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APPLICATION NUMBER:

125516Orig1s000

CHEMISTRY REVIEW(S)

OBP Review Cover Sheet

BLA STN 125516 Addendum

Unituxin

Sponsor: United Therapeutics Corp.

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**Chikako Torigoe, Ph.D.
Division of Monoclonal Antibodies**

Product Quality Review Data Sheet

(Includes only information updated since the initial review finalized on Sep 13, 2014)

1. **BLA#** STN 125516-0
2. **REVIEW #:** 2
3. **REVIEW DATE:** February 27, 2015

4. **REVIEWERS:** Chikako Torigoe Chikako Torigoe -A

Digitally signed by Chikako Torigoe -A
DN: cn=US, o=U.S. Government, ou=FDA, ou=People
0.9.2342.19200300.100.1.1=1300430897, cn=Chikako Torigoe
-A
Date: 2015.02.27 13:22:00 -05'00'

Laurie Graham, Team Leader

Laurie J.
Graham -S

Digitally signed by Laurie J. Graham -S
DN: cn=US, o=U.S. Government, ou=HHS
ou=FDA, ou=People
0.9.2342.19200300.100.1.1=130008068
-S, cn=Laurie J. Graham -S
Date: 2015.02.27 13:32:27 -05'00'

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS SINCE THE FINALIZATION OF THE INITIAL REVIEW:**

Communication/Documents

Date

Information Request	9/17/2014
Pre-meeting Document	9-24-2014
Late-Cycle Meeting (t-con)	10-6-2014
Information Request	10-29-2014
Information Request	2-9-2015
Information Request	2-17-2015
T-con	2-20-2015

6. **SUBMISSIONS REVIEWED UNDER THIS ADDENDUM:**

Submissions Reviewed

Document Date

125516/51	9-15-2014
125516/55	9-19-2014
125516/68	11-17-2014
125516/74	2-11-2015
125516/77	2-19-2015
125516/81	2-23-2015
125518/83	2-25-2015

Review

In this review, tables are directly copied from the submission unless otherwise stated.

125516/51

This submission contains the qualification/re-qualification protocol for the reference standard. The assessments are described elsewhere in this review with additional information provided by the sponsor.

125516/55

Summary

The sponsor provided the data of (b) (4) and ADCC activities for NCI and UTC lots in response to FDA information request sent on 9/17/2014.

FDA Comment

We note that Report DEV-13-5029 indicates that recent lots of drug substance and drug product (DP) manufactured by UTC consistently have higher ADCC activities compared to earlier lots manufactured by UTC. To support the higher ADCC activity observed in recent UTC lots, additional information is required to better understand the clinical experience of NCI material with regards to ADCC activity. Specifically, as part of your response to the Agency Information Request dated July 21, 2014, you submitted summary information (i.e. mean and standard deviation) on (b) (4) for 20 NCI lots. Provide a table with the (b) (4) for each of these NCI lots along with summary information on the clinical use of each lot.

Sponsor's Response

The sponsor states that the NCI lots and the UTC lots were switched in the response provided on 8/1/2014 and seven NCI lots and 20 UTC lots were used for the analysis. The updated data have been provided that include the data for the most recent UTC lots.



**First Approval for Indication
Priority Review of Orphan Drug**

Recommendation: Approval

**BLA 125516
3/1/2015**

Drug Name/Dosage Form	Unituxin for injection
Strength/Potency	17.5 mg/5 mL
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Indication	A treatment component for high risk neuroblastoma (b) (4) Unituxin is used in combination with granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin (RA)
Applicant/Sponsor	United Therapeutics Corp.

SUBMISSIONS REVIEWED	DOCUMENT DATE
STN 125516/0.1	4/11/2014
STN 125516/0.24	8/1/2014
STN 125516/0.30	8/19/2014
STN 125516/0.46	9/5/2014
STN 125516/0.47	9/11/2014
STN 125516/0.49	9/12/2014
STN 125516/0.51	9/15/2014
STN 125516/0.55	9/19/2014
STN 125516/0.68	11/17/2014
STN 125516/0.74	2/11/2015
STN 125516/0.77	2/19/2015
STN 125516/0.78	2/20/2015
STN 125516/0.81	2/23/2015
STN 125516/0.83	2/25/2015

Of note, the original PDUFA goal date for this application was December 10, 2014. However, the goal date was extended to March 10, 2014 based upon a major amendment to the BLA being received. The focus of the major amendment was addressing safety concerns related to increased antibody-dependent cellular cytotoxicity (ADCC) activity observed in recently manufactured lots of drug substance (DS) and drug product (DP). To address these safety concerns, additional clinical data were required. However, a number of additional CMC issues were resolved during this extension period. The primary CMC review of this BLA, therefore, consists of an original review document, covering all submissions above except STN 125516/68, and an addendum document. This executive summary includes all submissions.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Chikako Torigoe	OBP/DMA
Drug Product	Chikako Torigoe	OBP/DMA
Immunogenicity	Chikako Torigoe	OBP/DMA
Labeling	Jibril Abdus-Samad, Chikako Torigoe, Otto Townsend	OBP/DMA OPE/DMEPA
Facility and Microbiology	Colleen Thomas and Lakshmi Narasimhan	OC/BMAB
Team Lead	Laurie Graham	OBP/DMA
Tertiary Reviewer	Sarah Kennett	OBP/DMA

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Gina Davis	OND/OHOP/DOPII
Cross-disciplinary Team Lead	Suzanne Demko	OND/OHOP/DOPII
Medical Officer	Martha Donoghue	OND/OHOP/DOPII
Pharm/Tox	Dubravka Kufrin	OND/OHOP/DOPII
Clinical Pharmacology	Jingyu Yu	OTS/OCP/DCPV
Statistics	Sirisha Mushti	OTS/OB/DBV

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
			^{(b) (4)} Provided	No review required as all the relevant information was in the BLA.
			Provided	No review required as all the relevant was in the BLA.
			Provided	No review required as all the relevant information was in the BLA.
			Provided	No review required as all the relevant information was in the BLA.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Reviewed previously and no revision since last review

3 – Sufficient information in application

4 – Authority to reference not granted

5 – DMF not available

6 – Other (explain under "Comments")

² Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	4308	This is the NCI IND for this product

3. CONSULTS:

There were no formal consults during the review. The non-clinical team was consulted with regard to the toxicology assessment of the raw materials and extractables. The clinical pharmacology and clinical teams were consulted with regard to the need for an improved assay for the detection of neutralizing antibodies against Unituxin.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this time, the Office of Biotechnology Products (OBP), OPS, CDER, recommends, based on a benefit risk assessment, the approval of STN 125516 for Unituxin manufactured by United Therapeutics Corporation. This recommendation, however, is pending acceptable compliance checks as well as the adequate resolution of outstanding CMC issues through post-marketing commitments (PMCs).

- a. Approval action letter language
 - Manufacturing location:
 - Drug substance –
United Therapeutics Corporation
1040 Spring Street
Silver Spring MD 20910
FEI: 303368324
 - Drug product –
United Therapeutics Corporation
1040 Spring Street
Silver Spring MD 20910
FEI: 303368324
 - Fill size and dosage form: 5 mL at 3.5 mg/mL, injection
 - Dating period:
The Drug Substance (DS) and Drug Product (DP) specifications used to establish shelf-lives for drug substance and drug product are based, in part, on the additional clinical experience gained after the original PDUFA goal date for this application. The final shelf-lives will be:
 - Drug product: 18 months at 2-8⁰C.
 - Drug substance: (b) (4).
 - Exempt from lot release
 - Yes
 - Rationale if exempted – exempt per 21 CFR 601.2a (specified product)

B. Benefit/Risk Considerations –

1) Overview

This is a chimeric murine/human antibody that recognizes human disialoganglioside (GD2). The mechanism of action appears to be a combination of complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC).

Unituxin is indicated as a component of a treatment regimen for high risk neuroblastoma. This is a rare cancer that predominantly affects young pediatric patients. There are currently no FDA approved treatments for high risk neuroblastoma. This product is currently considered the standard of care for this indication in the United States. The clinical recommendation for approval was based primarily upon the randomized portion of study ANBL0032, also referred to as Study DIV-NB-301 (“Study 301”). In this study, clinically meaningful improvements in event free survival and overall survival were noted. The clinical risks include infusion related or allergic reactions, capillary leak syndrome, hypotension, systemic infection, neuropathy, and neurological disorders. Treatment is also associated with pain, which may be due to the antibody binding to the GD2 antigen on peripheral nerves or myelin in muscle tissues. Treatment requires analgesics, such as morphine sulphate, prior to and during infusion.

It should be noted that treatment is still potentially available through Study ANBL0032, which is on-going as a single arm open label study under IND 4308, referred to as DIV-NB-302 or “Study 302.” For children who do not meet the eligibility criteria for Study 302, treatment is possible through an expanded access program. However, approval of the BLA would be expected to provide future generations with access to this “standard of care” product. As clinical trials are still ongoing, there is the potential that review issues could be addressed through these on-going studies as post-marketing requirements (PMRs) and post-marketing commitments (PMCs).

The clinical data to support safety and efficacy of the product are derived from clinical trials conducted using material manufactured by the National Cancer Institute (NCI); the first NCI Phase I trial was initiated in 2001. In 2010, NCI entered into a Cooperative Research and Development Agreement with United Therapeutics Corporation (UTC). There were extensive manufacturing changes between the NCI and UTC processes, including

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It should be noted that there is extremely limited clinical experience with the material manufactured by UTC. However, as NCI no longer manufactures the product, the material currently being manufactured by UTC is the only material available for treatment and is being used under the NCI IND.

To support the changes in DS and DP manufacturing, UTC performed an analytical comparability assessment of NCI material vs. the first three batches of material manufactured by UTC. This assessment was performed using DP. In most cases, the sponsor used UTC DP formulated in (b) (4) rather than the final commercial histidine (b) (4).

The comparability assessment included release, characterization, and stability testing. The interpretation of the results was confounded by the age of the NCI lots, which were demonstrating degradation in certain assays. For these assays, available data would support that the differences observed between the UTC and NCI lots could be due to degradation. In addition to the analytical testing, the sponsor performed a clinical PK comparability study of NCI vs. UTC material. The clinical pharmacology reviewer concluded that the NCI and UTC materials were comparable in terms of PK. It should be noted that NCI has been using UTC lots in on-going clinical trials since January 2014. The clinical reviewer assessed the safety data from clinical trials using material manufactured by UTC and indicated that there were no obvious safety concerns. Cumulatively, the data provided in the BLA, therefore, were considered adequate to support the comparability of the material manufactured by NCI to material manufactured by UTC.

There were a number of CMC issues identified during review of the BLA. A benefit/risk assessment indicated that, at this time, the CMC issues identified do not preclude approval, but could be addressed as post-marketing commitments (PMCs). Each of these issues is summarized below.

2) ADCC Activity

Late in the original review cycle, the sponsor provided additional data on ADCC activity that suggested that recent DS and DP lots consistently had higher (approximately 200-227%) ADCC activity compared to the early DP lots of UTC material that were used in the analytical comparability assessment. There were concerns that these differences in ADCC activity may be clinically meaningful with regard to product safety, particularly the neuropathies observed in patients. This also raised concerns regarding process consistency. However, these risks were somewhat mitigated by the following:

- The ADCC assay is based on a Jurkat effector cell line that expresses the Fc gamma receptor IIIa and an NFAT luciferase construct. The Jurkat cells are incubated with a target cell line that expresses GD2. The assay measures Fc receptor mediated luciferase activity in the Jurkat cells. This is thought to correlate with granule exocytosis from effector cells. The sponsor, therefore, is not directly assessing cell cytotoxicity of the target cells, but rather is assessing Fc gamma receptor signaling in effector cells through a mechanism

that is highly influenced by Unituxin (b) (4). This does not necessarily reflect in vivo ADCC activity.

- (b) (4)
The variability in the ADCC results between the early and recent lots manufactured by UTC could be due to the assay format, (b) (4).
It is unclear that in vivo ADCC activity would be influenced to the same extent (b) (4). During the review cycle, the sponsor agreed to include (b) (4) as an additional control for ADCC activity in the final control strategy for drug substance. The sponsor will also add criteria for the (b) (4) as another control to ensure process consistency.
- While NCI did not measure ADCC activity in their lots, UTC provided information on (b) (4) and ADCC activity for seven and six clinical NCI lots, respectively. (b) (4) while the ADCC results ranged from 78-167%. It is noted that there was no ADCC activity information for the NCI lot (b) (4).
(b) (4) Cumulatively, the data indicate that there has been clinical experience with NCI lots with higher ADCC activity.

After discussion with Dr. John Jenkins, the director of the Office of New Drugs (OND), at an internal meeting held on October 21, 2014, it was determined that additional clinical data would be required to address the safety concerns associated with the increased ADCC activity in recently manufactured DP lots. It was decided that these data would constitute a major amendment that would extend the review timeline of the BLA. Whether the additional clinical data provided are sufficient to address the safety concerns is deferred to the clinical review team.

3) Specifications and shelf-life

The setting of specifications was confounded by a number of issues, including

- A lack of analytical data from NCI lots at the time of their clinical use for the cIEF, cSDS, and ADCC assays included in the proposed DS and DP specifications. This includes a lack of release and real time stability data for NCI lots.
- Limited product characterization and risk assessment information to understand the impact of product variants on safety and efficacy.

As a result, specifications in some cases needed to be based on the manufacturing and limited clinical experience with UTC lots. A PMC to reassess drug substance and drug product specifications based on additional clinical experience and product characterization information is currently recommended. In addition, it is

recommended that additional PMCs be communicated to the sponsor to update DS and DP specifications based upon additional manufacturing experience.

4) Reference Standard

The BLA did not include adequate protocols for qualification or re-qualification of reference standards. The current reference standard, which is (b) (4) months of age, is stored at (b) (4) °C and has been demonstrating (b) (4), particularly by cIEF. However,

- The current reference standard is the clinical drug product lot used in the clinical PK comparability trial. This lot was used clinically at (b) (4) months of age and, therefore, the changes observed are unlikely to impact PK.
- Available stability data indicate that activity, as assessed by GD2 binding and CDC activity assays, is acceptable.
- The sponsor indicated in the BLA that a new reference standard will be manufactured in (b) (4).
- The sponsor has indicated that they are moving towards a (b) (4) reference standard system in which the reference standard produced in 2014 will be placed at (b) (4) °C and will be used to qualify future reference standards.

The available reference standard information in the BLA was considered adequate to support approval. There will be a PMC for the qualification and requalification of a new reference standard.

Additional information will be needed to support the storage of the reference standard in the current formulation under (b) (4) °C conditions, as there have been (b) (4) issues with the UTC formulation, with (b) (4) being noted.

One Agency concern is that the use of one of the more recent lots of UTC material as the reference standard could result in product drift over time, particularly with regard to ADCC activity and (b) (4), because these quality parameters were atypically high in more recent lots. In this case, the sponsor may need to consider altering specifications when the new reference standard becomes available. Alternately, the sponsor may need to consider the use of a “corrective factor” in the interpretation of certain assays to compensate for the differences observed between reference standards. At the time of this executive summary, it appeared that the sponsor was planning to update specifications with the implementation of a new reference standard.

5) Host Cell Protein Assay

Information in the BLA indicated that the current host cell protein (HCP) assay used for release of DS has relatively poor coverage (approximately (b) (4)%) of the potential HCP that could be present. The sponsor indicated that they are currently working on an assay with improved coverage. There will be a PMC to develop, validate, and implement an assay for improved host cell protein coverage.

Specifications would need to be updated when the new assay is implemented. It might be possible that the sponsor could, eventually, remove this assay from the DS specifications with clearance data using the improved assay.

- 6) (b) (4)
Available information from forced degradation studies indicates that (b) (4) is a pathway of degradation for Unituxin that can impact potency. While there are assays in place that can detect (b) (4), the development and validation of an assay that can more sensitively detect this modification is warranted. There will be a PMC for the validation and implementation, into release and stability specifications, of an assay that can detect (b) (4)

7) Cell Line Clonality

There was no information available on the cloning procedures that were performed to produce the master cell bank (MCB) used by NCI. As a result of clonality concerns, the sponsor decided to (b) (4). Specifically, (b) (4). Overall, the information on clonality was considered adequate for approval. There will be a PMC to provide additional data to confirm the clonality of the master cell bank.

8) Working Cell Bank

Currently there is only a master cell bank. The BLA indicates that there were originally (b) (4). To address this concern, there will be a PMC to develop and appropriately qualify a working cell bank. This will need to include an assessment of comparability of material manufactured with the master and working cell banks. It should be noted that there was information in the BLA to indicate that a working cell bank is already being developed.

9) The end of production (EOP) cell bank

The EOP cell bank described in the BLA was generated (b) (4). While this can be an acceptable practice to generate EOP cells, there was insufficient information, including product quality information, provided in the

BLA to support

(b) (4)

There will be a PMC for the sponsor to generate end of production cells from a commercial scale

(b) (4)

10) Shipping

The sponsor did not perform studies designed to assess the impact of shipping on product quality. In addition, the sponsor proposes two different drug product shippers, but these shippers were not qualified with container closure systems that bracket, in size, the proposed container closure system for Unituxin. However, the sponsor does have the following to support drug product shipping:

- Drug product mechanical stress studies that assessed product quality
- Acceptable shipper qualification information for the (b) (4) shipper using (b) (4) compared to the Unituxin 5 mL vial
- Acceptable shipper qualification information for the (b) (4) shipper using a (b) (4)

This information was considered adequate for approval. There will be a PMC to provide additional shipping validation data.

11) Leachables

The sponsor had data from extractable studies performed for both DS and DP manufacturing and container closure components. For DS, this included the (b) (4)

For the DP, this included the stopper.

However, the sponsor did not provide an adequate risk assessment of the extractables observed in these studies to justify not performing leachable studies. There will be a PMC to include an assessment of leachables in real time DP stability studies. These studies should include consideration for the detection of the compounds observed in the DS and DP extractable studies.

12) Assay Validation

The validation of the cIEF, cSDS, and SE-HPLC assays did not include evaluations of accuracy or sensitivity for the purity assessments. In addition, these assays were not validated with respect to the impurities that are included in

the final DS and DP specifications. The assay validations were considered to be inconsistent with current guidance documents, such as ICH Q2 (R1). However, the assay data available in the BLA, including validation, release and stability data, support that the performance of the assays is acceptable for approval. As a PMC, the sponsor will be asked to confirm the validation of the cIEF, cSDS, and SE-HPLC assays.

13) Assay to Detect Neutralizing Antibodies to Unituxin

The overall immunogenicity rate in study 302 was approximately 17% with approximately 5% of subjects having neutralizing antibodies. The assay to detect neutralizing antibodies assesses the ability of antibodies against Unituxin to inhibit Unituxin-mediated CDC activity. In the presence of drug levels expected to be present in patient samples at the time of testing, this assay was determined to have poor sensitivity, ranging from 55.0 µg/mL to 147 µg/mL, depending upon the positive control used during assay validation. This issue was discussed with the clinical pharmacology review team who indicate that there was a trend for decreased efficacy in ADA positive patients noted in study 302, but a definitive conclusion could not be made. The clinical pharmacology reviewers indicated that a reliable neutralizing antibody assay might help delineate whether there is a correlation between anti-drug antibodies and decreased efficacy. The clinical review team concurred. There will be a PMC to develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against Unituxin in the presence of Unituxin levels that are expected to be present in samples at the time of patient sampling. In addition, there will be a PMR to conduct an assessment of neutralizing antibodies, using the validated assay, for all available clinical samples from study ANBL0032.

14) (b) (4) Lifetime Studies

The BLA contained information from reduced scale (b) (4) lifetime studies. However, it is unclear how representative of the full scale process these reduced scale models are with regard to predicting (b) (4) lifetimes. In addition, the reduced scale (b) (4) lifetime studies did not always use the maximum loads from the commercial process and data from these studies indicates that there are some age related changes in the performance of the columns. While the reduced scale data would support the (b) (4) lifetimes requested by the sponsor, the sponsor should verify the (b) (4) lifetimes at commercial scale. There will, therefore, be a PMC to conduct (b) (4) lifetime studies at commercial scale.

15) (b) (4) (b) (4) was observed over the shelf-life of both DS and DP. (b) (4) is the limiting assay for DP shelf-life.

The sponsor notes that this phenomenon was not observed for the NCI lots.

(b) (4)
Of note, the acceptance criterion at the end of shelf life

for DP manufactured by UTC is based on recent clinical experience with lots manufactured by UTC.. Of note, the overall control strategy contains assays that can detect the formation of product related impurities that could result in (b) (4) . (b) (4)

This was considered adequate for approval. However, there will be a PMC to investigate the (b) (4) observed on DP stability and, based on a risk assessment of the results, to implement appropriate corrective actions. This might necessitate the development of a new formulation.

16) Osmolality

Neither DS nor DP specifications include osmolality. (b) (4)

This study suggests a final formulation of osmolality around 300 mOsmol/kg. This level is considered acceptable (i.e., safe) for IV administered products. Because available information indicates that there is adequate control over the final formulation, this is not an approvability issue. There will be a PMC to update DP specifications with an assay and acceptance criteria for osmolality.

17) Compatibility

Compatibility testing of drug product was performed by diluting DP into infusion bags containing 0.9% sodium chloride. This is the dilution scheme indicated in the label. However, there was no information provided in the BLA on the materials of construction of the IV bags and administration sets that were tested for compatibility with the drug product. It appears that this information was not considered in the design of the compatibility studies. There will be a PMC to perform DP compatibility studies with IV bags and IV administration sets of different materials of construction. The label may, potentially, need to be updated based on the results.

18) Filter for Administration

It is noted that administration involves a relatively long infusion time (20 hours). Due to concerns regarding microbial control and serious infections observed in patients, the clinical review team requested that the sponsor consider the use of an in-line filter for administration. The sponsor has proposed that they will perform an initial study on protein concentration with the in-line filter (b) (4)

Subsequently, the sponsor will conduct a more detailed product quality study. The use of an in-line filter during administration is unlikely to adversely impact product quality. These compatibility studies will be additional PMCs.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following is draft language for numerous PMCs.

PMC #1: To re-assess drug substance (DS) and drug product (DP) specifications based on additional clinical experience with material manufactured using the commercial process and/or additional characterization data on product critical quality attributes. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#2: To manufacture, qualify, and implement a new reference standard and enter the reference standard into a requalification program. The reference standard qualification and requalification protocols and the qualification report for the new reference standard will be submitted in a prior approval supplement by XXX, XX, 20XX (UTC to provide date).

PMC#3: To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the dinutuximab drug substance release program. The anti-HCP antiserum will be evaluated using two-dimensional SDS-PAGE and western blot analysis of proteins from the production cell line or a representative cell line for the determination of the percent of potential HCP impurities that are recognized by this antiserum. The analytical procedure, validation report, reproductions of an appropriately stained two-dimensional gel and the corresponding western blot, the analysis of the approximate percent of HCP coverage, the proposed specification acceptance criterion, and the data used to set the acceptance criterion will be provided in a prior approval supplement by XXX, XX, 20XX (UTC to provide date).

PMC#4: To validate an assay for the detection of dinutuximab (b) (4) and implement this assay in the DS and DP release and stability specifications. The analytical procedure, validation report, the proposed specification acceptance criterion, and the data used to set the acceptance criterion will be provided in a prior approval supplement by XXX, XX, 20XX (UTC to provide date).

PMC#5: To establish and qualify a working cell bank (WCB) to be used for production of dinutuximab. Qualification of the WCB will include safety testing, an evaluation of the growth of WCB cultures relative to the growth of MCB cultures, testing of end of production cells generated from the commercial scale process, and a comparability assessment that includes the first three lots manufactured from the WCB using the commercial process. One lot manufactured using the commercial process will be placed on a stability protocol, and the data will be provided in the subsequent BLA annual reports. The WCB qualification report will be provided in a prior approval supplement by XXX, XX, 20XX (UTC to provide date).

PMC#6: To provide additional studies to confirm the monoclonality of the master cell bank. The final report will be submitted by XXX, XX, 20XX (UTC to provide date).

PMC #7: To perform validation studies to confirm acceptable product quality and shipper performance during shipping of dinutuximab drug product. This should include consideration for worst case shipping routes, including routes to testing sites. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality [e.g., opalescence, protein concentration, purity by SEC-HPLC, cSDS (reduced and non-reduced), cIEF, WCX, sub-visible particulates, and potency of dinutuximab], and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers. The final study report will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#8: To perform a leachable study of drug product through the end of shelf-life under recommended storage conditions. Testing will be performed at 0, 3, 6, 12, 24, and 36 month time points. This should include consideration for the detection of extractables observed in drug substance and drug product extractable studies. The analysis of leachables should include organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#9: To verify (b)(4) lifetimes at commercial scale using a validation protocol to evaluate (b)(4) capability and cleaning procedures through the intended lifetime of the (b)(4). The final approved validation protocol(s) will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#10: To further investigate the root cause for the (b)(4) observed in drug product stored under recommended conditions and to perform a risk assessment based on the root cause, the levels of (b)(4) observed, and the potential effects on safety and efficacy of dinutuximab. Appropriate corrective and preventative actions will be implemented based on the results of the root cause investigation and risk assessment. The root cause investigation and risk assessment reports and proposed corrective and preventive actions will be provided as a prior approval supplement by XXX, XX, 20XX (UTC to provide date).

PMC#11: To confirm validation of the SEC-HPLC assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications. The validation reports will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#12: To confirm validation of the cSDS reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications. The validation reports will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#13: To confirm validation of the cSDS non-reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications. The validation reports will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#14: To confirm validation of the cIEF assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications. The validation reports will be provided by XXX, XX, 20XX (UTC to provide date).

PMC#15: To develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against dinutuximab in the presence of dinutuximab levels that are expected to be present in samples at the time of patient sampling. The validation report will be submitted as a Prior Approval Supplement by XXX, XX, 20XX (UTC to provide date).

PMC#16: To develop, validate/qualify and implement an osmolality assay for the DP release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided as a CBE-30 by XXX, XX, 20XX (UTC to provide date).

PMC#17: To confirm compatibility of drug product with IV bags and IV administration sets of different materials of construction. The compatibility study will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement by XXX, XX, 20XX (UTC to provided date).

PMC#18: To confirm compatibility of the drug product with the use of an in-line filter during administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement by XXX, XX, 20XX (UTC to provided date).

PMC#19: To re-evaluate dinutuximab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report by XXX, XX, 20XX (UTC to provide date).

PMC #20: To re-evaluate dinutuximab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis, and the statistical plan used to evaluate

the specifications, and any proposed changes to the specifications will be provided in the final report by XXX, XX, 20XX (UTC to provide date).

(b) (4)



Signatures

Laurie Graham, MS

CDER/OPS/OBP DMA/Team Leader

Laurie J.
Graham -S

Digitally signed by Laurie J. Graham -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130008068
8, cn=Laurie J. Graham-S
Date: 2015.03.01 18:30:22 -05'00'

Sarah Kennett, PhD

CDER/OPS/OBP/DMA/Review Chief

Sarah B.
Kennett -S

Digitally signed by Sarah B. Kennett -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000597165,
cn=Sarah B. Kennett -S
Date: 2015.03.02 11:07:49 -05'00'

Kathleen Clouse, PhD

CDER/OPS/OBP/DMA/Division Director

Kathleen A.
Clouse Strebel -S

Digitally signed by Kathleen A. Clouse Strebel -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300054511,
cn=Kathleen A. Clouse Strebel -S
Date: 2015.03.02 13:01:15 -05'00'

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	BLA125516/000	Action Goal:	
Stamp Date:	22-NOV-2013	District Goal:	11-OCT-2014
Regulatory:	10-DEC-2014		
Applicant:	(b) (4)	Brand Name:	UNITUXIN (DINUTUXIMAB)
		Estab. Name:	
		Generic Name:	
Priority:	1	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	107		001; SOLUTION, INJECTION; DINUTUXIMAB; 17.5MG

Application Comment: NEW BLA (on 10-JUN-2014 by C. CAPACCI-DANIEL () 3017963532)

MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 04-JUN-2014 by T. WILSON () 2404024226)

FDA Contacts:	C. THOMAS	Facility Reviewer	(HFD-320)	3017964853
	C. TORIGOE	Prod Qual Reviewer	(HFD-123)	3017965233
	L. NARASIMHAN	Micro Reviewer		3017960059
	G. DAVIS	Regulatory Project Mgr	(HFD-107)	3017960704
	M. DONOGHUE	Team Leader	(HFD-107)	3017965284

Overall Recommendation: PENDING on 06-JUN-2014 by EES_PROD
PENDING on 04-JUN-2014 by EES_PROD

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** **FEI:** (b) (4)
 (b) (4)
 (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE RELEASE TESTER

Establishment Comment: RELEASE TESTING: (b) (4) FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
SUBMITTED TO BMR NEW BLA	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PRODUCT AND DRUG SUBSTANCE RELEASE TESTING OPERATIONS.					
RESUBMISSION FROM BMR	23-JUN-2014	Waive Inspection			PRABHAKARAR
BLA PILOT - TESTING LAB. NO PLI REQUIRED.					
OC RECOMMENDATION	23-JUN-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PRODUCT AND DRUG SUBSTANCE RELEASE TESTING OPERATIONS.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER

Establishment Comment: ALTERNATE PACKAGING AND LABELING OF DRUG PRODUCT (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
SUBMITTED TO DO	06-JUN-2014	10-Day Letter			CAPACCIDANIC
HAS SVS PACKAGING & LABELING BEEN COVERED AT THIS FACILITY?					
DO RECOMMENDATION	09-JUL-2014			ACCEPTABLE	KDORAZIO
THE GMP INSPECTION OF (b) (4) WAS CLASSIFIED "VAI" WITH ACCEPTABLE PROFILES.					
OC RECOMMENDATION	09-JUL-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4)-DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PACKAGING AND LABELING OPERATIONS. THE (b) (4) AND (b) (4) PROFILES WERE UPDATED AND ARE ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
 [REDACTED] (b) (4)
 [REDACTED]
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
 FINISHED DOSAGE OTHER TESTER
Establishment Comment: COMPLEMENT DEPENDENT CYTOTOXICITY FOR DRUG SUBSTANCE AND DRUG
 PRODUCT. (on 10-JUN-2014 by T. WILSON () 2404024226)
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	10-JUN-2014				WILSONT
SUBMITTED TO DO	10-JUN-2014	Product Specific and GMP Inspection			CAPACCIDANIC
NEW TESTING FACILITY *PDUFA IS 10-DEC-2014*					
ASSIGNED INSPECTION TO IB	10-JUN-2014	Product Specific and GMP Inspection			WALTERSJ
PS REQUEST; NEW TESTING FACILITY					
ASSIGNED INSPECTION TO IB	30-JUL-2014	Product Specific and GMP Inspection			LTHOMAS
RE-ASSIGNED TO IB TO GET THE INSPECTION LINKED IN FACTS.					
SUBMITTED TO BMR	25-SEP-2014	Request BMR Evaluation			CAPACCIDANIC
BMR CONSULT, WILL BMAB DO THIS INSPECTION OR DO?					
REQUEST DO PERFORM PS INSP	25-SEP-2014	Request DO perform a Product-Specif			QIUZ
SUBMITTED TO DO	25-SEP-2014	Product Specific and GMP Inspection			CAPACCIDANIC
ALREADY FACTS #9588076					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
 (b) (4)
 (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Establishment Comment: RELEASE TESTING OF DRUG PRODUCT: STERILITY (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PRODUCT TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					
RESUBMISSION FROM BMR	23-JUN-2014	Waive Inspection			PRABHAKARAR
BLA PILOT - TESTING LAB. NO PLI REQUIRED.					
OC RECOMMENDATION	23-JUN-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PRODUCT TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE: (b) (4)
 (b) (4) on 04-JUN-2014 by I. WILSON () 2404024226)
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING AND CELL BANKING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
RESUBMISSION FROM BMR	23-JUN-2014	Waive Inspection			PRABHAKARAR
BLA PILOT - TESTING LAB. NO PLI REQUIRED.					
OC RECOMMENDATION	23-JUN-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
 (b) (4)
 (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: RABBIT PYROGEN TESTING FOR DP RELEASE (on 22-SEP-2014 by C. CAPACCI-DANIEL () 3017963532)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	22-SEP-2014				CAPACCIDANIC
SUBMITTED TO BMR	22-SEP-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
RESUBMISSION FROM BMR	24-SEP-2014	Waive Inspection			QIUZ
OC RECOMMENDATION	25-SEP-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
 (b) (4)
 (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Establishment Comment: RELEASE TESTING OF DRUG PRODUCT: STERILITY (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
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OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE AND DRUG PRODUCT TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					

SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTB PROFILE WAS UPDATED AND IS ACCEPTABLE.					

RESUBMISSION FROM BMR	23-JUN-2014	Waive Inspection			PRABHAKARAR
BLA PILOT - TESTING LAB. NO PLI REQUIRED.					

OC RECOMMENDATION	23-JUN-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTB PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** [REDACTED] **FEI:** (b) (4)
[REDACTED] (b) (4)
[REDACTED]

DMF No: [REDACTED] **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: RELEASE TESTING: ANTIBODY DEPENDENT CELL-MEDIATED CYTOTOXICITY FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM [REDACTED] (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
RESUBMISSION FROM BMR	23-JUN-2014	Waive Inspection			PRABHAKARAR
BLA PILOT - TESTING LAB. NO PLI REQUIRED.					
OC RECOMMENDATION	23-JUN-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM [REDACTED] (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE: (b) (4) (on 04-JUN-2014 by T. WILSON ()
 2404024226)
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4)-DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS AN ABBREVIATED CGMP SURVEILLANCE INSPECTION COVERING DRUG SUBSTANCE TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
RESUBMISSION FROM BMR	23-JUN-2014	Waive Inspection			PRABHAKARAR
BLA PILOT - TESTING LAB. NO INSPECTION REQUIRED.					
OC RECOMMENDATION	23-JUN-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4)-DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS AN ABBREVIATED CGMP SURVEILLANCE INSPECTION COVERING DRUG SUBSTANCE TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** UNITED THERAPEUTICS
1040 SPRING ST
SILVER SPRING, MD 209104004
FEI: 3003368324

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 06-JUN-2014 by C. CAPACCIDANIEL () 3017963532)
MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 06-JUN-2014 by C. CAPACCIDANIEL () 3017963532)

Profile: BIOTECHNOLOGY DERIVED API (b) (4) **OAI Status:** NONE
STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	06-JUN-2014				CAPACCIDANIC
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SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BIOTECH DS, PAI NEEDED					

INSPECTION PERFORMED	13-JUN-2014		13-JUN-2014		QIUZ
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SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY BLT-DO FROM MAY 20-29, 2013 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING (b) (4) API AND STERILE DRUG PRODUCT MANUFACTURING OPERATIONS. THIS SITE HAS NO INSPECTIONAL HISTORY FOR BIOTECH DRUG SUBSTANCE MANUFACTURING. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA.					

INSPECTION SCHEDULED	23-JUN-2014		13-JUN-2014		PRABHAKARAR
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SUBMITTED TO OC	06-JUN-2014				CAPACCIDANIC
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SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA, DP MANUFACTURER					

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA A CAPACCI-DANIEL
09/25/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS “Communication Group” is “BLA Administrative Form” and the “Communication Name” is “FRM-BLAADMIN-61 – Establishment Evaluation Request Form.”

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes. For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: **December 10, 2014**

Applicant Name: United Therapeutics Corp.
U.S. License #: 1993 (pending)
STN(s): STN 125561/0
Product(s): dinutuximab (Unituxin)
Summary: New BLA - testing site added

NOTE: Initial TB-EER for a testing site that was added to the BLA.

FACILITY INFORMATION

Firm Name: [REDACTED] (b) (4)
Address: [REDACTED] (b) (4)
FEI: [REDACTED] (b) (4)

Short summary of manufacturing activities performed: rabbit pyrogen testing for DP release

OVERALL RECOMMENDATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

COLLEEN THOMAS
09/19/2014

BLA STN 125516

Dinutuximab

United Therapeutics Corporation

Chikako Torigoe, PhD
Division of Monoclonal Antibodies

<\\Cdsub1\evsprod\BLA125516\125516.enx>

OBP CMC Review Data Sheet

1. **BLA#:** STN 125516

2. **REVIEW DATE:** 9/13/2014

3. **PRIMARY REVIEW TEAM:**

Medical Officer: Martha B Donoghue

Nonclinical: Dubravka Kufrin, Whitney Helms (TL)

Product Quality Team: Chikako Torigoe, Laurie Graham (TL)

BMAB or Facilities: Lakshmi Narasimhan (DS), Colleen Thomas (DP), Patricia Hughes (TL)

Clinical Pharmacology: Jingyu Yu

Biometrics: Sirisha Mushti

OBP Labeling: Jibril Abdus-Samad

RPM: Gina Davis

4. **MAJOR GRMP DEADLINES**

Filing Meeting: 5/9/2014

Mid-Cycle Meeting: 7/9/2014

Wrap-Up Meeting: 9/17/2014

Primary Review Due: 9/13/2014

Secondary Review Due: 9/17/2014

PDUFA Action Date: 12/10/2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC Pre-BLA Meeting	1/14/2014
Teleconference 1	7/18/2014
Information Request #1	7/21/2014
Information Request #2	8/6/2014
Information Request #3	8/29/2014
Information Request #4	9/5/2014
t-con	9/11/2014

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125516/0	4/11/2014	Yes
STN 125516/24	8/1/2014	Yes
STN 125516/30	8/19/2014	Yes
STN 125516/46	9/5/2014	Yes
STN 125516/47	9/11/2014	Yes
STN 125516/49	9/12/2014	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

- a. Proprietary Name: Unituxin
- b. Trade Name: dinutuximab
- c. Non-Proprietary/USAN: dinutuximab
- d. CAS name: 1363687-32-4
- e. Common name:
- f. INN Name: dinutuximab
- g. Compendial Name:
- h. OBP systematic name: MAB CHIMERIC (IGG1) ANTI GD2 [ch14.18]
- i. Other Names: ch14.18

8. **PHARMACOLOGICAL CATEGORY:** Disialoganglioside, GD2-binding chimeric monoclonal antibody

9. **DOSAGE FORM:** Injection, solution

10. **STRENGTH/POTENCY:**

- (i) The concentration/strength of the Drug Product: 3.5 mg/mL
- (ii) Type of potency assay (s): GD2 binding ELISA, CDC assay, ADCC assay

11. **ROUTE OF ADMINISTRATION:** Intravenous infusion

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)

(b) (4)	Provided	No review required as all the relevant information was in the BLA.
	Provided	No review required as all the relevant was in the BLA.
	Provided	No review required as all the relevant information was in the BLA.
	Provided	No review required as all the relevant information was in the BLA.

13. INSPECTIONAL ACTIVITIES

During the period of June 9, 2014 to June 13, 2014 an inspection was performed of the United Therapeutics, Corp. in Silver Spring, MD. This is the commercial manufacturing facility of drug substance and drug product. Five CDER officials attended the inspection: Dr. Lakshmi Rani Narasimhan, Dr. Colleen Thomas and Dr. Patricia Hughes from the Biotechnology Manufacturing Assessment Branch (BMAB) in the Office of Compliance, and Dr. Chikako Torigoe and Ms. Laurie Graham from the Division of Monoclonal Antibodies (DMA) in the Office of Biotechnology Products. Eight observations were noted by BMAB and two observations were noted by DMA in the 483. The observations are stated below. The observations made by DMA are #8 and 9. From an OBP perspective, none of these issues preclude approval.

1. Supplier criticality levels are not always assessed in accordance with SOP QA-630.00, Supplier Management Program. For example, (b) (4) was incorrectly defined as a supplier that provides products and services that do not directly affect drug product quality, safety, purity, identity, and performance. Because the (b) (4) is used to manufacture a sterile (b) (4) product (dinutuximab), (b) (4) should have been defined as a more critical supplier and the required on site audits should be scheduled accordingly.
2. Growth promotion testing for (b) (4) did not include a full panel of representative organisms in accordance with the USP<71>. Specifically, (b) (4) were not tested for growth promotion with a representative mold.

3. The equipment requalification program for the (b) (4) is not followed. Specifically, the two year requalification of (b) (4) (ID # 1069 and 1070) was not completed as required in SOP TVA-501, Sterilization Process Validation, section 7.2.3. Cleaning validation of equipment used in the dinutuximab drug substance manufacturing process is not adequate (VA-43334R, VA-43335R, VA-43337R). Specifically, bioburden and endotoxin were not monitored during cleaning validation of the (b) (4).
4. Microbial control of (b) (4) is inadequate. Specifically, (b) (4) do not have established bioburden and endotoxin limits and are not monitored prior to use.
5. (b) (4) have not been adequately validated from a microbial control perspective. For example, the (b) (4) and the hold time validation studies included in BLA 125516 did not include bioburden and endotoxin monitoring at the end of the hold.
6. (b) (4) are not adequately monitored for microbial control during storage. Bioburden and endotoxin samples are not taken at the end of storage (b) (4).
7. There is an inconsistency between the current methods used for release testing of dinutuximab drug substance and the methods described in the BLA. For example, the methods currently used for the detection of host cell proteins (SOP TQC-915) and the binding activity to GD2 (SOP TQC-910) are not the methods described in the BLA.
8. There is no comprehensive safety risk assessment of potential (b) (4) in the dinutuximab drug substance.
9. There is no approved procedure in place to manage Biological Product Deviations.

For the observation # 8, the sponsor was asked to update the BLA to have currently used analytical methods. For the observation #9, an information request was sent to the sponsor on 7/21/2014 and the results of the risk assessment were provided on 8/1/2014. A nonclinical consult review was requested on 8/25/2014. The assessments are included in the review.

14. CONSULTS REQUESTED BY OBP

The sponsor performed risk assessments of raw materials and extractables from the drug substance and drug product manufacturing processes. OBP requested that the non-clinical review team assess the toxicological portion of these assessments.

15. QUALITY BY DESIGN ELEMENTS

Risk assessments were performed to identify critical quality attributes (CQAs) and critical process parameters (CPPs). DoE studies were performed to verify the ranges of PPs.

16. PRECEDENTS

There are no precedents set by the review of this application.

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Laurie Graham, MS Team Leader, Division of Monoclonal Antibodies	See appended electronic signature
Chikako Torigoe, PhD Primary Reviewer Division of Monoclonal Antibodies	See appended electronic signature

B. CC Block

Recipient	Date
Gina Davis Clinical Division BLA RPM	Provided electronically

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the manufacture of Unituxin™ (dinutuximab) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Unituxin™ (dinutuximab) be approved for human use (under conditions specified in the package insert) provided that the issues regarding final specifications for drug substance and drug product are sufficiently addressed prior to the action date.

II. List Of Deficiencies To Be Communicated

There are no CMC deficiencies precluding approval of this BLA.

III. List of Potential Post-Marketing Commitments/Requirements

- 1) To re-assess drug substance (DS) and drug product (DP) specifications based upon additional clinical experience in ongoing trials with material manufactured with the commercial process.
- 2) To manufacture, qualify, and implement a new reference standard. This new reference standard will also be entered into a requalification program.
- 3) To validate an improved assay for the detection of host cell proteins. DS specifications will be updated with the improved assay
- 4) To validate a (b) (4) assay for the detection of (b) (4). The assay will be included in DS and DP specifications.
- 5) To establish and qualify a working cell bank, which will include a comparability assessment and testing of end of production cells from material manufactured at commercial scale.
- 6) To provide additional testing to confirm the monoclonality of the master cell bank.
- 7) To perform studies to support acceptable product quality and shipper performance during shipping of Unituxin. This should include consideration for shipping to testing sites.
- 8) To perform a leachable study of drug product at the end of shelf-life. This should include consideration for the detection of extractables observed in drug substance and drug product extractable studies.
- 9) To perform commercial scale (b) (4) lifetime studies.

10) To conduct studies to determine the root cause of [REDACTED] (b) (4) [REDACTED] in drug product stored under recommended conditions. Based on a risk assessment of the results, appropriate corrective and preventative actions will be implemented.

11) To validate the SEC-HPLC, cSDS, and cIEF purity assays for accuracy and sensitivity, and to validate the performance of the assays for the detection of the applicable product related impurities included the final drug substance and drug product specifications.

IV. Review Of Common Technical Document-Quality Module 1

The sponsor requests a categorical exclusion from the requirement for an environmental assessment under 21 CFR 25.31(c). The claim of categorical exemption is accepted.

V. Primary Container Labeling Review

Labeling review was performed by Jibril Abdus-Samad and the review is on file.

VI. Review of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

A review of the immunogenicity assays is provided at the end of this review.

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234 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHIKAKO TORIGOE
09/13/2014

LAURIE J GRAHAM
09/13/2014

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: BLA125516/000 **Action Goal:**
Stamp Date: 22-NOV-2013 **District Goal:**
Regulatory:
Applicant: UNITED THERAPEUTICS CORPORATIO **Brand Name:** UNKNOWN
Estab. Name:
Generic Name:
Priority: **Product Number; Dosage Form; Ingredient; Strengths**
Org. Code: 331

Application Comment: NEW BLA (on 10-JUN-2014 by C. CAPACCI-DANIEL () 3017963532)

MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 04-JUN-2014 by T. WILSON () 2404024226)

FDA Contacts:

C. THOMAS	Facility Reviewer	(HFD-320)	3017964853
G. DAVIS	Regulatory Project Mgr	(HFD-107)	3017960704
M. DONOGHUE	Team Leader	(HFD-107)	3017965284

Overall Recommendation:

PENDING	on 06-JUN-2014	by EES_PROD
PENDING	on 06-JUN-2014	by EES_PROD
PENDING	on 06-JUN-2014	by EES_PROD
PENDING	on 06-JUN-2014	by EES_PROD
PENDING	on 04-JUN-2014	by EES_PROD

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] (b) (4)
FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Establishment Comment: RELEASE TESTING: [REDACTED] (b) (4) FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
SUBMITTED TO BMR NEW BLA	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR

BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM [REDACTED] (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PRODUCT AND DRUG SUBSTANCE RELEASE TESTING OPERATIONS.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER

Establishment Comment: ALTERNATE PACKAGING AND LABELING OF DRUG PRODUCT (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
SUBMITTED TO DO	06-JUN-2014	10-Day Letter			CAPACCIDANIC
HAS SVS PACKAGING & LABELING BEEN COVERED AT THIS FACILITY?					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED OAI. PLEASE RE-SUBMIT THIS TB-EER 15-30 DAYS BEFORE THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE EVALUATION OF THIS SITE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Establishment Comment: COMPLEMENT DEPENDENT CYTOTOXICITY FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 10-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	10-JUN-2014				WILSONT
SUBMITTED TO DO	10-JUN-2014	Product Specific and GMP Inspection			CAPACCIDANIC
NEW TESTING FACILITY *PDUFA IS 10-DEC-2014*					
ASSIGNED INSPECTION TO IB	10-JUN-2014	Product Specific and GMP Inspection			WALTERSJ
PS REQUEST; NEW TESTING FACILITY					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THERE IS NO FDA INSPECTIONAL HISTORY FOR THIS SITE. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Establishment Comment: RELEASE TESTING OF DRUG PRODUCT: STERILITY (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PRODUCT TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE: (b) (4)
 (b) (4) on 04-JUN-2014 by T. WILSON (J 2404024226)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
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OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING AND CELL BANKING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					

SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Establishment Comment: RELEASE TESTING OF DRUG PRODUCT: STERILITY (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE AND DRUG PRODUCT TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTB PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: RELEASE TESTING: ANTIBODY DEPENDENT CELL-MEDIATED CYTOTOXICITY FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR

BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: DRUG SUBSTANCE OTHER TESTER
 Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE: (b) (4) (on 04-JUN-2014 by T. WILSON ()
 2404024226)
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					
SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS AN ABBREVIATED CGMP SURVEILLANCE INSPECTION COVERING DRUG SUBSTANCE TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** UNITED THERAPEUTICS
1040 SPRING ST
SILVER SPRING, MD 209104004
FEI: 3003368324

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 06-JUN-2014 by C. CAPACCIDANIEL () 3017963532)
MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 06-JUN-2014 by C. CAPACCIDANIEL () 3017963532)

Profile: BIOTECHNOLOGY DERIVED API (b) (4) **OAI Status:** NONE
STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	06-JUN-2014				CAPACCIDANIC
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SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BIOTECH DS, PAI NEEDED					

SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY BLT-DO FROM MAY 20-29, 2013 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING (b) (4) API AND STERILE DRUG PRODUCT MANUFACTURING OPERATIONS. THIS SITE HAS NO INSPECTIONAL HISTORY FOR BIOTECH DRUG SUBSTANCE MANUFACTURING. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA.					

SUBMITTED TO OC	06-JUN-2014				CAPACCIDANIC
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SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA, DP MANUFACTURER					

SUBMITTED TO BMR	18-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY BLT-DO FROM MAY 20-29, 2013 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING STERILE DRUG PRODUCT MANUFACTURING OPERATIONS. THE SVS PROFILE WAS UPDATED AND IS ACCEPTABLE. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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/s/

RANJANI PRABHAKARA
06/19/2014

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER

Establishment Comment: ALTERNATE PACKAGING AND LABELING OF DRUG PRODUCT (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
SUBMITTED TO DO	06-JUN-2014	10-Day Letter			CAPACCIDANIC
HAS SVS PACKAGING & LABELING BEEN COVERED AT THIS FACILITY?					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE (b) (4)
 (on 04-JUN-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) -DO FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING AND CELL BANKING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Establishment Comment: RELEASE TESTING OF DRUG SUBSTANCE: (b) (4) (on 04-JUN-2014 by T. WILSON ()
 2404024226)
Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	04-JUN-2014				WILSONT
OC RECOMMENDATION	06-JUN-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY (b) (4) DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** UNITED THERAPEUTICS
1040 SPRING ST
SILVER SPRING, MD 209104004
FEI: 3003368324

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 06-JUN-2014 by C. CAPACCIDANIEL () 3017963532)
MANUFACTURE OF THE DRUG SUBSTANCE AND DRUG PRODUCT, STORAGE OF THE MASTER CELL BANK, QUALITY CONTROL TESTING OF PRODUCTION RAW MATERIALS FOR DRUG SUBSTANCE AND DRUG PRODUCT, IN-PROCESS TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT, ASEPTIC FILLING OF FINISHED PRODUCT, RELEASE AND STABILITY TESTING FOR DRUG SUBSTANCE AND DRUG PRODUCT. (on 06-JUN-2014 by C. CAPACCIDANIEL () 3017963532)

Profile: BIOTECHNOLOGY DERIVED API (b) (4) **OAI Status:** NONE
STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	06-JUN-2014				CAPACCIDANIC
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BIOTECH DS, PAI NEEDED					
SUBMITTED TO OC	06-JUN-2014				CAPACCIDANIC
SUBMITTED TO BMR	06-JUN-2014	Request BMR Evaluation			CAPACCIDANIC
NEW BLA, DP MANUFACTURER					

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/s/

CHRISTINA A CAPACCI-DANIEL
06/18/2014

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number:

Applicant:

Stamp Date:

STN 125516/0

United Therapeutics
Corporation (UTC)

Established/Proper Name:
Unituxin (dinutuximab)

BLA/NDA Type:
Standard/Priority review

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed <input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: <input type="checkbox"/> PI –non-annotated <input type="checkbox"/> PI –annotated <input type="checkbox"/> PI (electronic) <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Insert <input type="checkbox"/> package and container <input type="checkbox"/> diluent <input type="checkbox"/> other components <input type="checkbox"/> established name (e.g. USAN) <input type="checkbox"/> proprietary name (for review)	Y Y N Y N Y N Y N Y N Y N Y N Y N Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> compatible file formats <input type="checkbox"/> navigable hyper-links <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays <input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	<i>Defer to OBP</i>
<input type="checkbox"/> Novel Excipients	Y N	<i>Defer to OBP</i>
<input type="checkbox"/> Executed Batch Records	N	
<input type="checkbox"/> Method Validation Package	N	
<input type="checkbox"/> Comparability Protocols	N	

CTD Module 3 Contents	Present ?	If not, justification, action & status
Module Table of Contents [3.1]	N	
Drug Substance [3.2.S]	Y	
<input type="checkbox"/> general info	Y	
<input type="radio"/> nomenclature		
<input type="radio"/> structure (e.g. sequence, glycosylation sites)		
<input type="radio"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	<i>Specific role of release and stability testing sites are not defined. IR has been sent out.</i>
<input type="checkbox"/> description of manufacturing process and process control	Y	
<input type="radio"/> batch numbering and pooling scheme		
<input type="radio"/> cell culture and harvest		
<input type="radio"/> purification		
<input type="radio"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y N	<i>Defer to OBP</i>
<input type="radio"/> raw materials and reagents		
<input type="radio"/> biological source and starting materials		
<input type="radio"/> cell substrate: source, history, and generation		
<input type="radio"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and	Y	<i>Bioburden, endotoxin</i>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
intermediates <ul style="list-style-type: none"> ○ justification of specifications ○ stability <input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ specifications ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> ○ protocol ○ results 	 Y Y Y N Y Y Y Y Y N Y Y	 <i>No summary tables of bioburden and endotoxin results are included in the Process Validation section. Requested the sponsor to include the bioburden and endotoxin results in the table.</i> <i>Defer to OBP</i> <i>Defer to OBP</i> <i>Bioburden and endotoxin test at 9, 12 and 18 month time points</i>
Drug Product [3.2.P] [Dosage Form] <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula	 Y Y N Y Y Y	 Not applicable.

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
<input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
<input type="checkbox"/> controls of critical steps and intermediates	Y	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y	
<input type="checkbox"/> Filter validation	Y	Data is not summarized. Sponsor will be asked to provide a summary in 3.2.P.3.5.
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y	Some of the information is provided in attached validation reports, but not summarized in 3.2.P.3.5. The sponsor may be asked to provide summary information.
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y	Minimal information provided.
<input type="checkbox"/> Environmental Monitoring Program	Y	Provided in 3.2.A.1. The sponsor will be asked to move this information to 3.2.P.3.5.
<input type="checkbox"/> Lyophilizer validation	N	Not applicable.
<input type="checkbox"/> Other needed validation data (hold times)	N	The sponsor indicates that hold times were validated during media fills. This data will be requested.
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	N
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
<input type="checkbox"/> reference standards or materials	Y	N
<input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <input type="checkbox"/> administration device(s) 	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
validation; excipients of human/animal origin, other novel excipients) <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> ○ protocol ○ results 	Y N Y N Y N Y N	
Other components to be marketed (full description and supporting data, as listed above): <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit)	 Y N Y N	Not applicable.
Appendices for Biotech Products [3.2.A] <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed 	Y Y N	<i>Defer to OBP</i>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present ?	If not, justification, action & status
bulk <input type="radio"/> viral clearance studies <input type="radio"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	Y N	<i>Defer to OBP</i>
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <input type="checkbox"/> method validation package <input type="checkbox"/> comparability protocols	Y N Y N Y N	<i>Defer to OBP</i> Validation for micro assays provided in 3.2.P.5. <i>Defer to OBP</i>
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	NA
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	NA
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	NA
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen	N	Rabbit pyrogen test data will be requested.

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
<input type="checkbox"/> mycoplasma	Y N	<i>Defer to OBP</i>
<input type="checkbox"/> sterility	Y N	Not applicable.
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	NA
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

COLLEEN THOMAS
06/06/2014

LAKSHMI RANI NARASIMHAN
06/06/2014

ZHIIHAO PETER QIU
06/06/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS “Communication Group” is “BLA Administrative Form” and the “Communication Name” is “FRM-BLAADMIN-61 – Establishment Evaluation Request Form.”

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes. For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: **December 10, 2014**

Applicant Name: **United Therapeutics Corp.**
U.S. License #: **1993 (pending)**
STN(s): **STN 125561/0**
Product(s): **dinutuximab (Unituxin)**
Summary: **New BLA**

FACILITY INFORMATION

Firm Name: **United Therapeutics Corporation**
Address: **1040 Spring Street, Silver Spring, MD 20910**
FEI: **3003368324**

Short summary of manufacturing activities performed:

Manufacture of the drug substance and drug product, Storage of the master cell bank, Quality control testing of production raw materials for drug substance and drug product, In-process testing for drug substance and drug product, Aseptic filling of finished product, Release and stability testing for drug substance and drug product.

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Manufacture of the master and working cell banks

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Storage of the master and working cell banks

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Release testing of drug substance: (b) (4)

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Release testing: Antibody dependent cell-mediated cytotoxicity for drug substance and drug product.

Firm Name: (b) (4)
Address: (b) (4)
FEI: **None**
Short summary of manufacturing activities performed:
Release testing: Complement dependent cytotoxicity for drug substance and drug product.

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Release testing of drug substance: (b) (4)

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Release testing: (b) (4) for drug substance and drug product.

Firm Name: **United Therapeutics Corporation**
Address: **55 TW Alexander Drive, Research Triangle Park, NC 27709**
FEI: **3003825766**
Short summary of manufacturing activities performed:
Packaging and labeling of drug product

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Release testing of drug product: Sterility

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Release testing of drug product: Sterility

Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed:
Alternate packaging and labeling of drug product

OVERALL RECOMMENDATION

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/s/

LAKSHMI RANI NARASIMHAN
05/19/2014

COLLEEN THOMAS
05/19/2014