67. Millipore manufactures this FFMU product and supplies the product to (b) (4) under a shared manufacturing arrangement for the manufacture of the final *In Vitro* Product (IVP), Blood Grouping Reagent, (b) (4) submitted the original BLA (b) (4) for the final container Blood Grouping Reagent, Anti-k as a companion submission. The review of the companion submission is documented in a separate memo.

2. Background

Chronology:

CBER received this original submission on June 27, 2018. The submission was filed on July 10, 2018. CBER received four amendments dated November 13, 2018, November

19, 2018, November 29, 2018, and March 14, 2019 from Millipore in response to three information requests.

Meetings with FDA:
Millipore did not request any pre-submission meetings for this product.

Description of the Device:
The main component of Blood Grouping Reagent, Anti-k (Monoclonal) (IgG)(FFMU), is a monoclonal antibody specific to the human red blood cell antigen k (cellano). It is produced from cell culture supernatants of (b) (4) cell line P3A118OL67. The anti-k FFMU product is non-sterile, microbiologically controlled, and contains 0.1% (w/v) sodium azide as preservative. The final containers and closures include:

- 1L Polypropylene (b) (4) Containers/1L Polypropylene (b) (4) cap
- 10L Polypropylene (b) (4) Containers/10L Polypropylene (b) (4) cap
- 125mL Polypropylene (b) (4) Containers/125mL Polypropylene (b) (4) cap

This FFMU product will be further manufactured into final container Blood Grouping Reagent, Anti-k, which will be used for testing red blood cells for the presence or absence of the k antigen.

Marketing History:
Millipore (UK) Ltd has been manufacturing this FFMU product for sale in European and Rest-of-World (ROW) markets for over seven years.

3. Chemistry Manufacturing and Controls (CMC)

The application was submitted in accordance with the recommendations in FDA's Guidance for Industry: "*Content and Format of Chemistry, Manufacturing, and Controls Information and Establishment Description Information for a Biological in-Vitro Diagnostic Product*". All manufacturing is carried out in a controlled environment.

a. Manufacturing Summary

(b) (4) manufactures the anti-k supernatant from the cell line P3A118OL67. They are audited every (b) (4) years by Millipore as part of Millipore supplier management program. Per the quality agreement with Millipore, (b) (4) ensures that the products conform to all purchase specifications.
(b) (4) is a multi-product production facility. A campaign approach is used for the following critical processes: manipulation of one cell line at a time under the (b) (4) in tissue culture and (b) (4) and filling of one product at a time in the production unit.

I. Raw Materials (b) (4)

Master Cell Bank (MCB) and Working Cell Bank (WCB):

(b) (4)

II. (b) (4) Manufacturing Process Flow and in-Process Controls

(b) (4)

(b) (4)

(b) (4)

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Batch Release (b) (4) lot):

QA reviews the Batch Manufacturing Records, and if everything is acceptable, the product is released and dispatched to Millipore (UK) Ltd.

QC testing and specifications:

The (b) (4) product is controlled against another validated batch sample stored at (b) (4)

The specifications listed in the table below are copied from the Certificate of Analysis.

(b) (4)	

Test method	(b) (4)

(b) (4) provided a summary of the testing results for (b) (4) supernatant lots: (b) (4) and (b) (4). Lots (b) (4) were manufactured using the (b) (4) supernatant batch (b) (4). The testing results meet acceptance criteria.

(b) (4) Batch Manufacturing Records (BMR)

The batch record for the finished (b) (4) tissue culture supernatant lot (b) (4), volume (b) (4), manufacture date (b) (4), expiration date (b) (4) was included in the submission. The production period was from (b) (4). The batch record for Lot (b) (4) is acceptable.

III. Manufacturing and Controls by Millipore (UK) Ltd

The multi-product manufacturing site, located at Fleming Road, Kirkton Campus, Livingston, EH54 7BN, United Kingdom, is designed and built specifically for the manufacture of in vitro diagnostic reagents within environmentally controlled areas with restricted personnel access. The campaign manufacturing approach is used for critical processes that include the manipulation of one cell line at a time under the (b) (4) in tissue culture, formulation of FFMU in discrete (b) (4) in downstream processing (DSP) and (b) (4) and filling of one product at a time in the (b) (4) clean room.

The (b) (4) used in downstream processing during the formulation of the product are cleaned by a validated method. The QC laboratory utilizes disposable consumables. During (b) (4) and labelling, the clean room is (b) (4) work stations (b) (4) and licensed FFMU processing (b) (4) and filling) only takes place within area (b) (4) Only one process will be carried out within each work station at any time but concurrent processing of other batches in each work station can be carried out. Each work station has its own holding area and is (b) (4)

(b) (4) from the other work stations. The areas are defined by activity; the access, movement and general operation of the clean room is strictly controlled.

1). Manufacturing Methods and Process flow

Millipore uses the previously validated systems for the anti-k FFMU manufacturing. The anti-k FFMU manufacturing processes include following steps:

- Receipt testing and pre-purchasing testing to evaluate the critical raw material (b) (4) anti-k supernatant per the specifications.
- (b) (4)
- QA review and QC release testing: (b) (4) QC release testing. QA performs a review of batch manufacturing records and then releases the FFMU product.
- (b) (4) .

2). Quality Control testing method and specifications

The methods used to characterize this product are (b) (4) These methods are routinely used during the manufacture of the product at (b) (4) Quality Control testing.

(b) (4)

Millipore provided the QC release testing results for the three FFMU conformance batches: (b) (4) .

All three lots met the acceptance criteria.

3). Reference Standard Panel

Millipore (UK) Ltd assigns the primary reference standard as part of the development process for the product. The primary reference standard is stored at (b) (4) The current primary reference standard for Anti-k, P3A118OL67 is (b) (4) .

The in-house reference standards are tested against the primary reference standard or the current in-house reference according to the SOP. A range of (b) (4) of the proposed reference are tested for (b) (4) by a minimum of (b) (4) experienced technologists. The acceptable (b) (4) is selected following testing against the current in-house reference standard. The current working reference standard is (b) (4) .

4). Batch Manufacturing Records (BMR)

The BMR for the lot (b) (4) , manufacture date (b) (4) and expiration date (b) (4) was reviewed. The lot was manufactured using (b) (4) lot (b) (4) (Expiry date (b) (4) The BMR includes the manufacturing procedures and in-process testing and QC testing results. The BMR indicates that this lot was manufactured following the validated manufacturing procedures and methods. The testing results met acceptance criteria.

b. Bioburden (b) (4)

The bioburden level is monitored using the (b) (4) . The bioburden test method was qualified in accordance with (b) (4)

Millipore performed an (b) (4) and demonstrated that the proposed sodium azide concentration (0.1%) is effective and adequate in preventing microbial growth in accordance with (b) (4)

c. Stability Studies and Shipping studies

(b) (4) performed studies to validate the (b) (4) shelf life of the (b) (4) anti-k supernatant stored at (b) (4) after (b) (4) In addition, (b) (4) performed accelerated stability, the effect of (b) (4) and shipping studies on the anti-k supernatant. All test results are acceptable.

Millipore provided stability summary reports for the three FFMU conformance lots in the submission. The results demonstrate that all three batches are stable when stored at (b) (4) for (b) (4). Anti-k (Monoclonal) (IgG) (FFMU) has been assigned a shelf life of (b) (4) when stored at (b) (4) Millipore also performed simulated transport stability and shipping validation. All test results are acceptable.

d. CBER Lot Release

The FFMU will not be subject to CBER lot release.

c. Facilities Review/Inspection (DMPQ)

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of the Monoclonal Antibody Anti-k [(cell line P3A118OL67) (b) (4) Monoclonal (IgG) Product Code: FA] FFMU are listed in the table below.

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Justification/Results
Dowstream Processing, (b) (4) *and Filling* *Serological and Biochemical QC Release Testing* Millipore (UK) Limited Kirkton Campus	3002638287	6216074503	Waiver	Team Bio February 19-26, 2018 VAI

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Justification/Results
2 Fleming Road Livingston, UK				

Team Biologics performed a surveillance inspection of the Millipore (UK) Limited facility from February 19-26, 2018. All 483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

4. Environmental assessment (DMPQ)

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

5. Container/ Closure

The Monoclonal Antibody Anti-k [(cell line P3A118OL67) (b) (4) Monoclonal (IgG) Product Code: FA] FFMU is filled into 125 mL, 1 L, and 10 L containers with caps made of polypropylene manufactured by (b) (4) . The qualifications submitted in the BLA were performed by Millipore for containers filled at the Livingston, United Kingdom facility and included (b) (4) ; all the acceptance criteria were met.

6. Advisory Committee Meeting

Not applicable for this submission.

7. Other Relevant Regulatory Issues

There are no relevant regulatory issues for this submission. The review committee members reviewed their specific sections of the BLA and resolved issues through information requests with Millipore. The review team sought the expertise of their respective management, when warranted. No internal or external disagreements were communicated to the regulatory project manager or chairperson. All reviewers recommended approval of Blood Grouping Reagent, Anti-k (Monoclonal) (IgG) (FFMU).

8. Labeling

Millipore submitted a sample final container label for the anti-k FFMU; the label was reviewed and determined to be acceptable.

9. Recommendations and Risk/ Benefit Assessment

a. Recommended Regulatory Action

The review committee members, representing the necessary review disciplines recommend approval. These were independent conclusions based on content of the BLA, issues satisfactorily resolved during the review cycle, and concurred by their respective management. No internal or external disagreements were brought to the attention of the chairperson.

b. Risk/ Benefit Assessment

Licensing this Blood Grouping Reagent, Anti-k (Monoclonal) (IgG) (FFMU) will provide a new cell line that can be used to manufacture Anti-k BGR.

The validated manufacturing process reduces the risks associated with licensing this new FFMU product. In addition, the final product, (b) (4) will be subject to post market surveillance (medical device reporting) which will identify adverse events associated with this product.

c. Recommendation for Post-Marketing Activities

There are no postmarketing commitments associated with this submission.