

**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 125588/0

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

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

**Cc:** Deborah Trout, Team Lead, OCBQ/DMPQ/B1  
Babita Mahajan, 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* Nucleic Acid Test (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 specific DNA to *Babesia microti*

**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

---

\* 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 NAT 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 NAT 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 #32). All paperwork associated with this BLA is filed as a paper copy 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 NAT assay, specifically 7 items listed as item numbers: 14 – 20. 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 NAT CR Letter Items 14 – 20, the DMPQ review issues are considered resolved and the responses were determined as acceptable. DMPQ recommends approval of the NAT BLA STN 125588/0.

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

### **FACILITY**

#### **Item #14**

In your response document "BLA Complete Response BL125588/0 Imugen Response" dated December 14, 2016, to FDA CR Question 44 on categorical exclusion, your justification from a categorical exclusion for preparation of an environmental assessment for the NAT assay is not satisfactory. Please revise your justification to indicate how your finished device lots for the NAT assay meets the exclusion criteria.

**Imugen Response** (Amendment #32): 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 Nucleic Acid Test for 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 QUALIFICATION**

**\*Note:** Due to the similarities between the information requested in CR Letter Items #15 – 18, one reviewer comment will be noted following the conclusion of Item #18 summarizing the adequacy of the responses to Items #15-18.

#### **Item #15**

The equipment qualification reports you provided for the NAT Extraction Systems in your Complete Response Letter date December 14, 2016, response to question #47 do not appear to be performed in accordance with a protocol with defined acceptance criteria. In addition, the reports do not appear to include a sign-off review by Quality. Based on your performance qualification protocol for the new NAT extraction systems, please perform an evaluation of the results of the performance qualifications for the legacy NAT extraction systems and determine if the systems were adequately qualified and meet the criteria outlined in the protocol. Please provide a copy of the evaluation(s).

**Imugen Response (Amendment #32):** The performance qualifications of the Legacy NAT Extraction Systems were reviewed. Several of the extractors were re-validated to bring them up to current standards. All other extractors met current qualifications and as such were not redone.

Note, Table 15.1 was provided in the response which lists each machine and the corresponding IQ protocol, IOQ report, PQ protocol, and PQ report. All protocols and reports were provided as attachments in the Amendment.

#### **Item #16**

In the September 29, 2015, Complete Response Letter, question #47C, you were asked to provide the performance qualification report summaries for all data collected from all machines used on all shifts, however, you only provided the performance qualification data for (b) (4) (units) of the (b) (4) NAT extraction units. Please provide the performance qualification reports for the remaining legacy NAT Extraction systems (units (b) (4) in use for blood donor screening operations.

**Imugen Response (Amendment #32):** Refer to Table 15.1 in the Amendment for the NAT Extraction equipment qualification documentation.

#### **Item #17**

Please provide a summary and a copy of the procedure related to the performance verification activities that are performed on the current NAT extraction systems to ensure the systems are

functioning correctly and not resulting in a false positive or false negative test results. Please ensure your response describes the frequency of performing the verification activities.

**Imugen Response** (Amendment #32): A performance verification for the Extractors is now in place and will be performed (b) (4). The protocol is available for review as Attachment 17.1, LAB-IQC-146, (b) (4) Comparability Procedure for use in Blood Donor Screening.” Inter-instrument is performed every (b) (4). In this verification, (b) (4) extractions of each assay control (high positive, low positive and negative) are run on each machine and each extraction is amplified in (b) (4). The table below (Table 17.1) lists the acceptance criteria of each extraction.

NAT Assay Controls	Specifications
Babesia Negative Control	(b) (4)
Babesia Low Positive Control	
Babesia High Positive Control	
No Template Control (System Suitability)	

**Item #18**

We acknowledge that you intend to qualify additional pieces of NAT equipment to perform manufacturing and blood donor screening activities for licensure of your BLA. For each new piece of equipment, please provide the applicable equipment performance qualification (PQ) protocol and the executed report. The protocols shall include defined tests to be performed, representative number of samples to be tested, and the acceptance criteria.

**Imugen Response** (Amendment #32): The Amendment to STN BL 125588 – Biologics License Application for Imugen’s *Babesia microti* Nucleic Acid Test, “Added Equipment to Imugen’s NAT Device”, sent on June 12, 2017 contains qualifications for all new purchased NAT equipment. When additional equipment is purchased, further updates will be provided.

**Reviewer Assessment** (Items #15-18): DMPQ defers the review of the qualification protocols and reports for the NAT extraction equipment to the BLA Chair for assessment and review. The protocols and results center on cutoff values of positive and negative controls along with primer and probe suitability (exponential curves). DETTD’s expertise in the review of this data is better suited to assess the adequacy of the results and determine if the equipment is functioning as intended and providing the correct results (i.e. detection of *B. microti* positive samples). BLA Chair has reviewed the NAT extraction qualification reports for each of the NAT extraction units (LAB-RBT-EXT- (b) (4) as listed in Table 15.1 of the Amendment; the reports were provided in either Amendment #32 or Amendment #29 (Imugen noted the qualification reports for the new equipment was provided in the June 12, 2017 update

response (received June 13, 2017)). Amendment #29 also contained PQ reports for the PCR system and thermocycler, both of which were reviewed by the BLA Chair. The BLA Chair has reviewed the results contained in each PQ report for the NAT extraction equipment along with the PCR system and thermocycler; she reports the data is satisfactory and meets the criteria. DMPQ does not have any further issues regarding the qualification of the NAT extraction equipment as DETTD is mainly responsible to review and assess the results. In the response to Item #15, Imugen has taken the steps to re-validate the legacy systems and ensure the correct functioning per the updated procedure established for the newly installed units. This measure to re-validate is satisfactory. In response to Item #17, Imugen will perform a performance verification for the extractors on a (b) (4) basis; the implementation of this verification is a good measure to ensure consistent and accurate performance of the extractors. Overall, Imugen is implementing measures to improve the oversight and maintenance of the NAT extraction machines and these actions appear satisfactory. DMPQ has no further issues on the qualification of the equipment.

### **EQUIPMENT CLEANING**

#### **Item #19**

The cleaning of the NAT equipment used for manufacture of assay components and to perform blood donor screening shall be documented in procedures to ensure consistent cleaning between operators. Please provide a copy of the cleaning procedures.

**Imugen Response** (Amendment #32): Procedure LAB-IQC-112 was updated in response to the 483 Observation 13a. This document was provided in the June 2, 2017 amendment as a progress update to the 483 corrective actions.

**Reviewer Assessment:** The procedure, LAB-IQC-112 (b) (4) *Maintenance / Decontamination Protocol* (Revision 1.7), was provided in Amendment #27 (CBER receipt date June 5, 2017), and was evaluated by DMPQ under the CR Letter response review cycle.

The purpose of the protocol is to describe the maintenance and decontamination procedure for the extraction systems. The scope is to ensure consistent maintenance and cleaning is established and performed.

The procedure describes the steps and procedures for daily, weekly, monthly, and semi-annual maintenance. Each process step is clearly defined with sufficient detail for an analyst to follow. The procedure also contains a section on “Decontamination” and lists the steps for decontaminating the reagent reservoir, reagent tank, elution block/sample lysis thermoblock, and work table. The procedure on decontamination contains sufficient detail for an analyst to follow with step-by-step instructions on the cleaning solutions, drying time, areas to clean/wipe, etc.

Overall, the updates to this procedure are acceptable to define the cleaning process of the NAT extractors.

#### **Item #20**

Please perform an evaluation of the cleaning agents and cleaning process (indicated to include (b) (4) you utilize to determine if the cleaning is effective at removing contaminating material from your NAT equipment including the extractors, PCR set-up system, and thermocyclers. Please provide a copy of the applicable equipment cleaning reports demonstrating the removal of contaminants.

**Imugen Response** (Amendment #32): (b) (4) is the preferred form of decontamination in use at Imugen. Please see reports DOC-RPT-183, “Cleaning Effectiveness Study for the (b) (4) (Attachment 20.1) and DOC-RPT-184, “Cleaning Effectiveness Report for PCR Set-Up Machine” (Attachment 20.2).

For the Thermocycler, if contamination is suspected an investigation is initiated through LAB-EQP-4, Unplanned Servicing of Equipment which takes the piece of equipment out of service until the investigation is closed. Due to the high complexity and sensitivity of this instrument, Imugen only allows manufacturer’s technicians to perform any maintenance or decontamination.

**Reviewer Assessment:** DMPQ completed a review of the two reports, DOC-RPT-183 *Cleaning Effectiveness Study for the (b) (4)* and DOC-RPT-184 *Cleaning Effectiveness Report for PCR Set-Up Machine*. The reports were provided in Amendment #32. A summary of the two reports follows.

***NAT Extraction Equipment***

DOC-RPT-183 *Cleaning Effectiveness Study for the (b) (4)* (Revision 1.0, Effective Date: October 3, 2017)

The report summarizes the effectiveness study procedure that was performed on the (b) (4) instrument to evaluate Imugen’s cleaning/decon procedures. By the nature of the machine design, the design minimizes the risk of cross-contamination; however, in the event of a splash or spill, a (b) (4) solution is to be used.

The plan included applying the infecting agent on (b) (4) surfaces within the (b) (4) extractor on (b) (4) different days. The agent was removed using the (b) (4) solution as described in procedure LAB-IQC-112.

The following positive and negative controls were used in the study.

<b><i>Babesia</i> Control</b>	<b>Lot Number</b>	<b>Specifications</b>	
		<b><i>Babesia</i></b>	<b>HUMAN 18S</b>
<b>High Positive</b>		(b) (4)	
<b>Low Positive</b>			
<b>Negative</b>			

The acceptance criteria are: “No amplification seen; undetected for *B. microti* and Hu18S internal control must be undetected or (b) (4) to be acceptable. Controls must meet specifications.”

The data was provided in the report and reviewed. It is noted there was one deviation as the plate from Day 1 was repeated due to low positive control being out of range; the repeat plate was in range. This did not impact the outcome of the cleaning effectiveness study.

The results from the (b) (4) days of testing show that all results for the presence of *B. microti* were undetected and all Hu18S internal controls were either undetected for (b) (4) and all controls meet the specifications. The results demonstrate the cleaning procedure and process per LAB-IQC-112 is effective at removing *B. microti* (if present) in the event of a splatter or spill in the unit. DMPQ has no further issues regarding this study or the evaluation of the cleaning methods and agents to remove *B. microti* from the surfaces of the extraction equipment in the event of a spill.

**PCR Set-Up Equipment**

DOC-RPT-184 *Cleaning Effectiveness Report for PCR Set-Up Machine* (Revision 1.0, Effective Date: October 3, 2017)

The report summarizes the effectiveness study procedure that was performed on the (b) (4) PCR set-up instrument to evaluate Imugen’s cleaning/decon procedures. By the nature of the machine design, the design minimizes the risk of cross-contamination; however, in the event of a splash or spill, a (b) (4) solution is to be used.

The plan included applying the infecting agent on (b) (4) surfaces within the PCR set-up machine on (b) (4) different days. The agent was removed using the (b) (4) solution as described in procedure LAB-IQC-148.

The following positive and negative controls were used in the study.

<b>Babesia Control</b>	<b>Lot Number</b>	<b>Specifications</b>	
		<b>Babesia</b>	<b>HUMAN 18S</b>
<b>High Positive</b>	(b) (4)	(b)	(4)
<b>Low Positive</b>			
<b>Negative</b>			

The acceptance criteria are: “No amplification seen; undetected for *B. microti* and Hu18S internal control must be undetected or (b) (4) to be acceptable. Controls must meet specifications.”

The data was provided in the report and reviewed. The report noted there was one deviation as the plate from Day 1 failed due to multiple human 18s values that were (b) (4); therefore not meeting the criteria. To remedy this deviation, an additional plate was run on the following day and all values met the specifications.

The results from the (b) (4) of testing (not including the original first run) show that all results for the presence of *B. microti* were undetected and all Hu18S internal controls were either undetected for (b) (4) and all controls meet the specifications. The results demonstrate the

cleaning procedure and process per LAB-IQC-148 is effective at removing *B. microti* (if present) in the event of a splatter or spill in the unit. DMPQ has no further issues regarding this study or the evaluation of the cleaning methods and agents to remove *B. microti* from the surfaces of the PCR set-up equipment in the event of a spill.

***Thermocycler***

Regarding the cleaning of the thermocycler, Imugen has noted that if contamination is suspected, the unit will be removed from operation and an investigation opened per LAB-EQP-4 *Unplanned Servicing of Equipment*. Imugen notes that only a representative from the manufacturer can perform the maintenance or decontamination for this piece of equipment as it is complex. Overall, this plan to remove the unit from operation and open an investigation following their unplanned servicing of equipment procedures appears acceptable as the unit will not be used until a representative is available and perform the necessary cleaning or decontamination.