

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125516Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA:	125516
Applicant:	United Therapeutics Corp.
US License Number:	1993 (pending)
Submission Reviewed:	Original BLA
Product:	dinutuximab (Unituxin)
Indication:	Treatment of high risk neuroblastoma.
Dosage Form:	Sterile, preservative-free 3.5 mg/ml solution for intravenous infusion supplied in single-use vials.
Manufacturing Sites:	United Therapeutics, Silver Spring, MD (FEI: 3003368324)
FDA Receipt Date:	11 April 2014
Action Date:	10 March 2015

Conclusion and Approvability Recommendation

The drug product portion of the BLA was reviewed from a sterility assurance perspective and is recommended for approval. There are three post-marketing commitments.

1. Conduct a comparison study between the LAL kinetic chromogenic test and the rabbit pyrogen test for drug product that has been spiked with endotoxin and then held prior to testing.

2. Conduct studies to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product.
3. Validate the dye ingress test using dinutuximab drug product vials. The validation study should identify the range of breach sizes detectable by the assay. The positive control used for the dye ingress test should be based on the validation study data.

Product Quality Microbiology Assessment: Drug Product

For submissions with multi-disciplinary information, only drug product quality microbiology information was reviewed.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	11 April 2014	Original BLA
0018	17 July 2014	Amendment
0021	1 August 2014	Amendment
0022	1 August 2014	Amendment
0025	8 August 2014	Amendment
0057	29 September 2014	Amendment
0063	30 October 2014	Amendment
0064	31 October 2014	Amendment
0067	17 November 2014	Amendment
0068	21 November 2014	Amendment

Module 3.2

P.1 Description and Composition of the Drug Product

The drug product (DP) is a sterile, preservative-free 3.5 mg/ml solution for intravenous infusion with a pH of 6.8. The DP is supplied in single-use vials. The fill volume is (b) (4) ml. The table below, which was provided in section P.1, lists the DP unit formula.

Table 1: Unit Formula for ch14.18

Component	Quality Standard	Quantity
ch14.18	House	3.5mg/mL
Histidine	USP/EP	3.10mg/mL
Sodium Chloride	USP/EP/JP	8.77mg/mL
Polysorbate 20	USP/EP	0.55 mg/mL
Hydrochloric Acid	USP/EP/JP	(b) (4)
Water for Injection	USP/EP/JP	(b) (4)

DESCRIPTION IS SATISFACTORY

P.2 Pharmaceutical Development

Reviewer's comment: Container closure integrity testing by microbial ingress is reviewed under section P.7.

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Colleen Thomas -S

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: November 12, 2014
To: Administrative File, STN 125516/0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Biological License Application (BLA)
US License: 1993 (Pending)
Applicant: United Therapeutics Corporation (UTC)
Facility: United Therapeutics Corporation, 1040 Spring Street, Silver Spring, MD 20910 (FEI # 3003368324)
Product: ch14.18, Unituxin (dinutuximab)
Dosage: Sterile solution (17.5 mg/5 mL) for intravenous injection
Indication: Treatment of high risk neuroblastoma in combination with granulocyte macrophage colony-stimulating factor, interleukin-2, and isotretinoin.
Due Date: December 10, 2014

Recommendation for Approvability: The drug substance section of the BLA, as amended, is recommended for approval from a microbial control and microbiology product quality perspective with the following post-market commitments (PMC):

1. Conduct the bioburden method qualification studies for the [redacted] (b) (4) [redacted] using two additional batches and for the drug substance using 3 different drug substance lots. [redacted] (b) (4) [redacted] the results should be submitted.
2. Submit the final established [redacted] (b) (4) [redacted] after trending the data from 10 drug substance batches.

SUMMARY:

This addendum addresses sponsor's responses for the following studies provided on September 26, 2014 (Sequence 0056) and on October 31, 2014 (Sequence 0064).

- Drug substance [redacted] (b) (4) qualification data from microbiological perspective.
- [redacted] (b) (4) qualification data from microbiological perspective.

The information request responses in amendment submitted on October 08, 2014 (Sequence 0059) was also reviewed.

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Satisfactory

Conclusion

- I. The drug substance section of the BLA, as amended, was reviewed from a microbial control and microbiology product quality perspective and recommended for approval.
- II. Information and data not related to microbial control of the drug substance should be reviewed by the OBP reviewer.
- III. A pre-license inspection (June 9-13, 2014) was conducted by BMAB and OBP at United Therapeutics Corporation, 1040 Spring Street, Silver Spring, MD 20910 facility and was classified as VAI.

CMC Microbiology Deficiencies for STN 125516/0 Unituxin (dinutuximab)

Information Requests sent

October 07, 2014:



(b) (4)

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/s/

LAKSHMI RANI NARASIMHAN
11/13/2014

PATRICIA F HUGHES TROOST
11/13/2014



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: September 19, 2014
To: Administrative File, STN 125516/0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Biological License Application (BLA)
US License: 1993 (Pending)
Applicant: United Therapeutics Corporation (UTC)
Facility: United Therapeutics Corporation, 1040 Spring Street, Silver Spring, MD 20910 (FEI # 3003368324)
Product: ch14.18, Unituxin (dinutuximab)
Dosage: Sterile solution (17.5 mg/5 mL) for intravenous injection
Indication: Treatment of high risk neuroblastoma in combination with granulocyte macrophage colony-stimulating factor, interleukin-2, and isotretinoin.
Due Date: December 10, 2014

Recommendation for Approvability: The drug substance section of the BLA, as amended, was reviewed from a microbial control and microbiology product quality perspective. However, (b) (4) qualification data are pending and the sponsor has committed to submit (b) (4) data by September 30, 2014 and (b) (4) qualification data by October 31, 2014. The pending data will be reviewed and documented in an addendum to this review memo.

In addition, the sponsor has agreed to perform the following studies:

1. Conduct the bioburden method qualification studies for the (b) (4) (b) (4) using two additional batches and for the drug substance using 3 different drug substance lots. (b) (4) the results should be submitted.
2. Submit the final established (b) (4) (b) (4) after trending the data from 10 drug substance batches.

SUMMARY:

United Therapeutics Corporation submitted this BLA for dinutuximab for the treatment of high risk neuroblastoma. Dinutuximab drug substance and drug product are manufactured by United Therapeutics Corporation, Silver Spring, MD. This review covers the evaluation of the drug substance aspects of the application from a microbiological control and microbiology product quality perspective.

This BLA was submitted in eCTD format and included Module 1.1.2 - FDA form 356h, Module 1.2-Cover letter, and Module 2 and 3. The original submission and the amendments submitted on

May 05, 2014 (Sequence 0002), June 02, 2014 (sequence #0008), August 01, 2014 (sequence #0022), August 20, 2014 (sequence #0032), August 27, 2014 (sequence #0040), September 15, 2014 (sequence #0049), and September 18, 2014 (sequence #0053) were also reviewed.

INTRODUCTION

United Therapeutics Corporation submitted a new biologics license application, STN 125516 to license dinutuximab and the associated drug substance and drug product manufacturing facilities. Dinutuximab was granted orphan drug status for the treatment of neuroblastoma in the US on 20 December 2010. Dinutuximab is indicated in combination with granulocyte-macrophage colony-stimulating factor, interleukin-2, and isotretinoin for high-risk neuroblastoma (b) (4) treatment. Dinutuximab is to be administered by intravenous infusion for four consecutive days during five monthly courses at a daily dosage of 17.5 mg/m².

This review covers the evaluation of the drug substance aspects of the application from a microbiological control and microbiology product quality perspective. For the review of drug product aspects of the application, please see review by Dr. Colleen Thomas.

ASSESSMENTS:

3.2.S. DRUG SUBSTANCE

Dinutuximab is a chimeric IgG1 monoclonal antibody, produced in a murine myeloma cell (SP2/0 hybridoma cell) (b) (4)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

FDA questions (April 29, 2014):

1. *The responsibilities of the drug substance and drug product testing sites are not clearly defined. Please update Table 1 of sections 3.2.S.2.1 and 3.2.P.3.1 to indicate which assays are performed by each testing site (e.g. "sterility testing only" or "all drug product release tests except for sterility").*
2. *The pre-license inspection will cover dinutuximab drug substance manufacturing and may also cover drug product manufacturing (b) (4). To facilitate inspection planning, please provide updated manufacturing schedules for the following:*
 - a. *Dinutuximab drug substance*
 - b. *Dinutuximab drug product, any other drug product (or placebo) manufactured (b) (4)*

Firm's response in Sequence # 0002 dated May 05, 2014 included the responsibilities of the drug substance and drug product testing sites and the updated manufacturing schedules for the drug substance and drug product.

Dinutuximab drug substance is manufactured, tested and released by the sites listed below:

United Therapeutics Corporation

1040 Spring Street, Silver Spring, MD 20910 FEI#: 3003368324

Manufacture of the drug substance, storage of the master cell bank, quality control testing of production raw materials, in-process, and stability testing for drug substance. All drug substance release tests except: (b) (4)

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/s/

LAKSHMI RANI NARASIMHAN
09/19/2014

PATRICIA F HUGHES TROOST
09/19/2014