

## Memorandum

**Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality**

**To:** Administrative File: STN 125589/0

**From:** Lori Peters, Lead Facility Reviewer, OCBQ/DMPQ

**Through:** Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1

**Cc:** Deborah Trout, Team Lead, OCBQ/DMPQ/BI  
Robert Duncan, Committee Chair, CBER/OBRR/DETTD  
Iliana Valencia, RPM, CBER/OBRR/IO

**Applicant:** Oxford Immunotec, Ltd.\*

**Facility Site:** 315 Norwood Park South, Norwood, MA 02062

**Product:** *Babesia microti* Arrayed Fluorescence Immunoassay (AFIA) (Note, The assay is manufactured at the Norwood, MA facility and is also used in-house to test donor samples for the presence of *Babesia microti*.)

**Indication:** Intended for the detection of human antibodies in blood samples to *Babesia microti* (in-vitro diagnostic test)

**Subject:** BLA Review Memo for Complete Response Letter dated June 13, 2017: Purpose of this memo is to determine the adequacy of the DMPQ items included in the CR Letter dated June 13, 2017.

**Final Action Due Date:** April 11, 2018

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\* Applicant name change info: The original BLA applicant was Imugen, Inc.; however, after the original BLA filing, Oxford Immunotec, Ltd purchased Imugen, Inc in July 2016. The name change was officially submitted to the Agency under NAT BLA Amendment #24. The revised 356h Form indicates the applicant is "Oxford Immunotec, Ltd". The official name of the company in the United States is "Oxford Immunotec, Inc doing business as (dba) Imugen". Note, the acquisition of Imugen by Oxford Immunotec, Ltd did not have an impact on the facility location (315 Norwood Park S, Norwood, MA) where the manufacture of the assay and testing of the blood donor samples is occurring. Note, throughout this review memo, Imugen is noted as the facility location as this company name is still in-use following the acquisition.

## **SUMMARY**

This review memo will solely focus on the DMPQ related items included in the June 13, 2017 Complete Response Letter issued to Imugen regarding their AFIA assay. During the review of the BLA, Imugen, Inc. and Oxford Immunotec, Inc dba Imugen have been issued two Complete Response Letters regarding this assay, issue dates September 29, 2015 and June 13, 2017, respectively. The review of the response to the September 29, 2015 CR Letter is documented in a separate review memo by DMPQ which is included in the EDR file for the BLA. This memo covers the remaining topics included in the June 13, 2017 CR Letter. Separate review memos are also maintained for the responses to the 483 observations. This memo solely focuses on the review issues for the AFIA assay; for inspection related items, please reference the 483 Response Review Memos.

The second Complete Response Letter was sent to Oxford Immunotec, Inc dba Imugen on June 13, 2017 and responses were received by CBER on October 10, 2017 (Amendment #27). Imugen maintains paper copies of the amendments with electronic scans uploaded in the EDR; there is no eCTD format for this sponsor. The responses were classified as a Type II response due to the extensive nature of the requested information.

This memo will only cover the DMPQ issues included in the June 13, 2017 CR Letter for the AFIA assay, specifically 5 items listed as item numbers: 4, 18 – 21. The memo will note each CR Letter Item followed by Oxford Immunotec, Inc dba Imugen's response and an evaluation of the response.

**Reviewer Recommendation:** Following review of the responses by Oxford Immunotec, Inc dba Imugen to the AFIA CR Letter Items 4, 18 – 21, the DMPQ review issues are considered resolved and the responses were determined as acceptable. DMPQ recommends approval of the AFIA BLA STN 125589/0.

## **CR LETTER ITEMS: OXFORD IMMUNOTEC, INC. DBA IMUGEN RESPONSE**

### **Item #4 (AFIA Process Validation)**

In review of your process validation report, DOC-RPT-45 *Validation Report to Manufacture a Babesia microti AFIA Finished Device Lot*, you note two exceptions were encountered during the manufacture of the negative control lots, specifically exception E-16-063 due to product contamination on lot (b) (6) and E-16-061 due to lack of documentation regarding the negative blood donor on lot (b) (6).

- a. Please provide the investigation for both exceptions and an evaluation of the impact of the exceptions on the outcome of the negative control lots, specifically lots (b) (6) and (b) (6).

### **Imugen Response (Amendment #27):**

E-16-061- Exception was opened to address a missing record, the record was subsequently located therefore at the time of the audit, the exception had already been voided. The evidence that lead to the voiding can be reviewed in Attachment 4.1.

E-16-063- Exception was mistakenly opened in 2016 for a contamination event that occurred in 2014. After the opening of this exception, a 2014 exception report (E-14-025)

was located which addressed this event. The evidence that lead to the voiding can be reviewed in Attachment 4.2.

**Reviewer Assessment:**

Exception E-16-061: The exception report and investigation for exception E-16-061 was provided in the Amendment as Attachment 4.1. The record was reviewed and the investigation was satisfactory. The exception noted that the documentation required for the incoming receipt and bulk processing of *B. microti* AFIA negative plasma was not included in the batch filed for review and therefore, exception E-16-061 was opened. The paperwork was later found and the exception was voided (note, the void was dated March 1, 2017 which preceded the PLI by a few days). As part of the investigation, Imugen performed an analysis of the negative plasma that was used in the negative control and found there was no impact on the performance of the negative control. Overall, the investigation was complete and no risk was determined due to the missing paperwork. No further follow-up is necessary regarding this exception and impact on the negative control lot.

Exception E-16-063: The investigation for the contamination as identified in exception E-14-025 was reviewed. During the manufacture of the negative control lot (Lot #

(b) (6) ),

(b) (4)

Imugen has opened a change control to improve the process to prevent this incident from occurring. Since 2014, Imugen has implemented numerous quality oversight improvements to improve the process. DMPQ is satisfied with Imugen's actions to

investigate the cause and open a change control to improve the process and prevent future occurrences. DMPQ defers the analysis of the contamination exception to OBRR/DETTD to determine if the negative control lot (Lot # (b) (6)) is impacted. This deviation was further discussed with Dr. Duncan (AFIA BLA Chair) and he explained that the deviation had no impact on the validation. The main item to note is that the negative control lot was being used in a pre-clinical stability study and not in routine blood donor screening; therefore, no blood donor results were impacted. Also, it is noted that corrective measures were implemented and are effective as no subsequent lots have developed contamination.

Overall, DETTD has determined no impact to the validated process and Imugen has implemented satisfactory corrective actions to prevent the issue from re-occurring. The issue is resolved.

- b. We note that these deviations were not included in the exception log provided to the FDA during the pre-license inspection. Please comment.

**Imugen Response:** At the time of the pre-license inspection, the aforementioned exceptions had been closed as “void” and as such, were excluded from the exception log provided during the pre-license inspection.

During the inspection, the practice of voiding exceptions was discussed with FDA investigators and exceptions that had been closed as voids were presented for inspection. Observation 3(c) of the 483 issued on 3/10/2017 identified that exception voiding practices were not included in the SOP, and the SOP was revised accordingly following the inspection.

**Reviewer Assessment:** The practice of voiding exceptions was discussed with Imugen during the inspection and the corrective action for observation #3c is satisfactory to resolve the inspection item; for additional details please reference the DMPQ review memos “483 Response Review Memo”. A second list of exceptions which were voided is maintained by Imugen and that is the reason why the voided exceptions were not included in the open/closed exception log reviewed during the inspection. The voided exceptions were reviewed by inspector Justine Corson, ORA, during the inspection which ultimately lead to observation #3c. This response clarifies the confusion why the voided exceptions were not included in the open/closed exception log. No further review issues are noted regarding this topic.

## **FACILITY**

### **Item #18 (Categorical Exclusion from Preparation of an EA)**



Your justification for a categorical exclusion from preparation of an environmental assessment for the AFIA assay is not satisfactory as provided in your December 13, 2016, Complete Response Letter to Item #48. Please revise your justification to indicate how your finished device lots for the AFIA assay meets the exclusion criteria.

**Imugen Response** (Amendment #27): Imugen is requesting a categorical exclusion of an environmental assessment based on 21 CFR 25.31(c), which states that, “Action on...a biologic product...for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment,” are categorically excluded from environmental impact considerations and, therefore, ordinarily do not require the preparation of an EA or an EIS. The justification for this categorical exclusion for the Imugen Arrayed Fluorescence ImmunoAssay for the Detection of *Babesia microti* is that, as for other licensed blood donor screening tests, the volumes of reagents and the materials disposed of from use of the product are extremely small, the reagents contain constituents that are naturally occurring, and the product is used by a clinical laboratory that must meet federal, state, and local requirements for waste disposal. Therefore, to Imugen’s knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment, as per 21 CFR 25.15(d).

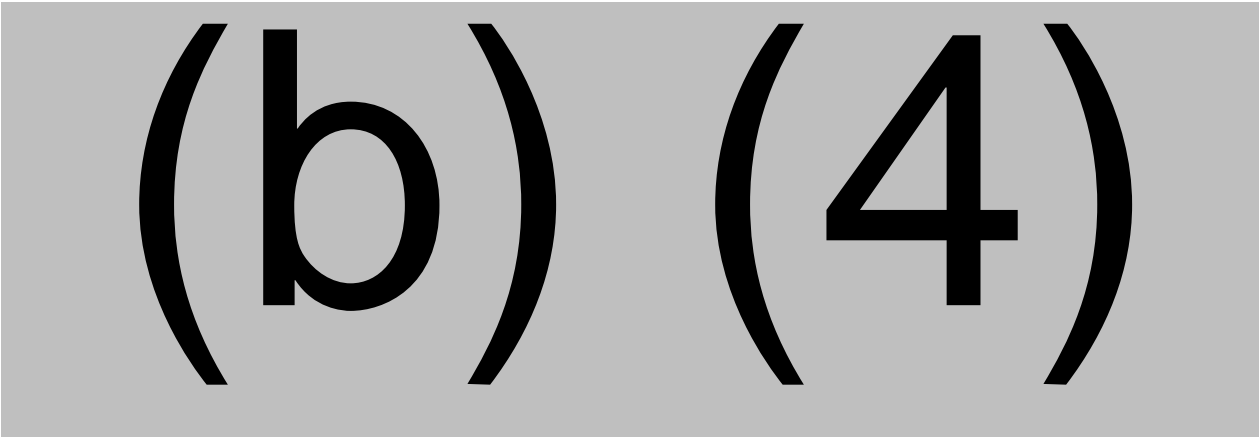
**Reviewer Assessment:** The justification provided by Imugen is acceptable as they describe the reagents contain constituents which are naturally occurring and that the assay components are used as a laboratory based test and are not consumed or injected in to the body and excreted as waste. Overall, the request is acceptable.

#### **EQUIPMENT**

(b) (4)



(b) (4)



2 pages have been determined to be not releasable: (b)(4)