# Summary Basis for Regulatory Action

**From:** Meihong Liu, Chair of the Review Committee

**BLA STN#:** 125715/0 and 125716/0

**Applicant Name:** Millipore (UK) Limited

**Date of Submission:** August 26, 2019

**MDUFA Goal Date:** June 28, 2020

**Proprietary Name:**
Blood Grouping Reagent, Anti-Le$^{a}$ (Murine Monoclonal) (IgM) (For Further Manufacturing Use),
Blood Grouping Reagent, Anti-Le$^{b}$ (Murine Monoclonal) (IgM) (For Further Manufacturing Use)

**Established Name: Not Applicable**

**Intended Use:**
Intended for further manufacturing of Blood Grouping Reagents Anti-Le$^{a}$ and Anti-Le$^{b}$ for in vitro use.

**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<br>• *CMC (Product Office)*<br>• Bioburden (*OCBQ/DBSQC*)<br>• *Facility Review* (*OCBQ/DMPQ*) | Meihong Liu, OBRR/DBCD/DRB<br>Review Memo- November 22, 2019<br>Approval Memo-April 28, 2020<br>Hyesuk Kong, OCBQ/DBSQC/LMIVTS<br>Review Memo (Approval), January 30, 2020<br>Timothy Martin, OCBQ/DMPQ/BII<br>Priscilla M. Pastrana, OCBQ/DMPQ/BII<br>Inspection Waiver memo- May 15, 2020<br>Review Memo (Approval)- May 13, 2020 |
| Labeling Review(s)<br>• *Product Office* | Meihong Liu, OBRR/DBCD/DRB<br>Review Memo (Approval)-April 28, 2020 |
| 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 two original Biologics License Applications (BLAs) requesting approval to manufacture and distribute Blood Grouping Reagent, Anti-Le$^a$ (Murine Monoclonal) (IgM) (For Further Manufacturing Use) [FFMU] manufactured from the cell line (b) (4) and Blood Grouping Reagent, Anti-Le$^b$ (Murine Monoclonal) (IgM) (FFMU) manufactured from the cell line (b) (4). These products were previously manufactured by (b) (4) and the cell lines are being transferred to Millipore. Millipore will use an alternate method to manufacture of the Anti-Le$^a$ and Anti-Le$^b$ FFMU materials so as to (b) (4)

Millipore will supply the FFMU products to (b) (4), under a shared manufacturing arrangement. (b) (4) intends to use the FFMUs to manufacture Blood Grouping Reagent, Anti-Le$^a$ (Murine Monoclonal), (b) (4) and Blood Grouping Reagent, Anti-Le$^b$ (Murine Monoclonal), (b) (4) submitted companion Prior Approval Supplements (b) (4) for the transfer of the cell lines and the change in the manufacturing method of the Anti-Le$^a$ and Anti-Le$^b$ FFMU material. The review of the companion submissions is documented in a separate memo.

## 2. Background

*Meetings with FDA:*

Millipore did not request any pre-submission meetings for these products.

*Market History:*

Millipore does not have a marketing history for Anti-Le$^a$ (Murine Monoclonal) (Clone (b) (4) and Anti-Le$^b$ (Murine Monoclonal) (Clone (b) (4) FFMU products.

*Description of the Device:*

Blood Grouping Reagent, Anti-Le$^a$ (Murine Monoclonal) (IgM)(FFMU), and Blood Grouping Reagent, Anti-Le$^b$ (Murine Monoclonal) (IgM)(FFMU), are derived from cell culture supernatants of murine (b) (4) cell lines (b) (4) respectively.

These two FFMU products are non-sterile, microbiologically controlled, and contain (b) (4) as preservative. The final containers and closures include: (b) (4)

*Chronology:*
CBER received this original submission on August 29, 2019. The submission was filed on August 26, 2019. CBER received four amendments dated September 20, 2019, November 22, 2019, December 4, 2019 and May 19, 2020 from Millipore in response to four information requests.

## 3. Chemistry Manufacturing and Controls (CMC)

### a. Manufacturing Summary

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.

### I. Raw Materials

Master Cell Bank (MCB) and Working Cell Bank (WCB):
(b) (4) established the murine (b) (4) cell clone (b) (4) from (b) (4)

(b) (4) established the murine (b) (4) cell line (b) (4)

(b) (4)

(b) (4) vials of the cell lines (b) (4) to Millipore to establish cell banks. Millipore established the MCB using the cell lines transferred from (b) (4) and through validation of (b) (4) testing. The MCB was tested to be free of mycoplasma and (b) (4) different Mouse Antibody Production (MAP) viruses and confirmed as the immunoglobulin class IgM. The WCB was produced from (b) (4) of the MCB. The MCB and WCB vials are stored in the (b) (4) at the Livingston facility as well as at a different location as backup.

## II. Manufacturing and Controls by Millipore (UK) Ltd

The multi-product manufacturing site 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 (b) (4) under the laminar air flow hood in tissue culture, formulation of FFMU in (b) (4)

The preparation (b) (4) containers used in downstream processing during the formulation of the product are cleaned by a validated method. The Quality Control (QC)laboratory utilizes disposable consumables. The areas are defined by activity; the access, movement and general operation of the clean room is controlled by a SOP.

1). Manufacturing Summary

The following is the process flow for manufacture of the FFMU products:

- (b) (4)

- (b) (4)

2). QC test methods and specifications for Anti-Le[a] and Anti-Le[b] in final containers and specifications are listed in the table below:

| | Specifications | Test method |
|---|---|---|
| (b) (4) | (b) (4) | |

| | | |
|---|---|---|
| (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| IgM concentration by (b) (4) | Anti-Le$^a$: (b) (4)<br>Anti-Le$^b$: (b) (4) | (b) (4) |
| (b) (4) | Anti-Lea: (b) (4)<br>Anti-Leb: (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |

Millipore provided the QC release testing results for the three Anti-Le$^a$ FFMU conformance batches: (b) (4) and three Anti-Le$^b$ FFMU conformance batches: (b) (4)
All these lots met the acceptance criteria.

Millipore assigns the primary reference standard as part of the development process for the FFMU products. The current primary reference standards are lot (b) (4) of Anti-Le$^a$ and lot (b) (4) of Anti-Le$^b$. The primary reference standards are stored at (b) (4)

3). Batch Manufacturing Records (BMR)

The BMRs for Anti-Le$^a$ lot (b) (4), manufacture date (b) (4) and expiration date (b) (4) and Anti-Le$^b$ lot (b) (4), manufacture date (b) (4), and

expiration date (b) (4) were reviewed. The BMRs include the manufacturing procedures and in-process testing and QC testing results. The BMRs indicate that the lots were manufactured following the validated manufacturing procedures and methods. The testing results met acceptance criteria.

**b. (b) (4) Tests**

The (b) (4) level is monitored using the (b) (4) test and the (b) (4) test method was qualified in accordance with (b) (4) samples are collected (b) (4) is complete. Testing results from the three lots of Anti-Le[a] and anti-Le[b] FFMUs showed (b) (4) levels of (b) (4) which met the pre-determined acceptance criterion.

Millipore performed an (b) (4) and demonstrated that the proposed (b) (4) is effective in preventing microbial growth in accordance with (b) (4)

**c. Stability Studies and Shipping studies**

Millipore provided stability summary reports that include testing results of Anti-Le[a] and Anti-Le[b] FFMUs (three lots each). The products were tested for (b) (4) in parallel with the references using the (b) (4) The stability testing results met acceptance criteria. The results demonstrated that the three Anti-Le[a] lots were stable for (b) (4) respectively, and three Anti-Le[b] FFMU lots were stable for (b) (4). The Anti-Le[a] FFMU has been assigned a shelf life of (b) (4) when stored at (b) (4) and the Anti-Le[b] FFMU has been assigned a shelf life of (b) (4) when stored at (b) (4)

The FFMU products are shipped using previously qualified procedures with (b) (4) containers. Per the quality agreement between (b) (4) and Millipore, (b) (4) is responsible for transportation requirements for product shipment from the

Millipore facility to (b) (4). Each shipment is temperature controlled and contains a (b) (4) tracker as a control measure.

### d. CBER Lot Release

These FFMU products are for further manufacturing use and therefore will not be subject to CBER lot release.

### c. Facilities Review/Inspection (DMPQ)

Facility information and data provided in the BLA bundle were reviewed by CBER and found sufficient and acceptable. The facilities involved in the manufacture of the Monoclonal Antibodies Anti $Le^a$ (Murine Monoclonal) (IgM) (Cell Line (b) (4) FFMU and Anti $Le^b$ (Murine Monoclonal) (IgM) (Cell Line (b) (4) FFMU are listed in the table below.

| Name /Address | FEI Number | DUNS Number | Inspection /Waiver | Justification /Results |
|---|---|---|---|---|
| *Cell Culture, Downstream Processing, Filtration and Filling* | 3002638287 | 6216074503 | Waiver | Team Biologics February 20-27, 2020 VAI |
| *Serological and Biochemical QC Release Testing*<br><br>*Millipore (UK) Limited*<br>*Kirkton Campus 2*<br>*Fleming Road*<br>*Livingston, UK* | | | | |

Team Biologics performed a surveillance inspection of the Millipore (UK) Limited facility on February 20 – 27, 2020. All inspectional 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 (DMPQ)

The Monoclonal Antibodies Anti $Le^a$ (Murine Monoclonal) (IgM) (Cell Line (b) (4) and Anti $Le^b$ (Murine Monoclonal) (IgM) (Cell Line (b) (4) FFMU are filled into (b) (4) . Millipore Limited (UK) verified the container integrity by assessment of minimum application (b) (4) of the container/closure. Prevention of microbial contamination and particulates was also assessed. In addition, (b) (4) testing was performed; all 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-$Le^a$ (Murine Monoclonal) (IgM) (FFMU) and Anti-$Le^b$ (Murine Monoclonal) (IgM) (FFMU).

### 8. Labeling

Millipore submitted sample final container labels for the anti-$Le^a$ FFMU and Anti-$Le^b$ FFMU; the labels were 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

The FFMUs referenced in this application are manufactured using a different method to produce the bulk antibodies. This alternate method will (b) (4) to manufacture Anti-Le$^{a}$ and Anti-Le$^{b}$ BGRs.

Evaluation of the validation studies and manufacturing process reduces risks associated with licensing the two new FFMU products. In addition, the final products, Anti-Le$^{a}$ (Murine Monoclonal) and Anti-Le$^{b}$ (Murine Monoclonal), (b) (4) , will be subject to post market surveillance (medical device reporting) which will identify adverse events associated with the two products.

### c. Recommendation for Post-Marketing Activities

There are no post marketing activities associated with this submission.