# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022458Orig1s000

# MICROBIOLOGY REVIEW(S)

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** **April 18, 2012**

**TO:** **Jessica Benjamin, Sr. Regulatory Health Project Manager, OND/ODE3/DGIEP**

**FROM:** **Vinayak B. Pawar, Ph.D., Senior Reviewer, New Drug Microbiology Staff, OPS**

**THROUGH:** **John W, Metcalfe, Ph.D., Senior Reviewer, New Drug Microbiology Staff, OPS**

**SUBJECT:** **Addendum to Quality Microbiology Review of NDA 22-458**
**Product:** (b) (4) (taligucerase alfa injection).
**Sponsor:** Protalix Ltd.

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(b) (4) facility was responsible for product sterility and endotoxins testing service for Protalix Ltd. in support of the NDA 22-458. The Agency issued a Warning Letter to (b) (4) as a result of a pre-approval inspection (b) (4) A Teleconference was held with the sponsor on March 21, 2012, to discuss the impact on the currently contracted services and to seek an agreement on an alternate testing facility. On March 22, 2012, Protalix Ltd. responded to the T-con IR through Glen D. Park, Sr. Director, Clinical & Regulatory Affairs, Target Health Inc. and announced that the testing responsibilities for (b) (4) ™ (taliglucerase alfa) for injection formerly assigned to (b) (4), have been withdrawn from the NDA application and reassigned to:

- Sterility testing at release and stability - (b) (4) facilities which were part of the original NDA filing and have been routinely testing taliglucerase alfa drug product for sterility release and stability. In support, Validation reports were included for (b) (4) (Validation Report R-004) and for (b) (4) (Validation Report RPT-7061).

- Endotoxins testing at release and stability - Protalix Ltd., Israel and (b) (4). In support, Validation reports were included for Protalix Ltd., Israel (Validation Report 70-60-043) and for (b) (4) (Validation Report RPT-7036).

The following is Product Quality Microbiology Review of the Validation Reports:

**I. Validation of Sterility Test:**

Validation Reports from both (b) (4) [Report R-004] and (b) (4) [Report 7061] documented validation of sterility test for B & F properties of Protalix product according to Harmonized Sterility Methods in current USP <71> and EP 2.6.1 using Millipore Steritest Method. All samples tested had neither bacteriostatic nor fungistatic properties that could affect the reliability of Sterility Test.

**Acceptable**

**II. Validation of Bacterial Endotoxins Test:**

[redacted] ***-Validation Report 7036***

Inhibition/Enhancement testing of [redacted] Drug product was performed on 3 batches (016489, 014461 & PR2007) of [redacted]™. Acceptance criteria outlined in protocol LMEXE-000009703 'Verification of the Kinetic Turbidimetric Limulus Amebocyte Lysate (LAL) Assay for the Determination of Endotoxin in [redacted] Drug Product Samples' were met for the 3 verification runs.

The test samples consisted of the following dilutions of the drug product: [redacted]

The following results were posted:

[redacted]

[redacted] states that the data obtained during validation study were considered acceptable [redacted]

**Acceptable**

***Protalix Ltd. Israel – Validation Report 70-60-043***

The purpose of this study was to perform qualification of the [redacted] system for the determination of endotoxins in Protalix drug product – taliglucerase alfa drug substance and drug product. The system enables detection of endotoxin levels at [redacted]. This study was conducted in compliance with the USP <85> requirements.

[redacted]

(b) (4)

A summary table of the (b) (4) Test and of the endotoxin determination test is presented below.

**11.7 Validation results** (b) (4)

(b) (4)

*Conclusion:*
The sponsor states that all data obtained during this validation study were considered acceptable and show that this procedure can be used for the accurate and precise determination of bacterial endotoxins in the drug product samples.

**Acceptable**

**Comment:** Both Protalix Ltd. Israel and (b) (4) would be acceptable sites for testing Bacterial Endotoxins at release and stability time points. Please inform the sponsor accordingly.

**END**

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/s/

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VINAYAK B PAWAR
04/19/2012

JOHN W METCALFE
04/19/2012
I concur.

# Product Quality Microbiology Review

**December 18, 2011**

**NDA:** 22-458

**Drug Product Name**
**Proprietary:** (b) (4)™
**Non-proprietary:** taliglucerase alfa

**Review Number:** 2

**Dates of Submission(s) Covered by this Review**

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| August 1, 2011 | August 1, 2011 | September 6, 2011 | September 7, 2011 |

**Submission History (for amendments only)**

| Submit Date(s) | Microbiology Review # | Review Date(s) |
|---|---|---|
| December 7, 2009 | N/A | N/A |
| July 20, 2010 (re-submission) | 1 | February 20, 2011 |

**Applicant/Sponsor**
**Name:** Protalix Ltd. (US Agent Target Health Inc.)
**Address:** 261 Madison Avenue, New York, NY 10016
**Representative:** Glen Park, Pharm D (Target Health Inc.)
**Telephone:** 212-681-2100, GPark@TargetHealth.com

**Name of Reviewer:** Vinayak B. Pawar, Ph.D.

**Conclusion:** The application is recommended for approval from product quality microbiology standpoint.

# Product Quality Microbiology Data Sheet

**A. 1. TYPE OF SUBMISSION:** Amendment to Original NDA

**2. SUBMISSION PROVIDES FOR:** Response to the issues in the Complete Response Letter dated February 24, 2011.

**3. MANUFACTURING SITE:**
1. (b) (4)
2. (b) (4)

**4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 212 Units of taliglucerase alfa/vial, 60U/kg administered via 1-2 hour intravenous infusion once every two weeks.

**5. METHOD(S) OF STERILIZATION:** (b) (4)

**6. PHARMACOLOGICAL CATEGORY:** Treatment of Gaucher disease.

**B. SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4) for information pertaining to the rubber stoppers.

**C. REMARKS:**
The Original NDA 22-458 was submitted electronically on a rolling basis with modules 4, 5 and 6 to be submitted by December 15, 2009. In response to the FDA's Information Request letter dated January 25, 2010, the sponsor submitted a Quality Amendment on April 26, 2010 with a request for a Priority Review of this NDA. The July 20, 2010 submission completed the rolling submission. The review of this submission resulted in an approvable status, pending resolution of Product Quality Microbiology issues. The sponsor responded to the deficiencies in a letter dated July 30, 2011. This response was submitted in an eCTD format and is the subject of this review.

The sponsor, in the initial submission authorized the review of DMF (b) (4) for information pertaining to the rubber stoppers. The DMF review by OGD (b) (4).doc] was found to be inadequate to support this NDA and the deficiencies were conveyed to the DMF holder. The DMF has since been reviewed by OGD (b) (4).doc, March 16, 2011] and was found adequate for sterility assurance.

**Filename:** N022458R2

# Executive Summary

## I. Recommendations

**A. Recommendation on Approvability –** The application is recommended for approval based on the resolution of the Product Quality Microbiology Deficiencies.

**B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –** N/A

## II. Summary of Microbiology Assessments

**A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The manufacturing process contains several steps, including (b) (4)

These steps are described in more details in section P of this review.

**B. Brief Description of Microbiology Deficiencies –** None

**C. Assessment of Risk Due to Microbiology Deficiencies –** N/A

## III. Administrative

**A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER

**B. Endorsement Block** _____
Bryan S. Riley, Ph.D., NDMS, OPS, CDER

**1. CC Block**
N/A

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VINAYAK B PAWAR
12/20/2011

BRYAN S RILEY
12/21/2011
I concur.

# Product Quality Microbiology Review

**February 9, 2011**

**NDA:** 22-458

**Drug Product Name**
**Proprietary:** [redacted]™
**Non-proprietary:** taliglucerase alfa

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| December 7, 2009 | December 7, 2009 | January 5, 2010 | January 7, 2010 |
| **Resubmission** | | | |
| July 20, 2010 | July 20, 2010 | N/A | N/A |

**Submission History (for amendments only) –** N/A

**Applicant/Sponsor**
**Name:** Protalix Ltd. (US Agent Target Health Inc.)
**Address:** 261 Madison Avenue, New York, NY 10016
**Representative:** Glen Park, Pharm D (Target Health Inc.)
**Telephone:** 212-681-2100, GPark@TargetHealth.com

**Name of Reviewer:** Vinayak B. Pawar, Ph.D.

**Conclusion:** The application is approvable pending resolution of product quality microbiology issues cited at the end of this review.

# Product Quality Microbiology Data Sheet

**A. 1. TYPE OF SUBMISSION:** Original NDA

**2. SUBMISSION PROVIDES FOR:** N/A

**3. MANUFACTURING SITE:**

1. (b) (4)
2. (b) (4)

**4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 212 Units of taliglucerase alfa/vial, 60U/kg administered via 1-2 hour intravenous infusion once every two weeks.

**5. METHOD(S) OF STERILIZATION:** (b) (4)

**6. PHARMACOLOGICAL CATEGORY:** Treatment of Gaucher disease.

**B. SUPPORTING/RELATED DOCUMENTS:** The sponsor authorizes the review of DMF (b) (4) for information pertaining to the rubber stoppers. This DMF has been found to be inadequate to support this NDA and the DMF holder has been notified.

**C. REMARKS:**

The Original NDA 22-458 is in support of the drug product, taliglucerase alfa for the treatment of patients with a confirmed diagnosis of Gaucher Disease. Per agreement with the Agency, portions of this NDA were to be submitted *electronically* on a rolling basis with modules 4, 5 and 6 to be submitted by December 15, 2009. In response to the FDA request on January 25, 2010 for significant pieces of information necessary to complete the NDA review by 25 January 2011, the sponsor submitted a Quality Amendment on April 26, 2010. With this amendment the sponsor proposed an additional drug product manufacturing site at (b) (4) In the cover letter, dated April 26, 2010, the sponsor also requested a Priority Review of this NDA. With revised pieces of information needed, sections of the application were resubmitted on July 20, 2010. It is this submission that completed the rolling submission. No IQA was filed for this NDA. This was an eCTD submission.

**filename: N022458R1**

# Executive Summary

## I. Recommendations

**A. Recommendation on Approvability –** The application is approvable pending resolution of product quality microbiology issues cited at the end of this review.

**B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –** N/A

## II. Summary of Microbiology Assessments

**A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The manufacturing process contains several steps, including (b) (4) [redacted]. These steps are described in more details in section P of this review.

**B. Brief Description of Microbiology Deficiencies** - None

**C. Assessment of Risk Due to Microbiology Deficiencies –** N/A

## III. Administrative

**A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER

**B. Endorsement Block** _____
Bryan S. Riley, Ph.D., NDMS, OPS, CDER

**C. CC Block**
N/A

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VINAYAK B PAWAR
02/10/2011

BRYAN S RILEY
02/10/2011
I concur.