CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125516Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125516 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:Division of Oncology Products 2 PDUFA Goal Date: 12/10/14 Stamp Date: 4/11/2014

Proprietary Name: Unituxin (proposed)

Established/Generic Name: dinutuximab

Dosage Form: 17.5 mL/5 mL

Applicant/Sponsor: United Therapeutics Corporation

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of high risk neuroblastoma

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

GINA M DAVIS
06/25/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

BLA # 125516	Original BLA	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Unituxin Established/Proper Name: dinutuximab Dosage Form: Injection, for intravenous infusion		Applicant: United Therapeutics Corporation Agent for Applicant (if applicable): N/A
RPM: Gina Davis		Division: Division of Oncology Products 2 (DOP 2)

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

Actions	
• Proposed action • User Fee Goal Date is March 10, 2015 (ext. by 3 months)	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes info. advisory ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other - Bursts
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval Letter: March 10, 2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included March 2, 2015
• Original applicant-proposed labeling	☒ Included April 11, 2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included February 25, 2015
Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	July 10, 2014 – Letter June 30, 2014 - Review
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ June 10, 2014 DMEPA: ☒ August 18, 2014 OBP: ☒ December 5, 2015 OPDP: ☒ February 19, 2015 PMHS: ☒ Peds. Rev. February 13, 2015 Maternal Rev. November 3, 2014
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2) June 10, 2014
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included BLA - not applicable
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Applications receiving orphan designation for their proposed indication are exempt from PREA and a subsequent PeRC review. Pediatric page uploaded in DARRTs.	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	3/9/2015 – Label PMR/PMC disc. 3/9/2015 – Label PMR/PMC disc. 3/9/2015 – Label PMR/PMC disc. 3/4/2015 – Label PMR/PMC disc. 3/2/15 – Label PMR/PMC disc. 2/25/15 – I/R 2/23/15 - Label PMR/PMC disc. 2/18/15 – I/R 2/17/15 – I/R 2/15/15 – Label PMR/PMC disc. 2/9/15 – I/R 2/06/15 - I/R 2/5/15 – Labeling Discussions 1/5/15 – I/R 12/7/14 – Ltr extending goal date 12/1/14 – I/R 11/19/14 – I/R 11/19/14- I/R 11/5/14 - I/R 11/4/14 – I/R 10/29/14 – I/R 10/29/14 – I/R 10/19/14 – I/R 10/15/14 – I/R 10/7/14 – I/R 10/7/14 – I/R 9/24/14 – Late Cycle Communic. 9/23/14 – I/R 9/17/14 – I/R 9/17/14 – I/R 9/12/14 – I/R 9/10/14 – I/R 9/10/14 – I/R 9/10/14 – I/R 9/9/14 – I/R 9/5/14 – I/R 9/5/14 – I/R 8/29/14 – I/R 8/28/14 – I/R 8/27/14 – I/R 8/26/14 – I/R 8/25/14 – I/R 8/25/14 – I/R 8/20/14 – I/R 8/20/14 – I/R 8/19/14 – I/R

	8/19/14 – I/R 8/18/14 – I/R 8/15/14 – I/R 8/15/14 – I/R 8/7/14 – I/R 8/6/14 – I/R 8/6/14 – I/R 7/29/14 – I/R 7/28/14 – I/R 7/21/14 – I/R 7/21/14 – I/R 7/18/14 – I/R 7/18/14 – M.Cycle communication 7/17/14 – I/R 7/10/14 – I/R 7/2/14 – I/R 7/2/14 – I/R 7/2/14 – Ggeneral advice letter 7/2/14 – Labeling discussions 6/25/14 – I/R 6/24/14 – 74 day Letter 6/10/14 – Filing Letter 5/31/14 – I/R 5/22/14 – 1/R 5/22/14 – I/R 5/14/14 – I/R 5/13/14 – I/R 5/8/14 – I/R 5/8/14 - I/R 4/30/14 – I/R 4/25/14 – Ack. Letter 4/25/14 - I/R – App. Or. Memo
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	3/9/15- Telecon(uploaded 3.11.15) 3/3/15 –Telecon(uploaded 3.4.15) 2/24/15 – memo - peds. voucher 10/21/14 – Discussion with OND 10/3/14 – Oct monthly meeting 9/10/14 – Sep monthly meeting 8/25/14 - Aug monthly meeting 7/18/14 – July monthly meeting converted to post-midcycle meeting – discussion with UTC. 6/2014 – June – no monthly mtg 4/25/2104 – Planning Meeting
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	March 7, 2014 all disciplines mtg January 14, 2014 - CMC mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ July 18, 2014
• Late-cycle Meeting *(indicate date of mtg)*	☒ October 6, 2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	

Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	March 10, 2015
Division Director Summary Review *(indicate date for each review)*	March 9, 2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	March 6, 2015
PMR/PMC Development Templates *(indicate total number)* – PMRs (5) PMCs (24)	March 11 and March13, 2015
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review - see CDTL Review
• Clinical review(s) *(indicate date for each review)*	March 5, 2015 (addendum) September 16, 2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 27 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	September 12, 2014– REMs review - REMs not required
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	October 14, 2014 October 6, 2014 September 18, 2014 September 19, 2014
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	September 13, 2014

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	February 8, 2015 (addendum) September 12, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	September 17, 2014
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	September 12, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ March 1, 2015
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☒ September 13, 2014 February 27, 2015 (addendum)
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Reviewer DS – September 19, 2014 Reviewer DP – December 10, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 8 of the CMC review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)* ***(see email attached to AP checklist)***	Date completed: March 10, 2014 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)* **N/A**
• Finalize 505(b)(2) assessment	☐ Done **N/A**
❖ For Breakthrough Therapy(BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)* **N/A**
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done – March 10, 2015
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done – March 10, 2015
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done – March 10, 2015
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done - March 10, 2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516 – United Therapeutics Corporation – Unituxin (dinutuximab) - Teleconference

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Sponsor Attendees:

Mary Smith, PhD - Associate Vice President, Product Development
Noah Byrd, PhD, RAC – Associate Director, Regulatory Affairs
Dean Bunce – Executive Vice President, Regulatory Affairs & Compliance

FDA Attendees:

Suzanne Demko, P.A. – C, Medical Team Lead, Division of Oncology Products 2, (DOP 2)
Martha Donoghue, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2

Background:

On March 9, 2015, a teleconference was held with United Therapeutics Corporation (UTC) to discuss FDA's changes/edits to the Unituxin (dinutuximab) package insert (PI).

Discussion:

On March 9, 2015, DOP 2 discussed additional edits to the Unituxin (dinutuximab) PI. UTC agreed with the Division's changes.

Action:

UTC will formally submit the label containing agreed upon changes/edits, between UTC and FDA, on March 9, 2015.

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/s/

GINA M DAVIS
03/11/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; FDA Proposed labeling

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

We also refer to our communication dated March 2, 2015, and to your amendment dated March 4, 2015 regarding the Unituxin (dinutuximab) package insert (PI). We have reviewed your March 4, 2015, submission and made edits to the PI. Please review the attachment that will be discussed at today's teleconference.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
FDA Proposed Labeling

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GINA M DAVIS
03/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC - PMR

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please also refer to our amendment dated February 15, 2015, regarding the post-marketing requirements (PMRs)/post-marketing commitments (PMCs) associated with Unituxin (dinutuximab). Our safety requirements team has reviewed the PMRs and the PMCs listed in that communication and determined that PMC #20, associated with PMR #5, is a PMR.

PMR 2878-3

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.

PMR Schedule Milestones:

Please review the PMR listed above and provide a response by close of business today, March 9, 2015 or sooner. If you have any questions or concerns please contact me.

Thank you,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
03/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; FDA Proposed labeling

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

We also refer to our communication dated February 15, 2015 and your February 20, 2015, response to the post-marketing requirements (PMRs)/post-marketing commitments (PMCs) associated with Unituxin (dinutixumab). We have reviewed your submission and request that you provide a date when you plan to submit your final report for the following PMC.

2878-26 Conduct a study, including analyses, to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product. Study results will be updated annually in the BLA Annual Report until the final PMC study report is submitted.

Final Report Submission:

Please provide a response to the aforementioned request by close of business today. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
03/09/2015

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

IND 110494

MEETING MINUTES

United Therapeutics Corporation
Attention: Noah Byrd, Ph.D.
Associate Director, Regulatory Affairs
55 TW Alexander Drive, P.O. Box 14186
Research Triangle Park, NC 27709

Dear Dr. Byrd:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for chimeric monoclonal antibody (mAb) 14.18 (ch 14.18).

We also refer to the meeting between representatives of your firm and the FDA on February 19, 2014. The purpose of the meeting was to discuss and reach agreement on the acceptability of the proposed Biologics License Application (BLA) submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

We have also reviewed your February 24, 2014, amendment requesting that the datasets to be provided to the Office of Scientific Investigations (OSI) be submitted as a late component to the marketing application for ch 14.18. Our response to your submission is noted as an addendum to the meeting minutes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Appendix I – OSI pre-NDA\BLA Request
Appendix II – Additional DOP 2 CDISC Guidance
Appendix III – CMC Meeting Minutes
Addendum – FDA response to February 24, 2014, amendment

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	pre-BLA Meeting
Meeting Date and Time:	February 19, 2014
Meeting Location:	CDER WO 22, Room 1313
Application Number:	IND 110494 – (BLA 125516)
Product Name:	ch 14.18
Indication:	Treatment of Neuroblastoma
Sponsor/Applicant Name:	United Therapeutics Corporation
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Gina Davis

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Gregory Reaman, M.D., Associate Director

Division of Oncology Products (DOP 2)
Patricia Keegan, M.D., Director, DOP 2
Suzanne Demko, P.A. – C., Clinical Team Lead, DOP 2
Joohee Sul, M.D., Medical Officer, DOP 2
Denise Casey, M.D., Medical Officer, DOP 2
Martha Donoghue, M.D., Medical Officer, DOP 2
Lola Fashoyin-Aje, M.D. Medical Officer, DOP 2
Karen Jones, Chief, Project Management Staff, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2

Division of Hematology Oncology Toxicology (DHOT)
Whitney Helms, Ph.D., Supervisor, DHOT
Dubravka Kufrin, Ph.D., Toxicology Reviewer, DHOT

Division of Clinical Pharmacology V (DCP V)
Nam Atiqur Rahman, Ph.D., Supervisor, DCP V
Hong Zhao, Ph.D., Team Lead, DCP V
Runyan Jin, Ph.D., Clinic Pharmacology Reviewer, DCP V

Division of Biometrics V (DB V)
Kun He, Ph.D., Team Lead, Division of Biometrics V (DB V)
Xiaoping Jiang, Ph.D., Statistical Reviewer, DB V

Division of Monoclonal Antibodies (DMA)
Laurie Graham, Ph.D., CMC Team Lead, DMA
Chikako Torigoe, Ph.D., CMC Reviewer, DMA

Division of Risk Management (DRISK)
Robert Pratt, PharmD., Risk Management Analyst

Eastern Research Group
Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Dr. L. Mary Smith, Senior Director, Product Development
Dr. Noah Byrd, Associate Director, Regulatory Affairs
Dr. Rita Lee, Regulatory Scientist, Regulatory Affairs
Mr. Dean Bunce, Executive Vice President, Compliance and Regulatory Affairs
Mr. Rex Mauthe, Associate Vice President, Regulatory Affairs
Dr. Allison Lim, Senior Clinical Research Scientist
Mrs. Jody Cleveland, Associate Director, Biostatistics
Mr. David Pressley, Senior Manager, Clinical Data Programming
Dr. Elizabeth Garrard, Senior Director, Safety Risk Management
Dr. Stephen Godin, Nonclinical Scientist
Dr. Wendy London, Associate Professor of Pediatrics, (b) (6) and Statistician COG

1.0 BACKGROUND

Ch14.18 is a chimeric mouse-human monoclonal antibody derived from the murine antibody [mAb 14.G2a] that binds to the ganglioside, GD2. Its proposed mechanism of action is via binding to GD2-expressing tumors and induction of antibody-dependent cell mediated cytotoxicity and complement-dependent cytotoxicity against GD2-expressing tumor cells. GD2 has been reported to be expressed in malignant melanoma, neuroblastoma, osteosarcoma and small cell carcinoma of the lung.

United Therapeutics Corporation (UTC) and the National Cancer Institute (NCI) executed a Cooperative Research and Development Agreement (CRADA) on July 1, 2010 to collaborate on the late-stage development of ch14.18 for the treatment of neuroblastoma (b) (4) in combination with granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2) and isotretinoin (RA).

UTC proposes to submit a BLA for ch14.18 for the treatment of patients with high risk neuroblastoma (b) (4) in

combination with GM-CSF, IL-2, and RA. Data derived from Study ANBL0032, entitled "Phase III Randomized Study of Chimeric Antibody 14.18 (Ch14.18) in High Risk Neuroblastoma Following Myeloablative Therapy and Autologous stem Cell Rescue," provide the primary basis to support this BLA. UTC also plans to submit supportive safety and efficacy data from additional studies conducted in patients with neuroblastoma and melanoma.

Study ANBL0032 is an open-label multicenter trial that randomized 226 patients (1:1) to receive either isotretinoin (160 mg/m^2/day divided into two daily doses on Days 1-14 of six consecutive 28-day cycles) or experimental therapy. Experimental therapy consisted of six 28-day day cycles of therapy according to the following regimen:

- Cycles 1,3,5**:** GM-CSF (250 µg/m^2/d) on Days 0- 13, ch14.18 (25 mg/m^2/day) on Days 3-6, and RA (160 mg/m^2/day) on Days 10-23
- Cycles 2 and 4**:** IL-2 (3.0 x 10^6 IU/m^2/day) on Days 0-3, IL-2 (4.5 x 10^6 IU/m^2/day) on Days 7-10, ch14.18 (25 mg/m^2/day) on Days 7-10 and RA (160 mg/m^2/day) on Days 14-27
- Cycle 6: RA (160 mg/m^2/day) for 14 days.

Eligible patients had high-risk neuroblastoma diagnosed at less than 31 years of age confirmed by central and local review. Patients were also required to fulfill the following additional criteria: completion of induction therapy, autologous stem cell transplantation, and radiotherapy; achievement of at least a partial response at the time of evaluation prior to ASCT; receipt of ASCT within 9 months after initiation of induction therapy; enrollment between day 50 and Day 100 following completion of ASCT; and absence of progressive disease (PD). Patients with biopsy-proven residual disease after autologous stem-cell transplantation were eligible for enrollment but were non-randomly assigned to receive the experimental regimen.

The primary endpoint of Study ANBL0032 was event-free survival (EFS), defined as the time from study enrollment to the occurrence of an event (relapse, PD, secondary malignancy, or death) in the intent-to-treat (ITT) population. Study ANBL0032 was originally designed to randomize 386 patients in order to provide 80% power to detect an absolute increase in 3-year EFS of 15% between the treatment groups (assuming 50% 3-year EFS in the control arm vs. 65% in the experimental arm), using a two-sided log-rank test at an alpha of 0.05. Enrollment of patients to the randomized portion of the study was suspended by the Data Safety Monitoring Board (DSMB) when a planned interim analysis of EFS after occurrence of 83 of the planned 137 EFS events (using data collected through January 13, 2009) met the criteria for early stopping of randomization on the basis of superiority of ch14.18 immunotherapy plus RA over RA alone. Since the close of randomization, Study ANBL0032 has remained open to treat patients with high-risk neuroblastoma with open-label ch14.18/IL-2/GM-CSF/RA following completion of the standard up-front regimen.

In the BLA submission, UTC proposes to provide two separate clinical study reports of data derived from Study ANBL0032: the DIV-NB-301 clinical study report which summarizes data from those patients who were randomly assigned to treatment per protocol ANBL0032

(amendment 8) prior to the close of randomization (January 13, 2009), and the DIV-NB-302 clinical study report which summarizes data from non-randomized patients. The DIV-NB-301 clinical study report provides analyses of data accumulated at three separate time points, including the interim analysis of efficacy leading to cessation of randomization (i.e., data accumulated prior to January 13, 2009), an analysis using a data cut-off date of June 30, 2009, and an analysis of follow-up data accumulated through June 30, 2012. The January 13, 2009 and June 30, 2009 analysis datasets contain 251 patients, including 113 randomized to the control arm, 113 randomized to the investigational arm, and 25 additional patients who were non-randomly assigned to receive investigational treatment. All data from the electronic Case Report Forms (eCRF) were included in the "soft lock database." The follow-up analysis data cut (June 30, 2012) contains data from 255 patients, including 114 randomized to the control arm, 114 randomized to the investigational arm, and 27 patients who were non-randomly assigned to receive investigational treatment.

In the interim efficacy analysis leading up to cessation of randomization, the 2-year point estimate of EFS was 66% (95% CI: 56%, 76%) in the experimental arm vs. 46% (95% CI: 36%, 57%); p=0.01. At the time of the interim analysis, 2-year overall survival was 86% (95% CI: 79%, 94%) in the investigational arm and 75% (95% CI: 65%, 84%) in the control arm; nominal p=0.02. In a follow-up analysis of overall survival using a data cut-off of June 30, 2012, the three year point estimates of overall survival (95% CI) were 82% (75%, 89%) for the investigational arm and 68% (59%, 77%) for the control arm.

On January 27, 2011, DOP 2 met with UTC to discuss the CRADA between UTC and NCI on the late stage development of the investigational product ch14.18, transfer of manufacturing responsibilities from NCI to UTC, UTC's intended approach to the manufacturing of ch14.18, and plans to demonstrate material comparability between ch14.18 produced by NCI and ch14.18 produced by UTC. At the meeting, UTC stated that in collaboration with NCI (SAIC-Frederick, BDP), they would assume manufacturing responsibility for on-going and future studies with the goal of filing a Biologics License Application (BLA) for use of ch14.18 in combination with GM-CSF, IL-2, and RA in patients with high risk neuroblastoma (b) (4) In this meeting, DOP 2 stated that if UTC provides data to demonstrate that UTC-derived ch14.18 is comparable to NCI-derived ch14.18, data from Study ANBL0032 can be submitted as the single trial supporting efficacy of ch14.18 in combination with GM-CSF and IL-2 as a component of standard treatment of patients with high risk neuroblastoma (b) (4) DOP 2 also emphasized that UTC was responsible for the content and quality of the application.

PHARMACOKINETICS

UTC is currently conducting Study DIV-NB-201 to compare the pharmacokinetic (PK) profile of UTC-manufactured ch14.18 to NCI-manufactured ch14.18. United Therapeutics intends to file the BLA once the PK report is available from this study.

UTC stated that pharmacokinetic studies in the proposed BLA will include two tissue distribution studies utilizing radio-labeled ch14.18 and/or 14.G2a in normal Beagle dogs and tumor-bearing mice. Limited absorption data is also available in the literature and will be summarized in the BLA. In addition, exposure assessments in monkeys and rats were conducted for safety pharmacology and repeat-dose toxicity studies. Standard metabolism and excretion studies were not conducted; however, it is known that mAbs undergo catabolism and are degraded into inactive protein fragments and individual amino acids.

UTC states that the data that describe the tissue distribution and pharmacokinetic profiles of ch14.18 and/or its murine predecessors, will be presented in detail in the BLA.

TOXICOLOGY

UTC stated that no formal toxicology program was conducted for ch14.18. However, anti-GD2 antibodies, (ch14.18 or 14.G2a) have been administered to mice, rats, rabbits and dogs in academic settings. These studies, as described in UTC's IND 110,494, did not identify any major safety concerns. In addition, good laboratory practice (GLP) compliant tissue cross-reactivity studies with rat, rabbit and human tissues were conducted and staining with ch14.18 was generally consistent with reported sites of GD2 expression.

UTC states that a GLP-compliant 28-day repeat-dose toxicity and toxicokinetic study (b) (4) 354-003, submitted SN0021 09 September 2013) using UTC-manufactured ch14.18 was also conducted.

CHEMISTRY, MANUFACTURING AND CONTROLS

The chemistry, manufacturing and controls (CMC) information for the ch14.18 program was previously discussed in detail during the CMC-specific pre-BLA meeting held on January 14, 2014, and therefore is not included as part of this briefing package. The CMC information to be included in the BLA is generally addressed in the TOC for the BLA. Meeting Minutes from the CMC meeting (Appendix III) are included.

The meeting package was received on January 20, 2014, and preliminary comments were provided on February 18, 2014.

2.0 OBJECTIVES

On December 17, 2013, UTC requested a pre-BLA meeting to discuss and reach agreement on the acceptability of their proposed BLA submission.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. United Therapeutics has provided the planned table of contents for the BLA for ch14.18 in this pre-meeting package in Appendix B. Does the Division concur that planned items appear adequate to support filing and review of the BLA?

   FDA Response: There is inadequate detail in the meeting package for FDA to make a determination regarding whether the items planned for inclusion in the BLA are adequate to support filing. Confirm that the following deficiencies will addressed in the proposed submission

   a. FDA stated that Appendix B (BLA Table of Contents) does not include an integrated summary of safety and integrated summary of efficacy. Please provide an integrated summary of safety and integrated summary of efficacy in module 5.3.5.3 of the BLA. For additional information regarding the requirements for an ISE and ISS in marketing applications, please refer to FDA's April 2009 Guidance for Industry entitled "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, " available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf.

      Please ensure that the contents of Module 5 are consistent with the guidelines described in FDA's 2001 Guidance for Industry entitled "M4E: The CTD – Efficacy," available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129865.pdf and the 1996 ICH E3Guideline for Industry, entitled "Structure and Content of Clinical Study Reports," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073113.pdf.

      Include the following clinical information in the BLA submission:

      i. The protocol and all amendments for Study ANBL0032;

         Discussion during the meeting: UTC acknowledged FDA's response and no discussion occurred.

      ii. The final statistical analysis plan (SAP) before the date of data cut-off for the final analysis;

         Discussion during the meeting: UTC clarified that there is no SAP for ANB L0032 separate from that contained in the protocol for Study

ANBL0032. UTC confirmed that the most recent version of the ANBL0032 protocol prior to the data cut-off (Amendment 8) will be included in the BLA as the analysis plan for the trial. UTC will provide their SAP for the analysis of study reports for supportive or integrated analyses. FDA stated that this is acceptable.

iii. Minutes of data safety monitoring board (DSMB).

Discussion during the meeting: UTC acknowledged FDA's response and no discussion occurred.

Finally, as discussed during the September 1, 2005, teleconference with NCI, please ensure that the following information and data are included in the BLA submission:

iv. Data establishing the contribution of each therapeutic component (ch14.18, IL-2, and GM-CSF). As discussed at this meeting, an application without such data will not be considered complete.

Discussion during the meeting: UTC noted FDA's prior discussions with NCI regarding the need to provide data establishing the contribution of each therapeutic component (ch14.18, IL-2, and GM-CSF).

UTC will address this requirement in the ISE by referencing published literature and clinical study data. FDA stated that the approach is reasonable: the adequacy of the information to isolate the effects of ch14.18 will be determined during the BLA review.

v. Analyses of efficacy across relevant patient subgroups in Study ANBL0032, such as subgroup analyses in patients receiving purged and in those receiving unpurged stem cells, in patients treated with A3973-type induction, in patients treated with ANBL0532 induction, in patients treated with one transplant, and in patients treated with two transplants. As described in FDA's 1998 Guidance for Industry, entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," analysis of efficacy results for consistency across key patient subsets is an important factor in determining whether a single adequate and well controlled study provides sufficient evidence to support an effectiveness claim.

Discussion during the meeting: UTC acknowledged FDA's response and no discussion occurred.

b. Include the following additional nonclinical data in module 4 of the BLA submission:

i. Full copies of all referenced literature reports on which UTC plans to rely on to describe the pharmacology of the drug (mechanism of action and proof of concept).

Discussion during the meeting: UTC acknowledged FDA's response and no discussion occurred.

ii. A justification for the species used for toxicological assessment of the drug. In addition to the tissue cross reactivity studies, any available data on binding potency between human GD2 and the toxicological species used for this assessment should be included.

Discussion during the meeting**:** UTC acknowledged FDA's response and no discussion occurred.

iii. Copies of any referenced literature or primary reports of toxicological data which UTC wishes to rely on to support the safety of its ch14.18 product.

Discussion during the meeting: UTC acknowledged FDA's response and no discussion occurred.

iv. Either long-term (3 month) toxicology studies in 2 species (a rodent and a non-rodent) to assess the safety of ch14.18 administration over multiple cycles or a justification for why these studies are unnecessary or not possible. As described in ICH S9 (available at ich.org), both a rodent and a non-rodent long-term toxicology study (typically three months study for anticancer products) are typically needed for a complete BLA submission. A single three-month study in a relevant species may be sufficient, as discussed in ICH S6.

Discussion during the meeting: UTC acknowledged FDA's response and no discussion occurred.

FDA notes that there is a substantial history of clinical use of this antibody. If it is determined that after a detailed review of the available clinical and nonclinical data that the data are inadequate to address the safety of the product, additional nonclinical studies reflecting the pediatric population to be treated (i.e., use of juvenile or adolescent animals) may be requested as a postmarketing requirement (PMR).

c. Please see FDA's responses to Questions 3 and 4 regarding information to be supplied in the BLA for Clinical Pharmacology and Safety sections, respectively, and FDA's additional comment 12.

Discussion during the meeting: UTC acknowledged FDA's response and no discussion occurred.

2. The ongoing pivotal Phase 3 study, ANBL0032, sponsored by the NCI, has been written up as two separate clinical study reports (CSR), one summarizing the randomized subjects (DIV-NB-301), and the other summarizing the non-randomized subjects (DIV-NB-302) for ease of review. The DIV-NB-301 CSR presents three separate data cuts. The January 2009 data cut serves as the primary analysis for efficacy as this is the data cut that halted randomization per the data safety monitoring board's (DSMB) recommendation. Unfortunately, the raw data from this data cut which was used to generate the analysis data sets utilized by the COG for the efficacy analysis were corrupted and could not be recovered. For data traceability, UTC used the next available raw data from a 30 June 2009 data cut to confirm the primary (January 2009) efficacy analysis and to provide the safety analysis for the randomized subjects.

Finally, the 30 June 2012, data cut was used to provide additional follow-up safety and efficacy for the randomized subjects. This meeting package addresses the presentation of the efficacy and safety data cuts presented in the DIV-NB-301 CSR in Section 11.1.1.2.

FDA Response: Although a specific question regarding the efficacy and safety data cuts is not apparent, your proposed data cut-offs for efficacy analyses in the all-randomized population appear reasonable.

Discussion during the meeting**:** UTC acknowledged FDA's response to question 2 and no discussion occurred.

3. Study DIV-NB-201 is the UTC-sponsored pharmacokinetic (PK) clinical study comparing UTC-manufactured ch14.18 to NCI-manufactured ch14.18. United Therapeutics intends to file the BLA once the PK report is available from this study. Preliminary safety data (31December 2013 data cut) from the DIV-NB-201 study will be included in the Integrated Summary of Safety (ISS). A brief description of the study and preliminary data is presented in Section 11.1.3.

FDA Response: FDA acknowledges UTC's intention of filing the BLA once the PK report is available from study DIV-NB-201. Please apply the following advice in preparing the clinical pharmacology sections of the BLA submission:

a. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies. Refer to the Guidance for Industry *Bioanalytical Method Validation* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm368107.pdf

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(a) and no discussion occurred.

b. Submit the methods and validation reports for assays used for the detection of anti-product antibodies. Refer to the Guidance for Industry *Assay Development for Immunogenicity Testing of Therapeutic Proteins* at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf*

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(b) and no discussion occurred.

c. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK and PD. For example, domains related to safety (e.g., AE's) and efficacy, demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.

Discussion during the meeting: UTC has obtained data from all studies with ch14.18 conducted by NCI and COG and will provide datasets for PK where this information was collected in the clinical datasets. If PK data was not collected in the clinical datasets, summary information will be provided. UTC confirmed that patient identifiers will be consistent between PK, safety and efficacy datasets for Study ANBL0032 and Study DIV-NB-201. The PK comparability study will not have any efficacy data and will have only partial safety data. FDA acknowledged UTC's response.

d. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(d) and no discussion occurred.

e. Present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(e) and no discussion occurred.

f. Submit the following datasets to support the population PK analysis:

i. SAS transport files (*.xpt) for all datasets used for model development and validation
ii. A description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
iii. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
iv. A model development decision tree and/or table which gives an overview of modeling steps.

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(f) and no discussion occurred.

g. For the population analysis reports, submit:

i. The standard model diagnostic plots
ii. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
iii. Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
iv. A summary of the report describing the clinical application of modeling results.

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(g) and no discussion occurred.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for more information.

h. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for the product in the targeted patient population and include the results of this exploratory analysis in the BLA submission. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(h) and no discussion occurred.

i. Address the following clinical pharmacology related topics in the BLA submission:

i. Basis for selecting the dose(s) and dosing regimen used in the registration trial(s)
ii. Exposure-response relationships (dose-response, exposure-response) for efficacy
iii. Exposure-response relationships (dose-response, exposure-response) for safety
iv. Characteristics of distribution and excretion of ch 14.18
v. Any influence of the intrinsic factors (such as, but not limited to, gender, age, race, weight, disease, and genetic polymorphism) have on ch14.18 exposure and/or its pharmacodynamic response; their clinical impact if any; recommended dose and dosing regimen adjustments if any
vi. Any influence of the extrinsic factors (e.g. concomitant medications, etc.) have on ch14.18 exposure and/or its pharmacodynamic response; their clinical impact if any; recommended dose and dosing regimen adjustments if any
vii. Impact of immunogenicity on ch14.18 exposure and/or its pharmacodynamic response and their clinical impact
viii. Available data of the drug-drug interaction between ch14.18 and other drugs used in the combination or justification for not providing such data

Discussion during the meeting: UTC acknowledged FDA's response regarding 3(i) and no discussion occurred.

4. As the Division is aware, UTC did not enter into the CRADA with the NCI until July 2010 and, per DOP 2's EOP2 General Advice for Planned Marketing Applications, UTC does not have a formal quantitative safety analysis plan (QSAP), as this would have been created earlier in development. However, UTC has provided the statistical analysis plan (SAP) for the ISS as Appendix C of this meeting package. The SAP details the

integration of the available safety data across neuroblastoma trials and UTC has performed SAP-specified summaries against these data. United Therapeutics believes that the ISS contains the necessary elements as identified in the QSAP.

Does the Division concur?

FDA Response: Regarding the ISS, FDA has the following comments and requests for additional information to be submitted to the BLA:

a. Please ensure that the ISS includes an integrated and detailed discussion of safety data from the neuroblastoma trials in order to allow FDA to better assess the toxicity profile of ch14.18. If possible, also include analyses of adverse events by High-Level Terms (HLT) and High-Level Group Term (HLGT), and by Standardized MedDRA Queries (SMQs).

   Discussion during the meeting: UTC acknowledged FDA's response regarding 4(a) and no discussion occurred.

b. Section 11.3 (Page 20) of the Statistical Analysis Plan (SAP) for the ch14.18 Integrated Summary of Safety states that serious adverse events from Studies ANBL0032 and ANBL0931 are reported using CTCAE codes. Please ensure that all datasets and analyses of adverse events submitted to the BLA, including serious adverse events, are characterized using the verbatim term, MedDRA preferred term, and MedDRA SOC (and by HLGT and HLT if possible).

   Discussion during the meeting: UTC acknowledged FDA's response regarding 4(b) and no discussion occurred.

c. Please also clarify if analyses of adverse events by outcome i.e., (resolved vs. not resolved, leading to hospitalization, death or study drug discontinuation) will be performed and whether this information will be included in the adverse event datasets.

   Discussion during the teleconference: UTC stated that data regarding outcomes of adverse events will only be provided from Study ANBL0931 as this information was not collected in other studies. FDA acknowledged UTC's response.

d. Please provide shift tables for analyses of laboratory-related adverse events from baseline by CTCAE severity grade.

   Discussion during the meeting: UTC agreed to provide laboratory data for Study ANBL0931and shift tables for Study ANBL0931, if feasible, based on the manner

in which laboratory data were collected and captured in the datasets. FDA acknowledged UTC's response.

e. Section 11.5 (page 22) of the SAP for the ch14.18 Integrated Summary of Safety indicates that pregnancy data will not be summarized for the ISS. If there have been any pregnancies occurring during or within 30-days of study therapy across the clinical trials of ch14.18, please provide case narratives describing these events and their outcome in the BLA.

Discussion during the meeting: UTC acknowledged FDA's response regarding 4(e) and no discussion occurred.

5. Regarding the draft Guidance for Industry, Providing Submissions in Electronic Format – Summary Level Clinical Data for CDER's Inspection Planning, due to low patient enrollment (226 subjects enrolled across 90 clinical centers) over the course of eight years for the only randomized pivotal study (Study ANBL0032), the data available for the generation of the summary level clinical site data per guidance may be limited and therefore, per DOP 2's EOP2 General Advice for Planned Marketing Applications, UTC proposes to submit a table of clinical site information for the randomized pivotal study (Study ANBL0032) containing the following: site number, principal investigator, location (city/state), number of subjects randomized and number of subjects treated who prematurely discontinued. Number of subjects screened and number of protocol violations data is either unavailable or incomplete and therefore will not be included. United Therapeutics has prepared a table of site-specific data for the randomized portion of the Phase 3 study ANBL0032 (DIV-NB-301) and has included it in Appendix D for reference.

Does the Division agree UTC's proposal is acceptable?

FDA Response: Yes. The proposal to submit clinical site information is acceptable; however, submission of the summary level clinical data is voluntary. Please submit the information outlined in Parts 1 and Parts 2 of the OSI request (see Appendix I).

Discussion during the meeting: UTC acknowledged FDA's response to question 5 and no discussion occurred.

6. Given the fact that there is a single, randomized pivotal study, Study ANBL0032, UTC proposes that Section 2.7.3 Summary of Clinical Efficacy sufficiently serves as the Integrated Summary of Efficacy (ISE) and will therefore include a reference leaf in Section 5.3.5.3 to Section 2.7.3 for the ISE along with the appropriate analysis datasets.

Does the Division agree that this approach is acceptable?

FDA Response: Yes, this approach is acceptable provided that all of the information typically included in the ISE is provided in the SCE. For example, the summary of clinical efficacy should include a narrative analysis of the efficacy data from the non-randomized neuroblastoma studies and how these data relate to the efficacy results of Study ANBL0032. For additional information regarding the format and content of the ISE, please refer to FDA's 2008 Guidance for Industry, entitled "Integrated Summary of Effectiveness," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf.

Discussion during the meeting: UTC acknowledged FDA's response to question 6 and no discussion occurred.

7. Per prior discussion with the Division, UTC has collected electrocardiogram (ECG) data in a subset of patients enrolled in the ongoing, non-randomized portion of Study ANBL0032 through a protocol amendment with the NCI. Further, UTC is collecting ECG data in the UTC-sponsored PK study DIV-NB-201 as described in Section 11.1.3. United Therapeutics intends to submit all available ECG data from these two studies in the BLA.

FDA Response: FDA acknowledges UTC's revision to collect ECG monitoring in both Study ANBL0032 and Study DIV-NB-201 in response to the previous comments conveyed during the pre-IND meeting and UTC's intention to submit all available ECG data from these two studies in the BLA.

Discussion during the meeting: UTC will provide all available ECG data for Study ANBL0032 and Study DIV-NB-201 in the ISS and will include a listing of all patients with significant QT prolongation (e.g., QTc increases of 60 ms over baseline and QTc values greater than 500 ms). In addition, UTC will provide ECG data for thirty patients in a sub-study of Study ANBL0032 through the ECG warehouse. FDA acknowledged UTC's response.

8. United Therapeutics will provide CDISC compliant data implemented under SDTM IG v3.1.2 amendment 1 and ADaM IG v1.0. Data definition files will be provided in XML format for Study ANBL0032 (DIV-NB-301 and DIVNB-302), Study ANBL0931 (DIV-NB-303), and the ISS (DIV-NB-ISS). SDTM domains were created from CCG-0935, CCG-0935A and POG-9347 legacy study data where required for the ISS. A table summarizing the datasets for inclusion in the BLA is included in Section 11.1.4. Study Data Reviewer's Guides derived from the Pharmaceutical Users Software Exchange templates and a computational algorithm document will be provided for Studies ANBL0032 and ANBL0931.

Because of the nature of the ANBL0032 study all subjects (randomized and non-randomized) were represented in each database cut. United Therapeutics received three database cuts: one from June 2009, representing the randomized population from the DIV-NB-301 study report; one from June 2012, representing the follow-up data for the randomized population of the DIV-NB-301 study report and one from December 2013, representing the most current data reflected in the DIV-NB- 302 study report. United Therapeutics is proposing that we submit the June 2009 tabulation and analysis data as 'legacy' for DIV-NB-301, the June 2012 data as 'SDTM' and 'adam' for Study DIV-NB-301 and the December 2013 data as 'SDTM' and 'adam' for Study DIV-NB-302 and provide data definition files for each. Additionally, COG provided an analysis dataset of randomized patients which represented the data used at the time of their NEJM analysis in January 2009. United Therapeutics is proposing that we submit this analysis dataset as 'legacy' for Study ANBL0032 (DIV-NB-301).

FDA Response: FDA acknowledges UTC's proposal to submit the June 2009 tabulation and analysis data as 'legacy' for DIV-NB-301, the June 2012 data as 'SDTM' and 'ADaM' for Study DIV-NB-301, the December 2013 data as 'SDTM' and 'ADaM for Study DIV-NB-302, and the analysis dataset used for the January 2009 analysis of Study ANBL0032 reported by Yu et al in the NEJM in 'legacy' format. To ensure that the datasets conform to technical specifications that will enable reviewers to access and utilize the data for review, please refer to the February 2014 FDA Draft Guidance, entitled "Providing Regulatory Submission in Electronic Format – Standardized Study Data" available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM292334.pdf and the Study Data Standards for Submission to CDER resources page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

Please also refer to the attached documents that include requests for additional data to be included in the submission (for example, oncology specific variables – see Appendix II).

Please also include the following information in the BLA submission:

a. The stand-alone SAS programs that can be used to reproduce the major efficacy and safety results in the Clinical Study Report and the proposed labeling.

b. A document (.pdf) that provides descriptions of analyses, the names of datasets and variables used in the SAS programs.

c. A define file for the tabulated and analysis data sets in PDF format in addition to XML format.

Discussion during the meeting: UTC acknowledged FDA's response to question 8 and no discussion occurred.

9. Ch14.18 for the treatment of neuroblastoma has been granted Orphan Drug designation and UTC will be seeking priority review for the forthcoming BLA. Additionally, ch14.18 for the treatment of neuroblastoma has recently been granted "rare pediatric disease" status (Appendix E) by the Office of Orphan Products Development and UTC intends to request a rare pediatric disease priority review voucher (for future use) in the forthcoming BLA application.

   Does the Division concur that the BLA application for ch14.18 for the treatment of neuroblastoma warrants a priority review?

   FDA Response: A final determination regarding priority review can only be made after the BLA is submitted. Please ensure that the application contains your rationale for priority review request including a discussion as to how the application meets the requirements for priority review designation, as described in FDA's 2013 Guidance for Industry, entitled "Expedited Programs for Serious Conditions – Drugs and Biologics," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.

   If UTC believes that the requirements for eligibility for a priority review voucher have been met, include a request for a rare pediatric disease voucher in a cover letter to the BLA submission. For additional information regarding FDA's Rare Pediatric Disease Priority Review Voucher Program, please refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm375479.htm.

   Discussion during the meeting: UTC acknowledged FDA's response to question 9 and no discussion occurred.

10. The Phase 3 ANBL0931 clinical study report summarizes the comprehensive safety data for ch14.18 immunotherapy and RA treated subjects. Secondary endpoint data (event free and overall survival) for this study will not be presented in the clinical study report as these endpoint data are preliminary and under review by the COG; however, available data regarding survival will be included as a submitted abstract, at the time of BLA filing.

    FDA Response: FDA acknowledges that EFS and OS data for Study ANBL0931 will not be included in the clinical study report. Does UTC plan on including datasets for OS and EFS in the BLA submission? If not, please explain why this isn't possible. Please note that summary analyses for which the primary data are not submitted to the BLA generally are not included in product labeling and cannot be used in promotional materials, as FDA cannot verify the reported findings.

Discussion during the meeting: UTC stated that these data have not been cleaned and will not be available at the time of the BLA filing, but could be provided as a postmarketing commitment (PMC). FDA acknowledged UTC's response.

11. United Therapeutics does not believe that a REMS is necessary to ensure that the benefits outweigh the risks of ch14.18 as discussed in Section 11.1.5 of this document.

    Does the Division agree?

    FDA Response: Based upon the information that is currently available, FDA has determined that the application can be filed without a REMS; however, please provide a risk management plan for ch 14.18 for this indication. A final determination regarding the need for a REMS to ensure safe and effective use of ch14.18 for the proposed indication will be made upon review of the BLA.

    Discussion during the meeting: UTC acknowledged FDA's response to question 11 and no discussion occurred.

Additional Comments

Clinical

12. Please provide the following information in the BLA submission:

    a. Patient narratives for all serious adverse events, deaths while on study, premature discontinuations from study therapy or study participation (including those drop-outs categorized as "other", "lost to follow up" "physician discretion" or "subject decision"). Ensure that narrative summaries contain the following components:

        i. Subject age and gender
        ii. Signs and symptoms related to the adverse event being discussed
        iii. An assessment of the relationship of exposure duration to the development of the adverse event
        iv. Pertinent medical history
        v. Concomitant medications with start dates relative to the adverse events
        vi. Pertinent physical exam findings and test results (such as lab data, ECG data, etc.)
        vii. Discussion of the diagnosis as supported by available data
        viii. For events without a definitive diagnosis, a list of the differential diagnoses
        ix. Treatment provided
        x. Re-challenge and de-challenge results (if performed)
        xi. Outcomes and follow-up information

xii. An informed discussion of the case, allowing a better understanding of what the patient experienced.

Discussion during the meeting: UTC clarified that the ADEERS report will be provided for all patients experiencing death, premature discontinuation of treatment for toxicity and treatment-related serious adverse events in the ch 14.18 arm. In addition, ADEERS reports will be provided for the control arm; however, the requirements for data collection were different between the two arms. FDA acknowledged UTC's response.

b. Case report forms for each patient who died during the clinical study or who did not complete the study because of an adverse event, whether believed to be related to ch14.18 or not. UTC should be prepared to supply any additional CRFs that FDA deems necessary for review of the BLA with a rapid turnaround (i.e., within 7 days of request).

Discussion during the meeting: UTC acknowledged Comment 12b and no discussion occurred.

REGULATORY

Discussion of the content of a complete application

As stated in FDA's January 7, 2014, communication granting this meeting, an application that is the subject of this meeting is for a new molecular entity or an original biologic, will be subject to "the Program" under PDUFA V. During the interdisciplinary pre-BLA meeting, FDA and UTC should be prepared to discuss and reach agreement on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. UTC and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

- United Therapeutics Corporation (UTC) confirmed their plan to submit a complete marketing application for their investigational product, ch 14.18, based on the advice provided by FDA during this meeting and the pre-BLA CMC meeting held on January 14, 2014.

- UTC also confirmed that the BLA would include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that based on the information provided in the meeting package, FDA noted that substantial toxicity has been observed with this product. While FDA agreed that the proposed BLA could be filed with a risk management plan only, a final determination on the need for a REMS would be made during review of the safety information provided in the BLA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. UTC stated its intent to submit a complete application and therefore, there are no agreements for late submission of application components.

Pediatric Research Equity Act (PREA)

Under PREA (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this biological product for this indication has an orphan drug designation, you are exempt from this requirement.

Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA does not have any comments in regards to the questions contained within the briefing package; however, it is recommended that UTC submit a proprietary name for review if UTC intends to have one for this product. (See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

Office of Scientific Integrity (OSI)

In order for the application to be considered complete at final submission it must contain elements that fully address Part I (General Study Related Information and Comprehensive Clinical Investigator Information) and Part II (Subject Level Data Listings by Site) of the OSI Pre-NDA/BLA Request (See Attachment 1). Full compliance with Parts I and II in the application at or before final submission will facilitate and more importantly accelerate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the preparation of the inspection-supporting background packages. Inspection assignments and the background packages are essential to timely and successful clinical inspections conducted in support of the NDA.

Part III of the OSI Pre-NDA/BLA Request (Attachment 1) offers an opportunity for you to provide an electronic submission of Site Level Datasets on or prior to the complete submission of the NDA. These additional Site Level Datasets are for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the Site Level Dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link for the structure and format of this dataset.

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf)

APPENDIX I

Attachment I

OSI Pre-NDA/BLA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Part I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Part III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

Part I. Request for general study-related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
    a. Site number
    b. Principal investigator
    c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
    a. Number of subjects screened at each site
    b. Number of subjects randomized at each site
    c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the BA for each of the completed pivotal clinical trials:

4.

   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

5. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

6. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

Part II. Request for Subject Level Data Listings by Site

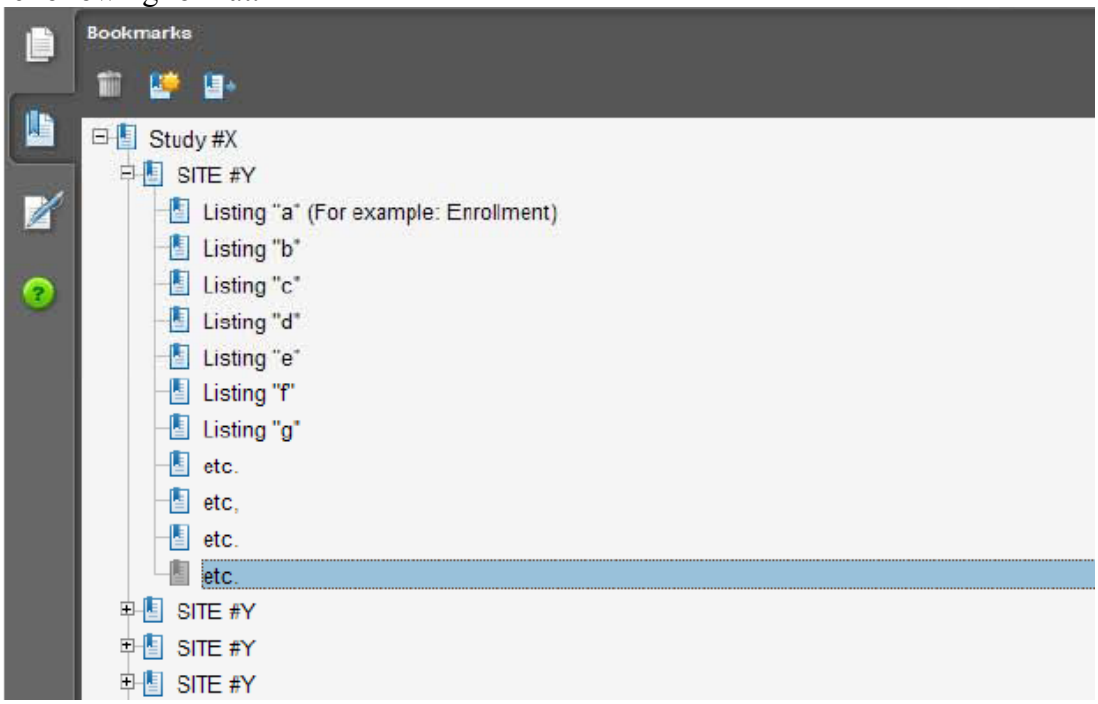
1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



Part III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

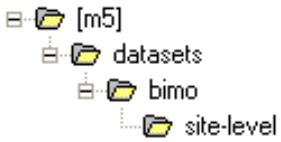
Attachment 2

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

OSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

APPENDIX II

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--

CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)
CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE,ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)

DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601
DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null

RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601
RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601

TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*
(2) RECIST Criteria - http://www.eortc.be/recist/
(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*
(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. *x.x* …….. One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3.*x x* …….. One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of “RADIOLOGIST 1” & “RADIOLOGIST 2”) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. “Percent Change From Nadir”) if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL=”INDEPENDENT ASSESSOR” and TREVALID=”RADIOLOGIST 1”. The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3.*x x* …….. One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

APPENDIX III
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA (CMC only)

Meeting Date and Time: January 14, 2014, 12:00-1:00 P.M. Eastern Standard Time (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: 110494
Product Name: chimeric monoclonal antibody (mAb) 14.18 (ch14.18)
Indication: Pediatric Neuroblastoma
Sponsor/Applicant Name: United Therapeutics Corporation

Meeting Chair: Laurie Graham, M.S.
Meeting Recorder: Lyndsay Hennessey

FDA ATTENDEES

Laurie Graham, M.S.	Team Lead, DMA
Chikako Torigoe, Ph.D.	Product Quality Reviewer, DMA
Patricia Hughes, Ph.D.	Team Lead, BMAB
Colleen Thomas, Ph.D.	Microbiology Reviewer, BMAB
Lakshmi Narasimhan Ph.D.	Microbiology Reviewer, BMAB
Martha Donoghue, M.D.	Medical Officer, OHOP
Lyndsay Hennessey	Regulatory Project Manager, OBP

SPONSOR ATTENDEES

Dr. L. Mary Smith	Senior Director, Product Development
Mr. Dean Bunce	Executive Vice President, Compliance and Regulatory Affairs
Dr. Noah Byrd	Associate Director, Regulatory Affairs
Mr. Rex Mauthe	Associate Vice President, Regulatory Affairs
Mr. Mark Farquharson	Senior Director, Biologic Process Development and Manufacturing
Dr. David Meh	Director of Process Development
Mr. Sam Mancuso	Senior Director, Quality
Mr. Patrick Poisson	Senior Vice President, Manufacturing, Sterile Products and Biologics
Mr. Thomas Higgs	Director, Quality Control

1.0 BACKGROUND

(i) **Purpose of meeting:** To discuss the status and acceptability of the manufacturing activities to support the filing of a BLA for ch14.18
(ii) **Drug product:** chimeric monoclonal antibody (mAb) 14.18 (ch14.18) for the treatment of neuroblastoma
(iii) **Brief history of events:** During a Type C meeting discussing the manufacturing and bioanalytical activities and topics in an Advice/Information Request letter dated June 28, 2012, as well as during an informal teleconference on August 28, 2013, the Division advised UTC to request a Pre-BLA, CMC-specific meeting to discuss the manufacturing program and the sufficiency of data and activities in greater detail to support the planned BLA filing around March 2014.

2.0 DISCUSSION

Question/Topic 1: Based on the ADCC data and transition plan provided in the pre-meeting package, does the Division concur with this approach and that the current CDC and GD2 ELISA potency assays are sufficient to support the BLA submission?

FDA Response to Question 1: *The acceptability of the plan will depend upon an overall risk assessment of the control strategy, including those attributes that can impact ADCC activity. For example, data provided in the meeting package indicate a correlation between ADCC activity and* (b) (4) *in which ADCC activity was impacted by even small changes in* (b) (4)*.*

Discussion: ***The sponsor stated that they plan to provide a risk assessment of the overall control strategy in the BLA.***

The sponsor indicated that they plan to continue to monitor ADCC activity as part of release and stability testing, but would file the BLA with the CDC and GD2 ELISA assays.

The Agency stated that for licensure, the overall control strategy would need to include control of ADCC activity.

The sponsor indicated that they will propose interim ADCC specifications in the BLA. The Agency expressed concerns about basing specifications on data from UTC manufactured batches as clinical use has relied mainly on NCI manufactured material and the NCI and UTC batches appear to differ in their ADCC activity. The sponsor indicated that they would provide some clinical use information for the UTC batches, but the data would be limited. The Agency indicated that the acceptability of the specifications would be a review issue based upon the totality of the evidence and recommended that specifications be set according to ICHQ6B.

Question/Topic 2: Does the Division concur with UTC's interpretation of the results of the forced degradation studies?

FDA Response to Question 2: *The forced degradation studies performed appear to be reasonable. However, a complete assessment of the stability data will be a BLA review issue. For the BLA, provide additional information on the stability impact ranking that was performed and reported in Table 7 of the meeting package. It is recommended that this table be updated to include all assays used in the studies, such as the CDC assay. Please confirm that the percent activity assessments in the forced degradation studies were based upon reference to 100% activity at time 0 (i.e. pre-treatment).*

Discussion: ***The sponsor accepted FDA's response, no discussion occurred.***

Question/Topic 3: United Therapeutics intends to file the BLA with 9 months Drug Substance and 24 months Drug Product stability data to support a minimum shelf-life of (b) ( ) months for Drug Substance and 18 months for Drug Product. Stability data available at the time of package preparation are included for discussion as it relates to material comparability and support of the proposed shelf-life.

FDA Response to Question 3: *Provide clarification as to whether the stability data in the BLA will be from the process validation batches or other batches that represent the commercial manufacturing process. Of note, as product quality changes have been observed in both DS and DP under real time storage conditions, additional information will be required to support that the specific changes observed are not likely to impact safety and/or efficacy of the product. This could include, for example, the identification of the different variants and an assessment of their impact on activity, safety, PK, and immunogenicity.*

Discussion: ***The sponsor stated that the BLA will contain stability data from both process validation and commercial batches. The sponsor confirmed that changes are not planned between commercial and validation processes.***

Question/Topic 4: During discussions with the Division over the course of ch14.18 product development, the need for the setting and narrowing of numerical acceptance criteria has been raised, specifically with regard to CDC, cIEF, and cSDS (reduced and non-reduced). United Therapeutics has established current product release and stability specifications for ch14.18 and has included them for drug substance and drug product in Section 10.5 of this pre-meeting package for discussion, as needed. Full justification for these specifications will be provided in the BLA.

FDA Response to Question 4: *Specifications will be a BLA review issue, but should include consideration for the principles described in ICH Q6B. It is recommended that polysorbate 20 levels be included in DP specifications.* (b) (4)

[redacted], *it is recommended that the DS bioburden release specification be set to* [redacted] *The BLA should contain a justification for the overall control strategy. For example, it is noted that the control strategy includes sub-visible particle testing* [redacted] *as well as multiple charge (i.e. cIEF and WCX) and SDS based assays (i.e. cSDS and SDS-PAGE) for both DS and DP.*

Discussion: ***The sponsor asked about the rationale for needing to include polysorbate 20 in specifications. The Agency specified that*** [redacted]. ***The sponsor stated*** [redacted] ***may not be possible prior to the currently proposed timeline for filing the BLA. The Agency recommended that the sponsor not alter their timing plans for filing the BLA. The Agency recommended that the sponsor include as much information as possible on the polysorbate 20 in the BLA, including raw material control information. This could include, but is not limited to, testing acceptance criteria, storage conditions, and stability (shelf-life) of any polysorbate 20 stock solutions.***

The sponsor also requested clarification on the need to lower the bioburden specification for the bulk drug substance and to increase the sample size for bioburden testing. [redacted] ***. The sponsor stated that they believed their process is robust and capable of maintaining microbial control because the process is conducted*** [redacted] ***. The Agency responded that the use of*** [redacted] ***may be justified given the*** [redacted] ***. However, a low bioburden specification is recommended for*** [redacted] ***drug substance bulks in order to maintain microbial control during storage.***

The sponsor suggested setting alert and action limits for bioburden. The Agency stated that the limits would be a review issue based on justification of operations and in-process limits.

Question/Topic 5: Process validation for drug substance and drug product has been completed. In addition, a summary of completed manufacturing activities is included in Section 10.6 in this pre-meeting package.

FDA Response to Question 5: *Insufficient information was provided for the FDA to comment on the process validation plans; therefore, this will be a BLA review issue.*

Discussion: ***The sponsor accepted FDA's response, no discussion occurred.***

Question/Topic 6: Does the Division agree that the current HCP method is sufficient to support the BLA submission and with UTC's plan that the updated assay be implemented upon availability?

FDA Response to Question 6: *The proposed strategy of filing the BLA with the current HCP assay may be acceptable depending upon the clinical development data to support the current HCP assay. The BLA will need to include qualification data for the antiserum, such as good quality copies of the 2-D gel and western blot images. However, in this situation, it would be the Agency's expectation that an assay with improved coverage would be developed and implemented post-licensure. The BLA should include available information on this updated HCP assay.*

Discussion: ***The sponsor accepted FDA's response, no discussion occurred.***

Question/Topic 7: United Therapeutics is inspection-ready. (b) (4) and a detailed schedule cannot be provided this far in advance; however, UTC is happy to work with the Division on scheduling an inspection during an active DP campaign if desired. A table of inspection history is provided in Section 10.8 for reference.

FDA Response to Question 7: *All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle.*

Discussion: ***The sponsor accepted FDA's response, no discussion occurred.***

ADDITIONAL CMC COMMENTS

The BLA should contain complete and detailed information generated to date to support the comparability of NCI and UTC manufactured material. Detailed information on manufacturing differences should be provided. The comparability assessment should include release, in-process, characterization data along with stability data comparing the rates and pathways of degradation. Any differences observed should be discussed in terms of the potential impact on safety and efficacy.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- *Evidence of bioburden and endotoxin monitoring at critical manufacturing steps using validated bioburden and endotoxin tests. The pre-determined bioburden and endotoxin limits should be provided. (b) (4) bioburden and endotoxin should reflect process capability. The BLA should indicate that bioburden monitoring samples are collected (b) (4) 3.2.S.2.4).*
- *Three successful (b) (4) validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
- *(b) (4) sanitization and storage validation data and information (3.2.S.2.5).*
- *Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).*
- *Data summaries of shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden and endotoxin release specifications. The bioburden limit should be (b) (4) (3.2.S.4).*
- *Qualification data for bioburden and endotoxin test methods performed for (b) (4) (3.4.S.4).*

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support aseptic processing operations and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

The following study protocols and validation data summaries should be provided in Section 3.2.P.3.5:

- *Bacterial (b) (4) retention study for the (b) (4).*
- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies. The equipment requalification program should be described and provided.*
- *In-process controls and hold times. Hold times should be validated at manufacturing scale.*
- *Three successful media fill runs, including summary environmental monitoring data obtained during the runs.*
- *A description of the routine environmental monitoring program.*
- *Isolator decontamination, if applicable.*
- *Data summaries of shipping validation studies.*

Provide the following information regarding drug product testing:

- *Qualification data for bioburden, sterility and endotoxin test methods performed for* (b) (4) *(where applicable) and the drug product.*
- *Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610(b).*
- *Performance of a validated container closure integrity test in lieu of the sterility test for stability samples is recommended every 12 months until expiry (3.2.P.2.5).*

The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

***Additional Meeting Discussion:* The Agency reminded the sponsor that hold time studies should be performed to determine the reliability of the endotoxin test results. Spiking studies on undiluted product should be performed to determine whether low endotoxin recovery occurs in the finished drug product.**

Discussion regarding inspection was also held. (b) (4) ***The Agency stated that a manufacturing schedule and product list should be provided in the BLA.***

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

All applications are expected to include a comprehensive and readily located list of all manufacturing facilities included or referenced in the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

ADDENUM

Memorandum

Date: March 6, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: IND 110494; United Therapeutics Corporation: FDA response to the February 24, 2014, request for information; This response will also serve as an addendum to the February 19, 2014, final meeting minutes

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Dear Dr. Byrd,

Please refer to your investigational new drug application (IND) submitted for the investigational product ch 14.18.

Please also refer to your February 24, 2014, amendment requesting that the datasets to be provided to the Office of Scientific Investigations (OSI) be submitted as a late component to the marketing application for ch 14.18.

We have reviewed your submission and have the following comment.

> At the February 19, 2014, pre-biologic license application meeting (BLA) you stated that a complete marketing application would be submitted to the Division of Oncology Products 2 (DOP 2) and there were no plans for submitting any late components to the original application. This agreement was made in accordance with the Prescription Drug User Fee Act V (PDUFA V).
>
> We are denying your February 24, 2014 request to submit datasets for use by OSI as a late component to the original application because a substantive review of your application cannot begin without these datasets. Therefore, you should delay submission of your BLA to ensure that your application is complete.

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
03/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 3, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516 – United Therapeutics Corporation – Unituxin (dinutuximab) - Teleconference

---

Sponsor Attendees:

Noah Byrd
Mary Smith
Hilary Hafeken
Allison Lim
Rex Mauthe
Dean Bunce
Sam Mancuso

FDA Attendees:

Suzanne Demko, P.A. – C, Medical Team Lead, Division of Oncology Products 2, (DOP 2)
Martha Donoghue, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2

Background:

On March 3, 2015, a teleconference was held with United Therapeutics Corporation (UTC) to discuss FDA's March 2, 2015, counter-proposal to UTC's February 12, 2015 proposal of the Unituxin (dinutuximab) package insert (PI).

Discussion:

On March 3, 2015, UTC stated that the March 2, 2015, FDA proposal of the Unituxin (dinutuximab) PI was acceptable. UTC stated that minor changes would be made with respect to typographical errors and formatting issues with respect to the tables listed in the PI.

Action:

UTC will formally submit the label containing agreed upon changes/edits, between UTC and FDA, on March 4, 2015.

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GINA M DAVIS
03/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 2, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Changes to the clinical POMR and FDA Proposed labeling

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.
Proposed

1. Please also refer to your February 27, 2015, amendment which provides revisions to the timelines for PMR #1 . We have revised PMR #1 listed below.

   Provide a comparison of comprehensive exposure and safety data for dinutuximab, pooling across lots and for each individual lot to the approximately 220 patients who complete treatment with dinutuximab with the historical experience observed in approximately 1100 patients treated with ch14.18 (manufactured by SAIC for the National Cancer Institute). Based on these data, provide thoughtful analyses of the safety and tolerability of marketed product, Unituxin, and an assessment regarding whether variations in antibody-dependent cell-mediated toxicity across dinutuximab lots alters the safety and tolerability of dinutuximab.

   The timetable you submitted on February 27, 2015, states that you will conduct this study according to the following schedule:

   PMR Schedule Milestones: Final Protocol Submission: September 2015
   Study/Trial Completion: June 2016
   Final Report Submission: December 2017

2. We also refer to your February 12, 2015, amendment in response to our February 5, 2015, proposal of the Unituxin (dinutuximab) package insert (PI). We have reviewed your submission and made edits to the PI. Please review the attachment that will be discussed at tomorrow's teleconference.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
FDA Proposed Labeling

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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GINA M DAVIS
03/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 25, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical Pharmacology

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> Final Report Submission (DIV-NB-302, -303, and -201): September 30, 2016
> Final Report Submission (NANT2011-04): June 30, 2019
>
> We would like to know how many patients will be included in each of the proposed reports and the total # of patients should not be less than 300. Please ask the applicant to provide the #.

Please provide a response to the aforementioned request by noon February 26, 2015. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
02/25/2015

Rare Pediatric Disease Priority Review Voucher eligibility checklist

Under section 529 of the Food, Drug, and Cosmetic Act, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act) for a rare pediatric disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product.

This checklist is intended to help determine if an NDA or BLA is eligible for a **Rare Pediatric Disease Priority Review Voucher.**

NDA/BLA	**Review Division**
BLA 125516 dinutuximab	**DOP 2**
Requirement	**Meets? (yes/no)**
For prevention or treatment of a *rare pediatric disease? (OOPD makes determination)*	Yes Designated 12/20/13
Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act?	Yes
FDA deems eligible for priority review?	Yes 6/10/14
Submitted under section 505(b)(1) (includes 505(b)(2) applications) of the FD&C Act or section 351(a) of the Public Health Service Act?	Yes
Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population?	Yes
Does not seek approval for an adult indication in the original rare pediatric disease product application?	Yes

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/s/

LARRY J BAUER
02/24/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 23, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC - PMR/PMC #13

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please also refer to your amendment dated February 20, 2015, regarding your proposed changes to the post-marketing requirement (PMR)/post-marketing commitment (PMC) correspondence. We have reviewed your submission and do not agree with your proposal (b) (4)

We proposed the following for PMR/PMC #13.

PMR/PMC#13:

> **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 nonvolatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semivolatile (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 XX/XX/20XX. Please propose milestone dates.**

You should include leachables in real time drug product stability studies. These leachable studies should include consideration for the extractables detected in drug substance and drug product extractable studies. To provide assurance that the study would represent worst case levels of drug substance container closure leachables, you may want to consider the use of drug substance at the end of expiry to manufacture drug product for this leachable study. Please provide milestone dates for the real time drug product leachable studies as described in the aforementioned PMR/PMC#13.

Please provide a response by noon on Wednesday, February 25, 2015. If you have any questions or concerns please contact me.

Thank you,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
02/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 18, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation – Unituxin (dinutuximab) Proposed PMC/PMRs language

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologic License Application (BLA), received on April 11, 2014, for your product dinutuximab. We are currently reviewing your submission and propose the following Post Market Commitments (PMC). This listing is provided to you in draft format and additional PMRs or PMCs may be required. We note that United Therapeutics Corporations will be required to provide reasonable timelines for completion of these PMCs including dates for submission of the final study protocol, trial completion date and submission of the final study report. United Therapeutics Corporation is required to exercise due diligence to ensure that these timelines can be met, including anticipating expected accrual and event rates, as well as administrative other potential delays.

PMCs

Microbiology

1. To determine whether endotoxin masking occurs in vivo, conduct a comparison study between the LAL kinetic chromogenic test and the rabbit pyrogen test for drug product that has been spiked with an endotoxin standard and then held prior to testing. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

2. Conduct studies to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

3. Validate the dye ingress test using dinutuximab drug product vials. The validation study should identify the range of breach sizes detectable by the assay. The positive control used for the dye ingress test should be based on the validation study data. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

4. Conduct the bioburden method qualification studies for the [redacted] (b) (4) using 2 additional batches and for the bulk drug substance using 3 different drug substance lots and submit the results. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

5. Submit the final established [redacted] (b) (4) after trending the data from 10 drug substance batches. Please propose milestone dates. (UTC to provide date).

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

Please review the and PMCs listed above and provide a response by close of business Friday, February 23, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
02/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February17, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

We also refer to our request for information dated February 9, 2015, and your amendment dated, February 11, 2015. We have reviewed your submission and have the following comment and request for information.

> The process parameters and process performance indicators removed from section 3.2.S.2.2 of the BLA should be returned and included as regulatory commitments. You should provide the values for these parameters and process indicators that you will use as your regulatory commitments. The proposed values should be submitted for review. At this time, you should not make any additional updates to the CMC sections of the BLA unless discussed with CMC team.

Please review the aforementioned comment and request for information and provide a response by close of business by February 19, 2015. If you have any questions or concerns please contact me.

Thank you,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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Center for Drug Evaluation and Research

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GINA M DAVIS
02/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 15, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation – Unituxin (dinutuximab) Proposed PMC/PMRs language

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologic License Application (BLA), received on April 11, 2014, for your product dinutuximab. We are currently reviewing your submission and propose the following Post Market Commitments (PMC) and Post Market Requirements (PMR). This listing is provided to you in draft format and additional PMRs or PMCs may be required. We note that United Therapeutics Corporations will be required to provide reasonable timelines for completion of these PMRs and PMCs including dates for submission of the final study protocol, trial completion date and submission of the final study report. United Therapeutics Corporation is required to exercise due diligence to ensure that these timelines can be met, including anticipating expected accrual and event rates, as well as administrative other potential delays.

PMRs

Clinical

1. Provide comprehensive comparative exposure and safety data from approximately 220 patients who complete treatment with dinutuximab and approximately 1100 patients treated with ch14.18 (manufactured by SAIC for the National Cancer Institute). Based on these data, provide thoughtful analyses of the safety and tolerability of dinutuximab compared to the safety and tolerability of ch14.18 in pediatric patients with neuroblastoma. Also submit an evaluation of the safety and tolerability of each lot of dinutuximab administered in comparison to ch14.18, and an assessment regarding whether variations in antibody-dependent cell-mediated toxicity among dinutuximab lots impacts the safety and tolerability of dinutuximab.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/2015
	Study/Trial Completion:	06/2016
	Final Report Submission:	03/2017

2. Submit datasets and safety analyses of laboratory data including serum complement, IgE, tryptase, histamine, and human anti-chimeric antibody levels obtained in patients with documented Grade 4 allergic reactions or anaphylaxis from a sufficient number of patients with neuroblastoma to allow for improved characterization of these adverse reactions to better inform product labeling. For each case identified, provide a narrative description that includes a summary of the allergic reaction or anaphylaxis adverse reaction, rechallenge information, and an assessment of whether the clinical presentation and laboratory data obtained were consistent with an allergic reaction or an infusion reaction.

PMR/PMC Schedule Milestones:	Analysis Plan Submission	08/2015
	Final Report Submission	08/2016

Nonclinical

3. To conduct a 5-month repeat-dose juvenile animal toxicology study in cynomolgus monkeys that will measure the chronic toxicity associated with the use of dinutuximab, particularly effects on the central and peripheral nervous system. Administration of dinutuximab should be reflective of the clinical administration schedule. Incorporate an evaluation of the effect of treatment on the proximal and distal nerves, and evaluation of the C1 level of the spinal cord in this study and include 7-8 slices for histopathological assessment of the brain. Evaluate the potential for long-term effects on nociception and pain threshold at the end of an appropriate recovery period.

PMR/PMC Schedule Milestones:	Final Protocol Submission	06/2015
	Final Report Submission	02/2017

Clinical Pharmacology

4. As presented in section 5.3.1.4 of the primary CMC review logged in DARRTS on September 13, 2014, the performance of neutralizing antibody (Nab) assay, particularly with regard to sensitivity, is poor. Given that this particular concern on immunogenicity is related to the safety, a PMR study is recommended as following from clinical pharmacology perspective. Please propose milestone dates.

PMR/PMC Schedule Milestones:	Final Protocol Submission:
	Study/Trial Completion:
	Final Report Submission:

5. To conduct an assessment of neutralizing antibodies response to dinutuximab with a validated assay (under CMC PMC) capable of sensitively detecting neutralizing antibody responses in the presence of dinutuximab levels that are expected to be present at the time of patient sampling. The clinical impact of the neutralizing antibody response should be evaluated in all available samples from [(b) (4)] DIV-NB-302], DIVNB-303, DIV-NB-201 studies and other studies under IND4308 [(b) (4)] NANT2011-04]. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

6. 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 XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

7. 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. Please propose a date.

8. 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 XX/XX/20XX. Please propose a date.

9. To validate an assay for the detection of dinutuximab [redacted] (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 XX/XX/ 20XX. Please propose a date.

10. 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 Master Cell Bank (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 XX/XX/20XX. Please propose a date.

11. To provide additional studies to confirm the monoclonality of the Master Cell Bank. The final report will be submitted by XXX, XX, 20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

12. To perform validation studies to confirm acceptable product quality and shipper performance during shipping of dinutuximab DP. 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-shipping 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 DP containers. The final study report will be provided by XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

13. 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 XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

14. To verify (b) (4) lifetimes at commercial scale using a validation protocol to evaluate (b) (4) capability and cleaning procedures throughout the intended lifetime of the (b) (4). The final approved validation protocol(s) will be provided by XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

15. To further investigate the root cause for (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 XX/XX/20XX. Please propose a date.

16. 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 XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

17. 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 DS and DP release and stability specifications. The validation reports will be provided by XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

18. 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 DS and DP release and stability specifications. The validation reports will be provided by XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

19. 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 DS and DP release and stability specifications. The validation reports will be provided by XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

20. 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 XX/XX/20XX. Please propose a date).

21. 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 XX/XX/20XX. Please propose a date.

22. 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 XX/XX/20XX. Please propose a date.

23. 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 XX/XX/20XX. Please propose a date.

24. 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 XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

25. 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 XX/XX/20XX. Please propose milestone dates.

PMR/PMC Schedule Milestones: Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

Please review the PMRs and PMCs listed above and provide a response by close of business Friday, February 20, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
02/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 9, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

1. Your regulatory commitments in section 3.2.S.2.2 for certain process parameters and process performance indicators are unclear. Specifically,

   - [redacted] (b) (4) includes information on observed ranges, means, and standard deviations.
   - Protein concentration in [redacted] (b) (4) includes information on observed ranges and expected ranges.
   - Protein concentration for the [redacted] (b) (4) includes an observed range, mean, and standard deviation.

   You should provide clarification on which values you are considering to be regulatory commitments (e.g. manufacturing outside of these ranges will be considered a manufacturing change that requires a supplement to be filed with the Agency). Those ranges that you are committing to should be the ones included in section 3.2.S.2.2.

2. We note that the BLA has not been updated with the certain changes to DS and DP specifications proposed in your 9/12/2014 submission. Specifically:

   - [redacted] (b) (4) DS release and stability should be limited to [redacted] (b) (4) while DP release and stability should be limited to [redacted] (b) (4). This is based on DP on stability not exceeding EP standard II. Provide updated specifications to the BLA.
   - For both DS and DP specifications, cSDS reduced light chain specifications should be set at [redacted] (b) (4)% and heavy chain at [redacted] (b) (4)%, respectively.

Please provide a response to the aforementioned requests by close of business February 13, 2015. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
02/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 6, 2015

From: Gina Davis, RPM, DOP2/OHOP/CDER/FDA

Subject: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website for: BLA 125516/0 – Unituxin (dinutuximab)

We are requesting your assistance in populating the attached tables for your New Molecular Entity, Unituxin (dinutuximab) that is currently under review in the Division, this information will be posted publically, if approved, at the FDA drug snapshot website: http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

We are asking this information to allow for greater transparency by providing information to the public about participation in clinical trials for newly-approved drugs and biologics.

The website will include information on the study design, the results of efficacy and safety studies, and whether there were any differences in efficacy and side effects among sex, race, and age subgroups. It is not intended to replace or replicate the package insert, which are intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focus on subgroup data and analyses
- Links to PI for the product and to the FDA reviews at Drugs@FDA
- Information will be published approximately 30 days after drug/biologic approval

Therefore, we are requesting that you provide your data and complete the attached tables as well as provide descriptions of the analyses used to generate the data and any programs used to generate or analyze the data, if these are not already in the BLA submission.

We are requesting you submit this information no later than February 17, 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Regards,

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager

PROPOSED SHELL TABLES

Table 1. Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in the Drug X Arm	No. of patients enrolled in the Comparator Arm

Table 2.1 Baseline Demographics, Single or Pooled Pivotal Efficacy Trials

Demographic Parameters	**Comparator/ Control** (n=) n (%)	**Treatment Group(s)** (n=)		**Total** (n=) n (%)
		Treatment arm #1 (n=) n (%)	**Treatment arm #2** (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 2.2 Baseline Demographics, Multiple Pivotal Efficacy Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 3 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Demographic Subgroup	Trial #1 (N=)			Trial #2 (N=)		
	Comparator/control (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)	**Comparator/control** (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)
Overall Response/All patients						
Sex						
Male						
Female						
Age Group						
<17 years						
≥17 - <65 years						
≥65 years						
≥75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source: list datasets or other sources of information

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication[2]			
All other than controlled trials conducted for this indication[3]			
Controlled trials conducted for other indications[4]			

[1] *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

[2] to be used in product's labeling

[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Table 5.1 Baseline Demographics, Safety Population, Single or Pooled Trials
(If efficacy population = safety population, refer to Table 2.1 or 2.2)

Demographic Parameters	**Comparator/ Control** (n=) n (%)	**Treatment Group(s)** (n=)		**Total** (n=) n (%)
		Treatment arm #1 (n=) n (%)	**Treatment arm #2** (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 5.2 Baseline Demographics, Safety Population, Multiple Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 6.1 Subgroup Analysis of TEAEs, Safety Population

Demographic Subgroup	Comparator/Control		Treatment		Relative Risk	95% CI	
	n (%)	Total, N	n (%)	Total, N		LL	UL
Any TEAEs							
Sex							
Male							
Female							
Age Group							
<17 years							
≥17 - <65 years							
≥65 years							
≥75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source: list datasets or other sources of information

Table 6.2 Subgroup Analysis by Sex of Common AEs, Safety Population (Events ≥ 2% of drug-treated subjects and more frequent than placebo)[1]

	Male (N=)		**Female** (N=)	
MedDRA System Organ Class Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Gastrointestinal disorders				
Nausea				
Vomiting				
Diarrhea				
Abdominal pain				
General disorders/administration site conditions				
Fatigue				
Edema peripheral				
Infections and Infestations				
Influenza				
Urinary tract infection				
Injury, poisoning and procedural complications				
Fall				
Contusion				
Investigations				
Weight increased				
Blood CPK increased				
Musculoskeletal & connective tissue disorders				
Arthralgia				
Nervous system disorders				
Dizziness				
Headache				
Psychiatric disorders				
Depression				
Insomnia				
Respiratory, thoracic & mediastinal disorders				
Cough				
Skin & subcutaneous tissue disorders				
Rash				
Pruritus				

Source: list datasets or other sources of information

Example of an application-specific adverse event

Table 6.3 Subgroup Analysis by Age of Dizziness/Gait Disturbance Adverse Events, Safety Population*

	Age ≥17-<65 years (N=)		**Age ≥65 years** (N=)	
MedDRA Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Dizziness				
Ataxia				
Vertigo				
Balance disorder				
Gait disturbance				
Coordination abnormal				
Cerebellar syndrome				
Cerebellar ataxia				
Vestibular ataxia				
Vestibular disorder				
Total				

*Pediatric subjects were not included in the safety population
Source: list datasets or other sources of information

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/s/

GINA M DAVIS
02/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 5, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; FDA Proposal - Labeling

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

We also refer to the Unituxin (dinutuximab) package insert (PI) submitted with your application. Attached to this memorandum is our proposal to your PI. Please review the attachment and provide feedback.

Please provide a response to the aforementioned requests by close of business February 12, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
FDA Proposed Labeling

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GINA M DAVIS
02/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 5, 2015

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information - Microbiology

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

> We note that, once prepared for administration (e.g. diluted in 0.9% Sodium Chloride for Injection, USP in IV bags), your product will be infused over a relatively long period of time. Due to microbial concerns regarding the long infusion time, an in-line filter should be used during administration. Specifically, the drug product should be administered by infusion using an in-line, 0.2 or 0.22 micron, low protein binding filter.
>
> As indicated in the late cycle meeting held on October 6, 2014, one potential post-marketing commitment will be to perform drug product compatibility studies. In order to understand the impact of the in-line filter on product quality, the in-line filter should be incorporated into these compatibility studies.

Please provide a response to the aforementioned comments and requests as soon as possible. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
01/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125516/0

**REVIEW EXTENSION –
MAJOR AMENDMENT**

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 TW Alexander Drive, P. O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mathue:

Please refer to your Biologics License Application (BLA) dated April 11, 2014, received April 11, 2014, submitted under section 351(a) of the Public Health Service Act for Unituxin (dinutuximab).

On November 14, 17, and 21, 2014, we received amendments to your application. These three submissions are being considered a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submissions. The extended user fee goal date is March 10, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 10, 2015.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
12/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 1, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please clarify the following discrepancies between the AdEERS reports and the exposure and subject level datasets for the following patients enrolled in Study 301:

1. Patient 744319: AdEERS report (ticket number 1159180) describes an event of anaphylaxis that occurred during Cycle 2 and states that this patient was taken off study therapy. A subsequent AdEERS report (ticket number 1473519) also includes information stating that the patient was removed from ch14.18 therapy due to the prior (Cycle 2) adverse event. However, the ADaM subject level (ADSL) dataset indicates that the patient completed study therapy and the SDTM exposure (EX) dataset indicates that this patient received subsequent cycles of ch14.18. Please confirm that the patient did in fact complete a full five cycles of ch14.18. If this patient did not receive ch14.18 after Cycle 2, please explain why the subject level (ADSL) and exposure (EX) datasets indicate that the patient completed five cycles of ch14.18 treatment.

2. Patient 748359: AdEERS report (ticket number 1427173) describes an event of anaphylaxis that occurred during Cycle 4 and states that this patient was taken off ch14.18 and would receive only RA in subsequent cycles. However, the ADaM subject level (ADSL) dataset indicates that the patient completed study therapy and the SDTM exposure (EX) dataset indicates that this patient received subsequent cycles of ch14.18. Which is correct? Please explain the discrepancy.

Please provide responses to the aforementioned requests by Friday, December 5, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
12/01/2014

Monthly Team Meeting Summary
November 4, 2014

BLA 125516/IND 110494

Product:	Unituxin (dinutuximab)
Submission Date:	April 11, 2014
Received Date:	April 11, 2014
Sponsor:	United Therapeutics Corporation (UTC)

Proposed Indication: For the treatment of Pediatric Neuroblastoma

Current Review Team for BLA 125516:
Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS)
Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Officer
Suzanne Demko, C-P.A. Medical Team Lead (TL and CDTL)
Sirisha Mushti, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jingy Yu, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Liang Zhao, Ph.D., Clinical Pharmacology (TL)
Dubravka Kurfin, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Chikako Torigoe, Ph.D., CMC
Laurie Graham, Ph.D., CMC
Lyndsey Hennessey, DMA RPM
Melinda McLawhorn- OPDP professional reviewer
Jessica Cleck Derenick- OPDP consumer reviewer
Olga Salis – OPDP RPM

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

Agenda Items:

1. **Review Status:**
   - Orphan Drug Designation - granted December 20, 2010
   - Exempt from Pediatric Research Requirements
   - Categorical Exclusion Requested
   - UTC requested to be awarded a rare pediatric disease priority review voucher – April 18, 2013
   - UTC claims seven year marketing exclusivity

2. **Dates Milestone Letters Must Issue: PDUFA V dates**

Milestone	6 month review	
Acknowledgment Letter	April 25, 2014	
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	June 10, 2014	
Deficiencies Identified Letter (74 Day Letter)	June 24, 2014	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	November 10, 2014 (subject to change)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 19, 2014	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off*** ***Compliance Check List (BLA)***	 September 13, 2014 September 17, 2014 November 19, 2014 November 30, 2014 December 10, 2014 November 12, 2014	
Compile and circulate Action Letter and Action Package	November 19, 2014	
FINAL Action Letter Due	December 10, 2014	

LATE CYCLE MEETING

- October 6, 2014 12:00 PM - 1:30 PM
- Meeting Packages to UTC - September 24, 2014
- Late Cycle Meeting Minutes to issue no later than by close of business November 5, 2014

UPDATES FROM THE TEAM

No additional updates from the team.

OTHER ISSUES

- On October 28, 2014, UTC was informed that an amendment submitted, to BLA 125516, in response to an FDA request (solicited amendment) has been deemed a major amendment, therefore review of the dinutuximab application has been extended by 3 months. A letter extending the PDUFA goal date for BLA 125516 will issue on or before December 10, 2014.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 19, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information - Microbiology

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information. BLA 125516 (UTC, dinutuximab)

1. Validation of the dye ingress test for container closure integrity will be a post-marketing commitment. Please commit to validate the dye ingress test using dinutuximab drug product vials. The validation study should identify the range of breach sizes detectable by the assay. The positive control used for the dye ingress test should be based on the validation study data.

2. Please respond to the following comments regarding the media fill information submitted in amendment 0063.

    a. The response to question 9f did not include growth promotion testing information for media prior to use. Please provide the growth promotion test procedure for media prior to use and update section 3.2.P.3.5 with the pre-use growth promotion test results for the media fills.

    b. The response to question 9h states that the environmental monitoring isolate recovered for media fill lot 1200000 was not identified, but deviation report 3857 states that the isolate was identified as *M. luteus*. Please clarify. Update section 3.2.P.3.5 with this information, including the impact of this deviation on media fill lot 1200000.

Please provide a response to the aforementioned comments and requests for information by November 21, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
11/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 19, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Unituxin (dinutuximab) Request for Information – Carton and Container

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please refer to your container label and carton labeling submitted on April 11, 2014, for BLA 125516.

Our comments reference the revised carton labeling submitted on November 5, 2014, for BLA 125516. Please respond by COB December 2, 2014.

A. Carton Labeling

Add the statement, "No U.S. Standard of Potency." to side panel under the storage and handling information per 21 CFR 610.61(r).

B. Container Label

Your response states the final carton and container label will reflect the proper highlighted text as represented below:

17.5 mg/5 mL
(3.5 mg/mL)

A revised Vial Container Label was not included in your submission. Submit a revised Vial Container Label.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
11/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 4, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Unituxin (dinutuximab) Request for Information – Carton and Container

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please refer to your container label and carton labeling submitted on April 11, 2014 for BLA 125516.

Please also refer to the October 6, 2014, late cycle meeting, regarding the following;

> In response to our September 10, 2014 Information Request – Carton and Container, it appears you removed the bolding from the strength per total volume. In the previous submissions, the strength per total volume "17.5 mg/5mL" was appropriately more prominent than the strength per milliliter "3.5 mg/mL". Revise the strength presentation to appear as:
>
> **17.5 mg/5 mL**
> **(3.5 mg/mL)**
>
> FDA stated that "(3.5 mg/mL)" should not be bolded. UTC acknowledged FDA's response and will ensure that "(3.5 mg/mL)" does not appear in bold type on the carton and container.

Please provide a response to the aforementioned requests by close of business November 5, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
11/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 29, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

1. Updated specifications should be provided to the BLA based upon available clinical experience. Specifically:

   a. Updated DS specifications should be provided to include (b) (4) acceptance criteria of (b) (4)%.

   b. Acceptance criteria need to be established that provide assurance that the (b) (4) profile will not drift over time from clinical experience. The acceptance criteria should, therefore, be based on lots used clinically. Provide updated (b) (4) acceptance criteria to DS specifications with justifications.

   c. Acceptance criteria for cIEF acidic and main species need to be established based upon clinical experience. As there are limited data available for NCI material at the time of clinical use, we recommend that you consider data from UTC lots at the time of their clinical use, which can be used to establish criteria at the end of drug product expiry. For example, it is known that the UTC reference standard, used in the PK clinical trial, was between (b) (4) month of age at the time of clinical use. This suggests clinical experience with UTC material at approximately (b) (4). The acceptance criteria at expiry of DP would be based on these limits.

   In order to stay within clinical experience and to account for the average apparent (b) (4)%/month change during DS storage and (b) (4)% change over DP storage, it is recommended that consideration be given to a cumulative shelf life of DS and DP of (b) (4) with a maximum possible DS shelf life of (b) (4) months. The maximum shelf-life of DP from sterile filtration would be (b) (4) months.

Based on this approach, acceptance criteria would be
DS release: [redacted]
DS stability
DP release:
DP stability

d. For cIEF, cSDS, and [redacted] assays, we recommend the inclusion of acceptance criteria of 'no unexpected peaks". For the cIEF and cSDS assays, these criteria should be incorporated into both DS and DP release and stability specifications.

e. We recommend that DP specifications include osmolality.

2. The following updates to 3.2.S.2.2 are recommended:

a. For [redacted] operations, provide more specific ranges for [redacted].
b. For [redacted], provide more specific range for protein concentration than mean and standard deviation values.
c. For the [redacted], provide a more specific protein concentration
d. For the [redacted], provide a more definitive time limit.

3. Submit the formulation stability studies for drug product (DP) referenced in 3.2.P.2 Formulation Development.

4. For the sub-visible particle assay included in DP specifications, you should provide information to verify the performance of the assay with your drug product.

5. Available additional information should be provided to address the linearity issues observed during validation of the cSDS reduced and non-reduced assays. This can include, for example, information to support that the linearity failure was due to the duration of the assay.

6. We recommend that drug product lot 1200041 be placed on stability to as it has lower main species at release.

7. The following updates to 3.2.P.3.3 are recommended:

a. We note a trend for [redacted] during drug substance (DS) stability. As such, it is unclear that there is sufficient control over [redacted] during DP manufacturing. [redacted] should be added as an in-process control for DP manufacturing.

b. We recommend that a [redacted] be added as an in-process control.

8. The total DP inspection reject rate of (b) (4)% appears to be unusually high. Provide a justification for this rate as well as the various other DP reject rates that are monitored, such as critical defects. Provide the criteria used to define the different reject categorizations. In addition, provide a comparison of the different reject rate results for the validation vs other commercial DP lots.

9. It appears that two of the DP validation lots, 1200041 and 1200021, have slightly different charge profiles. Specifically, compared to other DP lots, lot 1200041 has higher (b) (4) while lot 1200021 appears to have increased (b) (4) Provide clarification on why these two validation lots should be considered representative of your commercial manufacturing process rather than as outliers.

10. We recommend that you consider including sub-visible particulate testing more frequently in real time stability studies for DP.

11. Provide available data on the characterization of the disulfide bonds in ch14.18.

12. It is noted that the control strategy for DS has been updated to include (b) (4) . However, it is unclear that the assay used for (b) (4) included in DS specifications has been adequately validated as a quantitative assay for (b) (4) . Please comment and provide any additional information to support that the (b) (4) has been adequately validated for its intended use in the updated control strategy.

13. We note that there are plans to store the reference standard at (b) (4) C. Provide available data to support stability drug product stored at (b) (4) C.

14. Provide information on the timeline for preparation of a working cell bank. Provide available information on how the working cell bank will be qualified, including comparability testing.

15. Provide information, including any available protocols, describing the plans for validation of (b) (4) lifetimes at commercial scale. Provide available commercial scale data that support (b) (4) lifetimes.

16. The qualification protocol provided for the reference standard would not be adequate for all potential future reference standards. Specifically, (b) (4) Provide the protocol that will be used for the qualification of subsequent reference standards.

17. Provide any additional information relevant to addressing the CMC issues, including the potential post-marketing commitments, included in the late cycle meeting held on October 6, 2014.

Please provide a response to the aforementioned requests by November 19, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina
Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 29, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

We acknowledge receipt of your October 27, 2014 response to our October 15, 2014 communication requesting additional safety information from patients that have been treated with dinutuximab. Please provide the following additional information:

1. SDTM and ADaM datasets for Study 302 that include severe adverse event and serious adverse event data for patients exposed to dinutuximab from January 2014 through October 21, 2014. Please ensure that the ADaM datasets contain populated columns that provide the following information: the dinutuximab lot number received proximal to the time of occurrence of the adverse event, the cycle number during which the adverse event occurred, the CTCAE toxicity grade, intervention (dose reduction, infusion interruption, permanent discontinuation), and adverse event outcome (ongoing vs. resolved).
2. Provide analyses comparing the per-patient incidence of severe and serious adverse events (by system organ class and preferred term) per cycle and overall for each dinutuximab lot with the per-patient incidence (per cycle and overall) of these adverse events in patients exposed to ch14.18 in the integrated summary of safety (ISS) previously submitted to the BLA.
3. Also provide the information requested in items 1 and 2 above on an updated, cumulative basis on or before December 15, 2014 (using a data cutoff date of November 30, 2014 or later) and on or before February 15, 2015 (using a data cutoff date of January 31, 2015 or later). With these submissions, also provide the following:

a. Patient narratives for all serious adverse events on a cumulative basis from the time of switch to the UTC product in January 2014.

b. The number of patients exposed to each dinutuximab lot and overall since January 2014, and the median (range) of dinutuximab courses received per patient by lot and overall.

c. A brief narrative for all patient deaths that occurred within 60 days of the last dinutuximab dose. In each narrative, include the timing of death in relationship to the last dose of dinutuximab, adverse reactions that occurred within 60 days of death, and investigator assessment of the cause of death.

Please provide responses to items #1 and # 2 on or before November 14, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/29/2014

October 21, 2014 Discussion

BLA:	Unituxin (dinutuximab) BLA 125516
Applicant:	United Therapeutics Corporation
Proposed Indication:	Treatment of patients with (b) (4) high-risk neuroblastoma (b) (4) (b) (4)
PDUFA Goal Date:	December 10, 2014

History

- Unituxin (dinutuximab) is a first in class monoclonal antibody that binds to the glycolipid GD2, which is expressed on neuroblastoma cells and normal cells of neuroectodermal origin. The mechanism of action is induction of cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).
    - Clinical development commenced 23 years ago. The bulk of clinical development was conducted using investigational product (ch14.18) produced by SAIC for the National Cancer Institute. Clinical studies were conducted under the Cancer Therapy Evaluation Program IND by the Children's Oncology Group (COG).
- High risk neuroblastoma is rare, life threatening cancer that is diagnosed in approximately 650 pediatric patients each year in the United States (median age at diagnosis is 19 months, with 90% of patients diagnosed at less than 5 years of age).
- Anti-GD2 therapy in combination with interleukin-2 (IL-2) and granulocyte-macrophage colony stimulating factor (GM-CSF) and isotretinoin (RA) has been part of standard front-line therapy for high risk neuroblastoma in the U.S. for approximately five years. Ch14.18 and RA (without GM-CSF and supplied as an investigational agent by a different manufacturer) are part of standard of care for this patient population in Europe.
- Until January 2014, patients in the United States received anti-GD2 therapy with NCI product; since January 2014, dinutuximab has been used.

Primary Basis for Approval

- Efficacy of dinutuximab is primarily based upon results of a single, multicenter, open label, randomized study conducted by COG.
  - 226 patients were randomized 1:1 to receive either five cycles of ch14.18 in combination with GM-CSF, IL-2, and RA followed by one cycle of RA or six cycles of RA alone.
  - Prior to receipt of study therapy, patients were heavily pretreated with standard multiagent chemotherapy including myeloablative therapy with autologous stem cell rescue, maximum feasible surgical resection, and radiation therapy.
  - The primary efficacy endpoint was investigator-assessed event-free survival (EFS), and overall survival (OS) was a secondary endpoint. Randomization was stopped based upon the results of the seventh interim analysis conducted in January 2009 (Table 1, Figure 2).

Table 1: Efficacy Analysis

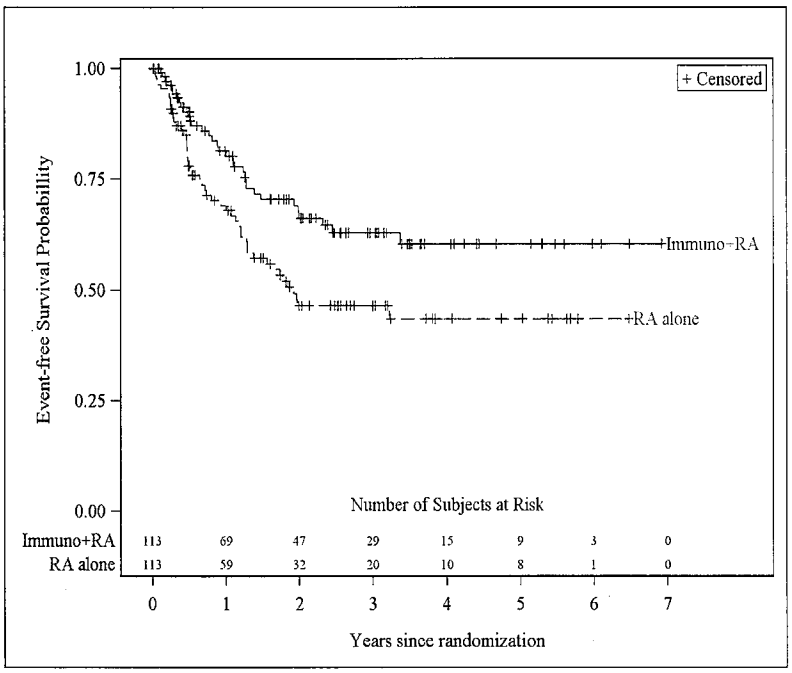
Efficacy Parameter		**Ch14.18 Combination Arm n=113**	**RA arm n=113**
EFS	No. of Events (%)	33 (29%)	50 (44%)
	Median (95% CI) (years)	NR (3.4 ,NR)	1.9 (1.3, NR)
	Hazard Ratio (95% CI)	0.57 (0.37, 0.89)	
	P-value (log-rank test)	0.01[1]	
OS[2]	No. of Events (%)	31 (27%)	48 (42%)
	Median (95% CI) (years)	NR (7.5,NR)	NR (3.9,NR)
	Hazard Ratio (95% CI)	0.58 (0.37,0.91)	

NR = not reached

[1] Compared to the allocated alpha of 0.01 pre-specified for the seventh interim analysis of EFS

[2] Based on an additional three years of follow up after the seventh interim analysis of EFS

Figure 2: Kaplan-Meier Curve of EFS (7th Interim Analysis January 2009)



Review Issues Related to Efficacy:

- The results of the seventh interim analysis of EFS are of borderline statistical significance; the results approached but did not meet the pre-specified stopping boundary. However, results of the OS analysis provide strong supportive evidence of efficacy.
- The efficacy trial was not designed to isolate the treatment effect of ch14.18 from that of GM-CSF and IL-2. These components, particularly IL-2, confer substantial additive toxicity but their contribution to efficacy is unknown. Moreover, neither RA, GM-CSF, or IL-2 is approved for the treatment of neuroblastoma.

- 72% of patients in the ch14.18 combination therapy group and 77% of patients in the RA group completed planned treatment. The most common reason for premature discontinuation of study therapy was adverse reactions in the ch14.18 combination therapy group (19%) and progressive disease (17%) in the RA group.
- The primary safety risks of dinutuximab are infusion-related or allergic reactions, capillary leak syndrome, hypotension, systemic infection, and neuropathy (which can manifest as pain or motor weakness, impaired pupillary light reflex, photophobia, or visual impairment). At least one serious adverse reaction was reported for 51% of patients in the ch14.18 combination therapy group.

- The toxicity profile of ch14.18 is supported by data from over 780 patients who have received ch14.18 in the expanded access trial. In contrast, approximately 60 patients have received dinutuximab (produced by United Therapeutics).

Review Issues Related to Safety:

- There are limited safety data from use of the United Therapeutics product (dinutuximab).
- Multiple product quality issues have been identified for dinutuximab during the course of the BLA review.
  - The most concerning issue is that recent lots of dinutuximab (sent to clinical sites starting this summer) have twice the ADCC activity compared to prior lots. The impact, if any, on the safety of dinutuximab is unknown. It is unlikely that safety information from use of newer lots of dinutuximab will be available from more than 10-15 patients by the December 10th goal date.
  - Other CMC issues may be addressed through post marketing commitments, but United Therapeutics has limited experience with the manufacture of biologics.

- The review team is working diligently with the Division of Advisory Committee and Consultant Management to clear SGEs in order to obtain external advice on this application, but it is unclear whether potential candidates will be cleared quickly enough to provide advice that is helpful to the review of this application.

OHOP's Current Thinking

We favor approval of dinutuximab as part of multimodality (b) (4) treatment of high-risk neuroblastoma based upon the numerical improvement in event-free survival and overall survival shown in the pivotal trial. Moreover, ch14.18 in combination with GM-CSF, IL-2, and RA is firmly embedded as part of standard of care for the treatment of patients with high-risk neuroblastoma in the United States and Canada, so conducting an additional efficacy trial would be considered unethical and unfeasible.

However, we have concerns regarding the paucity of safety data that is available for dinutuximab, particularly for the lots with higher ADCC activity. Additionally, the number of product quality issues identified is unusually high and there is a degree of uncertainty regarding whether the risk:benefit relationship for the use of dinutuximab in this patient population could be altered by these issues. We are internally discussing whether these uncertainties can be adequately addressed through postmarketing requirements for submission of additional clinical safety data from use of dinutuximab in ongoing clinical trials and postmarketing commitments to address the CMC/microbiology issues.

Meeting outcomes

Dr. Jenkins agreed with the Division and supports a three-month extension of the review for BLA 125516 to allow the applicant sufficient time to provide additional information to support approval of the marketing application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 19, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information - Microbiology

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information. BLA 125516 (UTC, dinutuximab)

1. Please provide the capping and crimping parameters for dinutuximab vials. Indicate whether the parameters are fixed. Clarify whether vials used for the microbial ingress study were capped and crimped using the production parameters.

2. Please respond to the following comments regarding microbial ingress testing for container closure integrity.

    a. Describe the test parameters, including time and pressure/vacuum cycles.

    b. Provide the CFU/ml count of the challenge organism at the end of the test.

    c. Describe preparation of the positive control vials and indicate the defect size(s) tested.

    d. In addition to the information requested above, provide the study report for reference.

3. Please respond to the following comments regarding dye ingress testing for container closure integrity (CCI).

    a. Describe the dye solution used for dinutuximab CCI testing. Clarify whether dinutuximab vials will be examined visually or spectrophotometrically. Provide the limit of detection for the dye solution in dinutuximab drug product solution.

b. The positive control for routine testing is prepared with a relatively large defect size. A positive control with a smaller defect size should be used for routine testing. The method validation report states that defects ranging from (b) (4) microns were detected.

4. Section 3.2.P.5.2 states that container closure integrity testing is performed by (b) (4) but section 3.2.P.3.1 indicates that (b) (4) performs sterility testing only. Please update section 3.2.P.3.1 accordingly.

5. Please indicate the number of drug product containers that will be used for sterility testing and container closure integrity testing.

6. Pyrogen or endotoxin testing of dinutuximab drug product is required only for release. Performing these tests for stability samples is optional. If you choose to omit pyrogen testing from the post-approval stability protocol, please update the BLA accordingly.

7. Please respond to the following comments regarding dose substantiation and dose audits for the (b) (4).

   a. Explain why the (b) (4) used for dose substantiation and dose audits is considered worst-case compared to the dinutuximab (b) (4).

   b. Please provide the dose substantiation report ((b) (4)).

8. Environmental monitoring information should be provided in section 3.2.P.3.5 of the application. Please move the air quality limit information provided in the appendix to section 3.2.P.3.5. Include the monitoring frequencies for classified areas and briefly describe the methods used. In addition, the microbiological air quality table lists the acceptance criterion for ISO 5 areas ((b) (4)) instead of the ((b) (4)). Please provide a corrected table in section 3.2.P.3.5 of the application.

9. Additional information regarding media fill batches M1102, M1103, M1104, and 1200000 should be summarized in section 3.2.P.3.5 of the application. Please provide the following information for each of these media fills.

   a. The container-closure system, if different from the dinutuximab container closure system.

   b. The medium and the fill volume.

   c. The date of the fill, total time for the fill, and duration of any hold times simulated.

d. The number of units that were filled but not incubated. Briefly explain why these units were excluded.

e. The incubation conditions for the filled vials including time, temperature, and vial orientation. The incubation times and temperatures for any group of units subjected to two or more different temperatures should be described.

f. The growth promotion test procedures and the growth promotion test results for the media.

g. Compare the media fill conditions to those used for routine production ((b) (4) and explain how media fills are designed to provide a worst-case challenge for aseptic processing operations.

h. Summarize the environmental monitoring results from each media fill. Indicate the number of samples taken and identify excursions. For viable monitoring excursions, describe any microorganisms that were identified.

i. In addition to the information requested above, provide the media fill summary reports.

10. The application states that (b) (4). Please provide summary data from the three most recent media fills (b) (4)

Please provide a response to the aforementioned comments and requests for information by October 30, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 15, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

As discussed in the late cycle meeting, we are considering a postmarketing requirement for the provision of updated safety data from ongoing clinical trials of dinutuximab to assess whether variations in ADCC activity in different lots of dinutuximab result in increased toxicity. In the meantime, we would like United Therapeutics to provide safety data from patients that have been treated with dinutuximab from the time of the March 2014 data safety cutoff date until the present in order to permit a more comprehensive assessment of the safety of dinutuximab during review of the BLA.

Please provide the following safety information for Study 302:

1. The number of patients treated with dinutuximab by lot number and the average number of doses received per patient.

2. Number of patients who have received each of the newer lots of dinutuximab that have higher ADCC activity (including lots 1200041 and 1600001 and any lots that have been released after these lots) and the number of doses administered to each patient.

3. A narrative summary of any targeted toxicities and serious adverse events that have been observed in patients who have received these lots. Include patient age and relevant past medical history; dinutuximab lot administered; a description of the adverse event; temporal relationship between the onset of the adverse event and study drug administration, including the cycle number and day and timing in relation to the infusion; intervention for the adverse event; adverse event outcome, including any available dechallenge or re-challenge information; and whether study drug has been discontinued permanently due to the adverse event.

Please also list the other clinical trials for which UTC is providing dinutuximab. Have lots 1200041 and 1600001 been distributed to clinical sites for these trials?

Please provide a response to the aforementioned requests by close of business Monday, October 27, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
10/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 7, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information - Microbiology

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. The [redacted] (b) (4) study (DEV-11-5063A1) was performed using one lot of dinutuximab (batch #1500625) at [redacted] (b) (4) C, please provide justification for not performing this study using 3 different lots of dinutuximab [redacted] (b) (4).

2. Please clarify if the [redacted] (b) (4) used for this study are the same as the ones used [redacted] (b) (4) during drug substance manufacturing. If not provide a justification.

3. Please submit the protocol used for executing this study.

4. In [redacted] (b) (4) study report, it is stated that the acceptance criteria for this study were based on the [redacted] (b) (4) sample criteria: Bioburden [redacted] (b) (4).
Please clarify if a sample size of [redacted] (b) (4) is used for [redacted] (b) (4) bioburden testing. In your response dated August 01, 2014, you have justified the use of [redacted] (b) (4) sample size for bioburden testing of the [redacted] (b) (4). Clarify the discrepancy.

5. Section 9.1 of the report states, "The hold times used for each [redacted] (b) (4) are shown in Error! Reference source not found ..." Please clarify.

Please provide a response to the aforementioned comments and requests for information by October 10, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 7, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> Please provide a the case report forms and narrative summary providing relevant details of the serious adverse events experienced by Subject 814123 (enrolled in Site 1873) in December 2011. According to our audit report, this patient experienced grade 4 seizure, grade 4 intracranial hemorrhage, grade 4 paralysis, and grade 4 depressed level of consciousness during cycle 4 of therapy, but we are unable to find information regarding these adverse events in the BLA. In the narrative summary, include the timing of these adverse events with respect to the last dose of ch14.18, cytokines, and 13-cis retinoic acid, results of tests that were performed just prior to and during this adverse event, intervention, patient outcome, and investigator assessment of attribution of the adverse event.

Please provide a response to the aforementioned request by Friday October 10, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/07/2014

Monthly Team Meeting Summary
October 3, 2014

BLA 125516/IND 110494

Product:	Unituxin (dinutuximab)
Submission Date:	April 11, 2014
Received Date:	April 11, 2014
Sponsor:	United Therapeutics Corporation

Proposed Indication: For the treatment of Pediatric Neuroblastoma

Current Review Team for BLA 125516:
Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS)
Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Officer
Suzanne Demko, C-P.A. Medical Team Lead (TL and CDTL)
Sirisha Mushti, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Xianhu Cao, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Dubravka Kurfin, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Chikako Torigoe, Ph.D., CMC
Laurie Graham, Ph.D., CMC
Lyndsey Hennessey, DMA RPM
Melinda McLawhorn- OPDP professional reviewer
Mathilda Fienkeng- OPDP consumer reviewer
Olga Salis – OPDP RPM

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

Agenda Items:

1. **Review Status:**
   - Orphan Drug Designation - granted December 20, 2010
   - Exempt from Pediatric Research Requirements
   - Categorical Exclusion Requested
   - UTC requested to be awarded a rare pediatric disease priority review voucher – April 18, 2013
   - UTC claims seven year marketing exclusivity

2. **Dates Milestone Letters Must Issue: PDUFA V dates**

Milestone	6 month review	
Acknowledgment Letter	April 25, 2014	
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	June 10, 2014	
Deficiencies Identified Letter (74 Day Letter)	June 24, 2014	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	November 10, 2014 (subject to change)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 19, 2014	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off*** ***Compliance Check List (BLA)***	 September 13, 2014 September 17, 2014 November 19, 2014 November 30, 2014 December 10, 2014 November 12, 2014	
Compile and circulate Action Letter and Action Package	November 19, 2014	
FINAL Action Letter Due	December 10, 2014	

LATE CYCLE MEETING

- October 6, 2014 12:00 PM - 1:30 PM
- Meeting Packages to UTC - September 24, 2014

UPDATES FROM THE TEAM

Clinical

Nonclinical

Clinical Pharmacology

Microbiology

Office of Surveillance and Epidemiology (OSE) – Labeling/Carton and Container

Chemistry Manufacturing and Control (CMC)

Stats - No issues to be discussed.

OTHER ISSUES

- OSI review is complete - acceptable.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 23, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

1. Sequence 0021 reports that the kinetic chromogenic LAL test has been replaced with the rabbit pyrogen test for drug product release testing. Rabbit pyrogen testing is inherently variable and should be considered only as an interim strategy until a more suitable release test for bacterial endotoxin in the drug product is developed. There will be two post-marketing commitments related to endotoxin testing of the drug product.

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

    b. Conduct studies to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product.

2. Please respond to the following comments regarding production (b) (4) (b) (4).

    a. (b) (4).

    b. Explain how the acceptable (b) (4) for this product is calculated from the (b) (4) data.

3. The [redacted] qualification report provided in sequence 0018 to support [redacted] does not clearly describe how the [redacted] studies were performed. Please respond to the following comments.

   a. Indicate the number of [redacted] Indicate the number of containers/totes monitored during each run.

   b. Describe the composition of the [redacted] used for [redacted]. Describe [redacted]. Diagrams would be useful.

   c. Explain how the [redacted] the dinutuximab [redacted].

4. Please provide [redacted] establishment information and data for the dinutuximab [redacted]. If applicable, justify the use of a [redacted] for establishment of the [redacted]

5. The test articles in the [redacted] reports are not identified. Please clarify whether [redacted] are performed with the [redacted]. If applicable, justify the use of a [redacted]

Please provide a response to the aforementioned requests by September 29, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 17, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

> We note that Report DEV-13-5029 indicates that recent lots of drug substance (DS) 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 (IR) 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.

Please provide a response to the aforementioned requests by September 19, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
09/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 17, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information - Microbiology

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information in response to your September 15, 2014, submission.

1. It is stated on page # 5 of TQC-617, "Bacterial Endotoxin Testing using Kinetic Test Method" (b) (4) . Only the qualified endotoxin test method, kinetic chromogenic method should be used for testing the drug substance and drug product.

2. Please clarify what endotoxin test method was used in (b) (4) ch1418 Drug Substance.

3. The BLA was updated to replace the LAL kinetic chromogenic test with the rabbit pyrogen test for drug product release testing, but the testing site was not listed in the BLA. Please identify the testing site and provide the FEI number in the BLA. In addition, provide the inspectional history for the last 4 years.

Please provide a response to the aforementioned comments and requests for information by close of business tomorrow, September 18, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
09/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 12, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

1. Please confirm that the hold time study with microbiological data for (b) (4) will be submitted by September 30, 2014.

2. You have agreed to perform the requested qualification studies for the (b) (4) testing method using two additional batches and also to re-qualify drug substance bioburden test method using a (b) (4) sample from 3 drug substance lots because current qualification was performed using (b) (4) sample size. Please note that a minimum sample volume of (b) (4) mL is sufficient for bioburden method qualification of drug substance. Complete the drug substance bioburden method qualification with 2 additional lots using a sample size of (b) (4) mL or with 3 lots using a sample size of (b) (4) mL and implement the use of validated sample size for drug substance bioburden testing.

3. You have stated the bioburden qualification studies will be completed by December 2014; please commit to submit these qualification data as a PMC to the BLA.

4. Please update Section 3.2.S.4.2 Analytical Procedures by including the Kinetic Chromogenic Method used for endotoxin testing of drug substance.

5. Please commit to submit the final established (b) (4) after trending the data from 10 DS batches to the BLA as a PMC. Provide a time line for submitting the established in-process limits.

Please provide a response to the aforementioned requests by September 15, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 10, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Teleconference – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

We have provided an agenda, noted below, in preparation for the CMC teleconference scheduled for September 11, 2014.

If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 10, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Teleconference September 11, 2014 - Agenda

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AGENDA

TELECONFERENCE - September 11, 2014

1. Discussion of recommendations for Drug Substance (DS) and Drug Product (DP) Specifications.

To help our discussions, for each UTC DP lot that has been used clinically, identify the specific clinical trials that utilized the lot, the age of the lot at the time of clinical use, as well as available information on the number of patients and number of doses. Provide confirmation that the PK clinical trial was conducted with the reference standard DP lot S110601 at (b) (4) months of age.

a. We recommend (b) (4) acceptance criteria of not more than EP standard II for DP and DS release and stability specifications.

b. We recommend that you remove (b) (4) from DS specifications.

c. We recommend that you remove (b) (4) from DP specifications.

d. For drug product release and stability specifications, acceptance criteria for sub-visible particles detected by light obscuration should be based on clinical experience with NCI lots. We recommend not more than (b) (4)

e. For the cSDS and cIEF assays included in DS and DP specifications, provide available data from NCI clinical lots to support the proposed acceptance criteria.

f. Until an improved ADCC assay can be developed with narrower acceptance criteria, we recommend that DS specifications include quantitative criteria for (b) (4). We recommend (b) (4) acceptance criteria of (b) (4) %.

g. Provide more meaningful criteria for the (b) (4) included in DS specifications, such as quantitative criteria for the (b) (4) and conforms to reference standard criteria.

h. We recommend that the cSDS assays include conforms to reference criteria, including no new peaks compared to reference.

i. Propose a lower limit for the host cell protein assay included in DS specifications.

j. We recommend that you update the DS specifications to indicate the testing that is performed on [redacted].

k. We recommend that you include an upper limit to fill volume in DP specifications.

2. Discussion of acceptance criteria for remaining assays included in specifications (i.e., SE-HPLC, GD2 binding, CDC, and ADCC assays)

3. Potential PMCs

4. Additional requests

a. We recommend that the acceptable range for [redacted] be narrowed to [redacted]%

b. If [redacted] is not routinely monitored during [redacted], then we recommend that you remove this parameter from 3.2.S.2.2.

c. Update the BLA with the protocol for the ADA assay that was used to assess clinical samples.

d. When updating section 3.2.S.2.3 of the BLA with information on how stability of the master cell bank will be monitored, you should provide the viability acceptance criteria that will be used.

e. Provide an update on when the reference standard protocols as well as the concurrent commercial scale [redacted] lifetime protocols will be available.

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GINA M DAVIS
09/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 10, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Unituxin (dinutuximab) Request for Information – Carton and Container

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please refer to your container label and carton labeling submitted on April 11, 2014 for BLA 125516.

Please also refer to your September 4, 2014, amendment submitted in response to our August 26, 2014 information request. We have reviewed your submission and have the following comments and requests for information.

Deficiencies

General Comment for all Container Labels and Carton Labeling

1. Add your assigned US License number 1993 to appear directly after the manufacturer information per 21 CFR 610.60(2) and 21 CFR 610.61(b).

Carton Labeling

2. Delete the word "Code" from the NDC statement.

3. Add the strength statement to appear below the proprietary name, proper name, and dosage form on the rear panel and side panel.

Unituxin
(dinutuximab)
Injection

17.5 mg/5 mL
(3.5 mg/mL)

4. Add dinutuximab (3.5 mg) to the list of ingredients. For example, "Each mL contains dinutuximab (3.5 mg), histidine (3.1 mg), … pH to 6.8."

Please provide a response to the aforementioned requests by close of business September 24, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 10, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – QT-IRT

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please provide the data for Study DIV-NB-201.

Provide a response to the aforementioned request as soon as possible. If you have any questions or concerns please contact me. Additional comments and requests for information may be forthcoming.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/10/2014

Monthly Team Meeting Summary
September 10, 2014

BLA 125516/IND 110494

Product:	Unituxin (dinutuximab)
Submission Date:	April 11, 2014
Received Date:	April 11, 2014
Sponsor:	United Therapeutics Corporation

Proposed Indication: For the treatment of Pediatric Neuroblastoma

Current Review Team for BLA 125516:
Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS)
Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Officer
Suzanne Demko, C-P.A. Medical Team Lead (TL and CDTL)
Sirisha Mushti, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Xianhu Cao, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Dubravka Kurfin, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Chikako Torigoe, Ph.D., CMC
Laurie Graham, Ph.D., CMC
Lyndsey Hennessey, DMA RPM
Melinda McLawhorn- OPDP professional reviewer
Mathilda Fienkeng- OPDP consumer reviewer
Olga Salis – OPDP RPM

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

Agenda Items:

1. **Review Status:**
   - Orphan Drug Designation - granted December 20, 2010
   - Exempt from Pediatric Research Requirements
   - Categorical Exclusion Requested
   - UTC requested to be awarded a rare pediatric disease priority review voucher – April 18, 2013
   - UTC claims seven year marketing exclusivity

2. **Dates Milestone Letters Must Issue: PDUFA V dates**

Milestone	6 month review	
Acknowledgment Letter	April 25, 2014	
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	June 10, 2014	
Deficiencies Identified Letter (74 Day Letter)	June 24, 2014	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	November 10, 2014 (subject to change)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 19, 2014	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off*** ***Compliance Check List (BLA)***	 September 13, 2014 September 17, 2014 November 19, 2014 November 30, 2014 December 10, 2014 November 12, 2014	
Compile and circulate Action Letter and Action Package	November 19, 2014	
FINAL Action Letter Due	December 10, 2014	

- **Late-Cycle Meeting Date:** September 17, 2014 (internal) 12:00 PM – 1:30 PM

  October 6, 2014 (sponsor) 12:00 PM – 1:30 PM

MEETING PACKAGE DUE TO UTC – September 23, 2014

3. OTHER ISSUES

- CMC teleconference scheduled with United Therapeutics Corporation on Thursday, September 11, 2014.
- Awaiting feedback on two IRs;

  Clinical Pharmacology - out September 9th /expecting response – September 11th

  CMC – out September 5th/ expecting response – September 11th
- Contacted TB-EER - a waiting for update on inspection.
- BMAB inspections are complete.

UPDATES FROM THE TEAM

Clinical

- No outstanding issues.

Nonclinical

- The nonclinical team has completed their review, to include a PMR, and it is with the Dr. John Leighton, Division Director, for final concurrence.
  - Postmarketing Requirement (PMR)
    - to further investigate the potential for long term neuropathy and neuropathic pain as well as to further explore the toxicity of dinutuximab as a monotherapy.

Clinical Pharmacology

- The clinical pharmacology team is close to finalizing their review. Awaiting response from UTC regarding long-term storage stability of PK samples.

Microbiology

- No representation from the microbiology team at the monthly meeting.

Office of Surveillance and Epidemiology (OSE) – Labeling/Carton and Container

- The Office of Surveillance and Epidemiology requested carton and container information on August 26, 2014. OSE asked if it were permissible to request UTC list the license number, Number 1993, on the carton and container. It is permissible and an IR will go out later today requesting this information. UTC will be informed that documenting the license number on the carton and container does not constitute approval of their product.

Chemistry Manufacturing and Control (CMC)

- Specifications - Final Testing
  - Potential PMCs
    - Reference standards – will have to have reference std by specific date
    - Improve AOCC and HPC assay
    - Testing of cell bank clonality
    - Re-do end of product cell product testing
    - No compatibility studies for infusion bags
    - No drug product shipping studies
    - May need leachable studies of drug product in real-time and end of study
  - Additional comments from CMC regarding carton and container issues for labeling.

Stats

- Stats has received all data from CSR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 9, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical Pharmacology

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> Please submit the results of the long-term storage stability of PK samples. The storage time in a long-term stability evaluation should equal or exceed the time between the date of first sample collection and the date of last sample analysis (Bioanalytical Method Validation guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf).

Please provide a response to the aforementioned request by close of business September 11, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 5, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Late Cycle Meeting/Teleconference

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Dear Dr. Bryd,

The Division of Oncology Products 2 has scheduled a late cycle teleconference/meeting with United Therapeutics Corporation to discuss the status of the review.

Late Cycle Teleconference

Monday October 6, 2014
12:00 PM – 1:30 PM
Call-in information - To be provided

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
09/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 5, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

1. Provide the [redacted] (b) (4) that were used for the drug substance (DS) validation lots.

2. Section 3.2.S.2.3 BLA should be updated to indicate materials that are compendial or non-compendial as well as the grade.

3. Section 3.2.S.2.3 should be updated to indicate that [redacted] (b) (4).

4. We note that your master validation plan for the DS indicate that batches [redacted] (b) (4). Provide clarification on whether the validation batches were [redacted] (b) (4). If not, provide a summary of the [redacted] (b) (4)

5. Provide clarification on how DS validation criteria were determined. For example, which batches were used for establishing criteria and whether the batches were full or reduced scale.

6. Prove available chemical stability data supporting the [redacted] (b) (4).

7. Update sections 3.2.S.4.2 and 3.2.P.5.2 with the SOP for the assays.

8. With regard to ADCC activity, provide available data comparing the NCI and UTC lots with the validated assay included in DS and drug product (DP) specifications.

9. For the forced degradation studies, provide an identification of the [redacted] (b) (4) that were impacted by the conditions tested.

10. We recommend that you move the master batch records from 3.2.S.2.2 and 3.2.P.3.3 to the regional section of the BLA.

11. For the [redacted], we note that [redacted]. Provide clarification on the root cause for this [redacted] and the steps that are in place to ensure that this situation does not occur in the commercial manufacturing process.

12. [redacted] the limit for residual DNA in DS specificaions exceeds the 10 ng value in the WHO guideline. Tighten the limit.

13. For DS specifications, [redacted] This is not acceptable. Implement protein concentration testing in DS stablity studies.

14. For the cIEF, cSDS (reduced and non-reduced), and SE-HPLC assays, provide a justification for not assessing accuracy and sensitivity for both purity and impurities as these assays appear to be quantitative impurity assays per ICH Q2(R1).

15. For those assays that provide a quantitative assessment of impurities, provide a justification for [redacted]

16. For the validation of the GD2 binding ELISA [redacted]-11-5037R, [redacted]-11-5037R1);

    a. In the system suitability and precision assessments, a significant [redacted] ([redacted]-11-5037A, page 5, page 8, page 9). Explain the root cause of these observations.

    b. [redacted]

    c. [redacted] Provide the rationale for these modifications.

    d. Explain how the LOD and LOQ were determined.

    e. Clarify if the samples were in the UTC formulation.

    f. Explain why the data for the [redacted] samples are significantly higher in [redacted]-11-5037R1 than those in [redacted]-11-5037.

17. For the validation of the CDC assay (BAL-11-070-012R);

    a. Explain why the [redacted] Also explain why the [redacted] concentrations are the same for the reference standard in the same table.

    b. Explain why the mean signal of IgG/ch14.18 [redacted] controls in Table 10, 11 and 12.

    c. It is difficult to distinguish the symbols for ch14.18 and IgG in Figure 1 and 2. Provide revised figures.

    d. Explain why accuracy criteria are [redacted] for intra-assay accuracy and inter-assay accuracy.

    e. Explain why assay run 1 and 2 show significantly lower values than assay run 3 – 6 in Table 6 (this is reflected in the large CV in Table 7 and 8).

18. In the validation of the [redacted] assay ([redacted] 12-5141A1R), [redacted] in Table 8.3. Explain how the recovery was calculated.

19. For the validation of TBP assay ([redacted] L-07-11-016R);

    a. Explain why the peak area ratio, number of [redacted] in the system suitability results (Table 1).

    b. Explain why linearity failed [redacted].

    c. Explain how the recovery was calculated in Table 5.

    d. Explain how the concentration of TBP was calculated in Table 8 and 9.

20. Provide the cumulative hold times for DP manufacturing, inclusive of labeling and packaging along with available product quality data to support these hold times.

21. We recommend that 3.2.P.3.3 include [redacted]

22. The comparability assessment in the BLA appears to have been performed primarily using DP from NCI and UTC material in [redacted]. Provide a comparability assessment of UTC DP vs NCI DP using UTC material in the final formulation and container closure system.

23. For the comparability assessment provided in the BLA, provide clarification on whether the UTC material in the comparability study was in the final DP container closure system.

24. For DP compatibility, it is unclear what materials of construction for the IV bags and administration sets have been studied. Provide clarification along with summary information from studies that assessed different materials of construction.

25. For the inspection and packaging section of 3.2.P.3.3, please remove reference to the use of "approved facilities" other than the ones listed in the BLA.

26. Provide clarification on whether different DS lots [redacted (b) (4)].

27. Provide summary information on the investigation and root cause analysis of the [redacted (b) (4)] that is seen under real time stability for drug product. Provide clarification on whether NCI lots also showed [redacted (b) (4)].

Please provide a response to the aforementioned requests by September 11, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
09/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 29, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

Section 3.2.S.2.2 of the BLA should be updated to include the following process parameters, with appropriate ranges.

1. (b) (4)

2.

2 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

20. Provide summary information for the DS validation batches on the (b) (4) that were used.

21. 21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. Provide information to confirm that identity testing of ch14.18 meets this CFR requirement.

Please provide a response to the aforementioned requests by September 5, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 28, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Non-clinical information

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> Please provide (or direct us to where it was previously provided) the signed pathology report for study (b) (4) 354-003: A 4-Week Repeated Intravenous Dose Toxicity Study of the Anti-GD2 Antibody ch14.18 in Rats with a 6-Week Recovery Period.

Please provide a response to the aforementioned request by close of business September 2, 2014. Your submission is still under review and additional comments and requests for information may be forth coming. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 27, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information - Labeling

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

Please provide the following information regarding revised proposed labeling submitted by United Therapeutics on July 8, 2014:

1. (b) (4)

2. (b) (4)

   Please provide references to specific locations in the BLA where the data supporting this information can be found. Include an explanation describing how the median duration of these adverse events was determined.

Please provide a response to the aforementioned requests by 10:00 AM, September 2, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/27/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 26, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Unituxin (dinutuximab) Request for Information – Carton and Container

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Please refer to your container label and carton labeling submitted on April 11, 2014 for BLA 125516. Currently your submission is under review and we have identified the following deficiencies that require a response.

A. General Comment for all Container Labels and Carton Labeling

1. Ensure the proper name, dinutuximab, is at least half as large as the proprietary name, Unituxin, per 21 CFR 201.10(g)(2).

2. Add the dosage form, Injection, to appear under the proper name, dinutuximab, in the identical font size and style as the proper name on the principal display panel (PDP) and all places where the proprietary and proper names appear together. Per USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1> Injections, Nomenclature and Definitions, the dosage form for this product is "Injection".

3. Revise the strength statements so there is a space between the number and unit of measure. For example:

17.5 mg/5 mL
(3.5 mg/mL)

The strength should be more prominent than the concentration. In the submitted carton labeling, the numeral "1" in the strength was not bolded like the other numerals ("1**7.5mg/ 5mL**).

Additionally, see comment B2 for strength presentation for the carton labeling and comment C3 for the container label.

4. Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t), 21 CFR 610.60, and 21 CFR 610.61. Thus, the Research Triangle Park, NC address in the "APPLICANT INFORMATION" section of the 356h form is the appropriate address for the manufacturer. If you wish to include the facility that manufactures the finished dosage form on the carton labeling, consider the following:

Manufactured By:
United Therapeutics Corporation
Research Triangle Park, NC
US License Number xxxx

(b) (4)

*Omit this facility from the container label due to space limitations.

5. Add the US License number to appear directly after the manufacturer information per 21 CFR 610.60(2) and 21 CFR 610.61(b). This US License number should also appear in the "APPLICANT INFORMATION" of the 356h form.

6. To maintain consistency with other labels and labeling, we recommend the addition of the equivalent storage temperature range in degrees Fahrenheit (°F).

B. Carton Labeling

1. Relocate the NDC from the side panel to the top of the PDP per 21 CFR 207.35(3)(i).

2. Revise the statement "(b) (4)" to read "For Intravenous Infusion Only. Dilute Prior to Administration". Thus, we recommend the PDP appear as follows:

Unituxin
(dinutuximab)
Injection

17.5 mg/5 mL
(3.5 mg/mL)

For Intravenous Infusion Only
Dilution Prior to Administration

3. Add the inactive ingredients to the back or side panel per 21 CFR 201.100(b)(5). Per USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients, list the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount).

4. Add the statement "No preservative" to the side panel to comply with 21 CFR 610.61(e).

5. Revise the statement "Keep the vial in the outer container to protect from light" to read "Keep vial in outer carton to protect from light."

6. According to 21 CFR 201.100(b)(2), the Unituxin carton labeling should bear a recommended or usual dosage statement. We recommend changing the following statement from, "See package insert for full prescribing information for preparation and administration." to "Usual Dosage: See package insert for full prescribing information, including dosage, preparation, and administration."

C. Container Label

1. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

2. Comment on if there is any text on the ferrule and cap overseal to comply with a revised USP standard [USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1> Injections/General Requirements] that went into effect on December 1, 2010. We refer you to the following address: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

3. Revise the presentation of the proprietary and proper names, dosage form, strength and route of administration as follows:

Unituxin
(dinutuximab)
Injection

17.5 mg/5 mL (3.5 mg/mL)

For Intravenous Infusion Only
Dilute Prior to Administration

Additionally, ensure the decimals in the strength statement are clearly readable.

4. Add a bar code per 21 CFR 610.67.

5. To create space on the right side of label to include a bar code:

   a. Revise the statement "SINGLE USE VIAL. DISCARD UNUSED PORTION" from UPPERCASE to "Single Use Vial. Discard Unused Portion".

   b. Revise the sentence "See package insert for full prescribing information for preparation and administration" to read "Usual Dosage: See package insert."

   c. Revise the statement "Keep the vial in the outer container to protect from light" to read "Keep vial in outer carton to protect from light."

   d. Abbreviate "Manufactured by:" to read "Mfd by:" Consider abbreviating "United Therapeutics Corporation" to "United Therapeutics Corp."

Please provide a response to the aforementioned requests by close of business September 5, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/26/2014

From: Davis, Gina
To: Noah Byrd (NByrd@unither.com)
Subject: BLA 125515 - United Therapeutic Corporation - Unituxin - Request for information - Clinical
Date: Monday, August 25, 2014 7:16:00 PM

Good evening Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

Please explain why the following adverse reactions are included in the ADAE dataset for Study 301, but don't appear in the ISS dataset:

STUDYID	USUBJID	TRTEMFL	AEDECOD	AEPTCD	AETOXGR	AESTDTC	AESTDY	SAFFL	TRT01A	TRTSDT	TRTEDT
ANBL0032	ANBL0032-748938	Y	EMBOLISM VENOUS	10014522	3	2006-06-06	180	Y	Immunotherapy + RA	16779	16982
ANBL0032	ANBL0032-754789	Y	EMBOLISM VENOUS	10014522	3	2007-02-02	176	Y	Immunotherapy + RA	17024	17199

It appears that the adverse events were recoded to the preferred term "Vascular access complication" in the ISS ADAE dataset (see below). Is this correct? If so, please explain why this was done.

USUBJID	TRTEMFL	AEDECOD	AEPTCD	AETOXGR	AESTDTC	AESTDY	SAFFL	TRT01A	TRTSDT	TRTEDT	ASTDT
ANBL0032-748938	Y	VASCULAR ACCESS COMPLICATION	10062169	3	2006-06-06	180	Y	Immunotherapy + RA	16779	16982	16958
ANBL0032-754789	Y	VASCULAR ACCESS COMPLICATION	10062169	3	2007-02-02	176	Y	Immunotherapy + RA	17024	17199	17199

Please provide a response to the aforementioned requests by Wednesday August 27, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.

Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 25, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. Please provide case report forms for the following patients in Study 301:

772362
777143
777199
777889
777915
777945

2. Regarding your August 22, 2014 submission of updated datasets for Studies DIV NB 301 and DIV NB 302, please explain why the revised Study 302 ADSL dataset has 41 subjects who appear to have been treated prior to December 31, 2013 that now have a safety flag equal to "Y" who previously had a safety flag of "N" in the original ADSL dataset submitted to the BLA. Should these patients have originally been included in the Study 302 dataset as part of the safety population? The patient ID numbers that this inquiry is in reference to are listed below.

   ANBL0032-827294
   ANBL0032-827513
   ANBL0032-827563
   ANBL0032-829238
   ANBL0032-829282
   ANBL0032-829362

ANBL0032-829576
ANBL0032-829676
ANBL0032-829805
ANBL0032-829857
ANBL0032-829926
ANBL0032-830146
ANBL0032-830239
ANBL0032-830365
ANBL0032-830426
ANBL0032-830482
ANBL0032-830487
ANBL0032-830554
ANBL0032-830569
ANBL0032-830940
ANBL0032-830977
ANBL0032-831017
ANBL0032-831077
ANBL0032-831220
ANBL0032-831283
ANBL0032-831335
ANBL0032-831386
ANBL0032-831428
ANBL0032-831512
ANBL0032-831589
ANBL0032-831800
ANBL0032-831952
ANBL0032-832045
ANBL0032-832100
ANBL0032-832144
ANBL0032-832196
ANBL0032-832198
ANBL0032-832263
ANBL0032-832285
ANBL0032-832324
ANBL0032-832614

Please provide a response to the aforementioned requests by close of business August 26, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/25/2014

Monthly Team Meeting Summary

August 25, 2014

BLA 125516/IND 110494

Product:	Unituxin (dinutuximab)
Submission Date:	April 11, 2014
Received Date:	April 11, 2014
Sponsor:	United Therapeutics Corporation

Proposed Indication: For the treatment of Pediatric Neuroblastoma

Current Review Team for BLA 125516:
Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS)
Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Officer
Suzanne Demko, C-P.A. Medical Team Lead (TL and CDTL)
Sirisha Mushti, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Xianhu Cao, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Dubravka Kurfin, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Chikako Torigoe, Ph.D., CMC
Laurie Graham, Ph.D., CMC
Lyndsey Hennessey, DMA RPM
Melinda McLawhorn- OPDP professional reviewer
Mathilda Fienkeng- OPDP consumer reviewer
Olga Salis – OPDP RPM

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

Agenda Items:

1. **Review Status:**
   - Orphan Drug Designation - granted December 20, 2010
   - Exempt from Pediatric Research Requirements
   - Categorical Exclusion Requested
   - UTC requested to be awarded a rare pediatric disease priority review voucher – April 18, 2013
   - UTC claims seven year marketing exclusivity

2. **Dates Milestone Letters Must Issue: PDUFA V dates**

Milestone	6 month review	
Acknowledgment Letter	April 25, 2014	
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	June 10, 2014	
Deficiencies Identified Letter (74 Day Letter)	June 24, 2014	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	November 10, 2014 (subject to change)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 19, 2014	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off*** ***Compliance Check List (BLA)***	 September 13, 2014 September 17, 2014 November 19, 2014 November 30, 2014 December 10, 2014 November 12, 2014	
Compile and circulate Action Letter and Action Package	November 19, 2014	
FINAL Action Letter Due	December 10, 2014	

UPDATES FROM THE TEAM

Clinical

- Data quality issues.
- There are MEDRA issues CTCAE (version 4).
- Issues with the Adverse Events Section of the label
  Numbers are not currently available to team – awaiting response from UTC.
  The quality control of the data received is sub-standard

Inspections

OSI

- CTEP – possible issues
  - Case report form issues – issues with data verification
  - Issues with data verification
  - Possible NCI meeting

BMAB

- Inspections are complete

EES

- EER – Status of EER. Will double check with Peter Qui

Special Government Employee

- Unavailable due to government conflicts. Currently interviewing (b) (6) (b) (6) as the special government employee (SGE).

Unituxin Label

- Adverse Event Section
  Numbers are currently unavailable to the team
- Dr. Keegan's comments in the dinutuximab label were not addressed

Nonclinical

- The nonclinical team is working towards completion of their review. Response to nonclinical I/R was received on August 25, 2014.
- No specification numbers – nonclinical is unable to set impurity specifications
  - UTC has a 1 month rodent study.
  - 3 month toxicology study using the clinical dosing schedule of a relevant species.
  - Rats are having a response to pain.
  - Some animal data provided via published literature.

Potential postmarketing requirement (PMR)

- Possible PMR post marketing requirement to further investigate the potential for long term neuropathy and neuropathic pain by a CRO or outside firm

Clinical Pharmacology

- The clinical pharmacology team is close to finalizing their review. Awaiting update on immunogenicity data.
-

Microbiology

- No representation from the microbiology team at the monthly meeting.

Office of Surveillance and Epidemiology – DMEPA

- The Office of Surveillance and Epidemiology will take the lead from the clinical team.

Chemistry Manufacturing and Control (CMC)

- CMC is experiencing some difficulty in obtaining data. ADA data has not been provided. All protocols are not in the BLA.
    - PMCs will be requested.

Stats

Stats has received all data from CSR.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 20, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information in response to your August 1, 2014 submission.

1. Table 1:"Bioburden Qualification of ch14.18 (b) (4)" included in your response does not include the lot numbers of the (b) (4). Please provide the lot number of the (b) (4) used for Bioburden Qualification.

2. (b) (4) Please implement using the qualified dilution for endotoxin testing of the samples as required. Alternatively, qualify (b) (4) of the samples for endotoxin testing using three different lots and submit the data.

Please provide a response to the aforementioned comments and requests by August 27, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 20, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. Please provide a comprehensive listing of patients who enrolled into Study DIV-NB-301 or DIV-NB-302 who were included in the safety population in the prior submissions to your BLA who are now known not to have received study therapy. Provide this information by patient number, study of enrollment, and treatment group. For patients who are not listed in the COG memo submitted to the BLA on 7/22/2014, please provide a brief explanation explaining why they were previously included in the safety population despite the fact that they didn't receive study therapy.

2. Please verify that the STDM dataset labeled "Serious Adverse Events" (AD) for Study 301 and the ADam dataset for the integrated summary of safety labeled "Serious Adverse Events" (ADSAE) submitted to the BLA contain MedDRA coded preferred terms in the field entitled "AEDECOD". The clinical study report states that MedDRA version 10 was used to code serious adverse events that were reported through AdEERs, but some of these data (e.g., "anaphylaxis", "immune system disorders – other, specify", " infections and infestations – other, specify") do not all appear to correspond to MedDRA version 10.0 preferred terms. If these data are not MedDRA preferred terms, please identify all terms in the AEDECOD domain that are not MedDRA coded terms and explain how they were derived.

Please provide responses to the aforementioned requests by noon on August 21, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 19, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical Pharmacology

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> Please provide the information regarding the impact of immunogenicity on the clinical efficacy and safety.

Please provide a response to the aforementioned request by close of business August 26, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 19, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> Please clarify whether subject 743731 (randomized to receive RA in Study 301) received study therapy and belongs in the safety population for Study 301. The ADEERS report indicates that this subject did not receive RA prior to death.

Please provide a response to the aforementioned request by August 22, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 18, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. Please provide a step by step description of how to identify the ch14.18 safety population included in the ISS ADSL (ADam) dataset provided to the BLA on April 4, 2014. Does the safety population (N=1144 including the two patients erroneously included in the safety population for DIV-NB-301, 743151 and 714449) included in the summary of clinical safety comprise those patients who have "Y" in the SAFFL field and a TRT01AN = "2", plus the four crossover patients from the randomized study (patients (772352, 773298, 775694, and 777910)? Please also explain the use/meaning of the fields TRT02A/TRT02AN, TR01PG1N, TR02PG1N, TR03PG1N, TR04PG1N, etc.

2. Please also provide a breakdown of the number of patients by study comprising the 1144 total in the ISS safety database (including the number of patients from Study 301, Study 302, Study 303, Study 201, etc that add up to the 1144 number

Please provide a response to the aforementioned requests by close of business August 21, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 15, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> Please clarify the data cutoff dates used for the updated integrated summary of safety submitted with the 120-day safety update for dinutuximab. The Study Data Reviewer's Guide states that the cutoff dates for the nonrandomized portion of the ANBL0032 study and DIV-NB-201 are December 31, 2013 and February 5, 2013, respectively. However, the cover letter indicates that the cutoff date for the ANBL0032 study is March 31, 2014 (and is silent regarding the cutoff date for the DIV-NB-201 study).

Please provide a response to the aforementioned request by close of business August 22, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 15, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

Comments

1. You have stated that the [redacted (b) (4)] will be established after trending the data from 10 DS batches. Please implement interim limits until [redacted (b) (4)] are established.

2. When performing bioburden qualification with additional lots for [redacted (b) (4)] please use SDA plates for yeast and mold and incubate the TSA plates at 30°C for 35ºC for 48-72 hours and SDA plates at 25ºC for not more than 5 days as qualified for the [redacted (b) (4)] bioburden samples.

The following deficiency has been identified in the review of the STN 125516:

3. In section 3.2.S.4.5. Justification of Specifications, you have stated that endotoxin limit, [redacted (b) (4)] was based on the established NCI limits for ch14.18. Please justify the set limits by providing the calculations based on patient's body surface area.

Please provide a response to the aforementioned comments and requests by close of business August 21, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/15/2014

Griffin, Norma

From: Griffin, Norma
Sent: Thursday, August 07, 2014 9:23 PM
To: 'Noah Byrd'; Rex Mauthe
Cc: Davis, Gina
Subject: BLA 125516 - United Therapeutics Corporation - Unituxin - FDA Clinical Information Request 8.7.2014

Importance: High

Good Evening Dr. Byrd and Dr. Mauthe,

Our Clinical Reviewer has the following comments and request for information. We ask that you provide your response within the next 10 days – by Tuesday, August 19, 2014.

Please provide an analysis comparing the per-patient incidence (PPI) of treatment-emergent adverse events (total TEAEs as well as grade 3 and above) and serious treatment-emergent adverse events for the randomized study broken down by preferred term and treatment regimen during which the adverse event occurred [ch14.18+IL-2 (Cycles 2,4) vs. ch14.18+GM-CSF (Cycles 1,3,5) vs. the control arm]. Please see the template below.
Please provide the data sorted by decreasing PPI for all TEAEs in the treatment arm.

Preferred Term	Cycles 1,3,5 Ch14.18 +GM-CSF		Cycles 2,4 Ch14.18+IL-2		All Cycles ch14.18 arm		Control Arm	
	All TEAEs n (%)	Severe TEAEs n (%)	All TEAEs n (%)	Severe TEAEs n (%)	All TEAEs n (%)	Severe TEAEs n (%)	All TEAEs n (%)	Severe TEAEs n (%)

Kindly respond to confirm receipt of this email.
Thanks,

Norma S. Griffin
Senior Regulatory Health Project Manager
CDER / OHOP / DOP2
Telephone 301.796.4255

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/s/

NORMA S GRIFFIN
08/07/2014

Griffin, Norma

From: Griffin, Norma
Sent: Wednesday, August 06, 2014 8:06 AM
To: 'nbyrd@unither.com'
Cc: Davis, Gina
Subject: RE: BLA 125516 - United Therapeutics Corporation - Unituxin - FDA CMC Information Request

Importance: High

Good Morning Dr. Byrd,

On behalf of your RPM, Gina Davis, I am covering your BLA submission this week while Gina is unexpectedly out of the office. Our CMC Reviewer has the following comments and information request and asks that you provide your response by **August 19, 2014**, or sooner if possible.

Please contact me via email if you have any questions.

3.2.S.2.3 Control of Materials

1. As described in DEV-10-5005, it appears that the master cell bank developed by NCI (b) (4) In addition, it appears that the cell line was also (b) (4) . Provide available information on the (b) (4) used during cell line development, such as documentation on (b) (4), commercial source, raw material testing requirements, and certificates of analysis. Provide a (b) (4)

2. Insufficient information has been provided to date to support the clonality of the production cell line. As stated in section 4.1 of dev-12-5001, there was no documentation that the (b) (4) You need to provide available information on the cloning procedures performed by NCI as well as detailed information on the cloning procedures performed by (b) (4) This includes detailed information on the (b) (4) Provide a calculation on the probability of clonality of the production cell line along with information on how the probability was calculated.

3.2.S.2.6 Manufacturing Process Development

3. For the ADCC assays used as part of the comparability assessment, for each figure (i.e. figures 8-63 to 8-68) provide the results expressed as percent activity compared to the reference standard run in the assay. For example, the data in each figure should be converted to percent activity of each lot relative to lot L1009014. Provide the raw data for each figure. If possible, for each figure, provide ED_{50} results for each lot expressed as a percentage of the reference standard.

4. There appears to be a significant difference between the NCI lots and the UTC lots with regard to the cIEF profiles and reduced SDS results (b) (4) . Provide any available information on the basis of the observed differences.

5. We note that information on end of production cell testing appears to have been performed on cells taken from a (b) (4) Provide clarification on the process development laboratory cell culture conditions, including scale. Provide available data to support that the process development and (b) (4) cell culture conditions

are representative of the full scale process. Alternatively, provide available end of production cell testing on cells grown for a longer period of time under commercial production conditions.

6. Section 3.2.S.2.3 of the BLA should be updated to include information on the generation and testing of the end of production cells.

7. The hold-time studies (DEV-11-5063, DEV-12-5118) appear to only include storage at (b) (4) the data supporting these hold times should be provided to the BLA and the (b) (4) conditions listed in section 3.2.S.2.4 should be updated accordingly.

8. Figure 1 in DEV-12-5118 appears to be inconsistent with the text as well as Table 1-4 in 3.2.S.2.4 with regards to the (b) (4) steps. Our understanding is that the (b) (4) (b) (4) e. Please confirm.

3.2.P.6 Reference Standard

9. We have concerns regarding whether the current reference standard, drug product lot S110601, is representative of the current commercial process and comparable to the previous reference standard. Specifically, it is noted that during comparability testing, this lot:

   a. (b) (4)

   b.

   c.

   d.

Therefore, provide additional information to explain the differences observed between lot S11060, the NCI reference standard, and the other drug product lots manufactured by UTC.

10. The stability data provided on the reference standard, drug product lot S110601, in section 3.2.P.8.3, suggests that the reference standard has (b) (4). For example, (b) (4)

11. You should provide a protocol that will be used to assess the stability of the current reference standard (i.e. a requalification protocol). This should include the time points, assays, and acceptance criteria that will be used.

12. Of note, the acceptance criteria provided in Table 1-1 of section 3.2.P.6 are not acceptable for either qualification or requalification of reference standards. The commercial Reference Standard must provide a link between the pivotal material and the commercial specification acceptance criteria. Specifically:

    a. (b) (4)

(b) (4)

b. The primary reference standard qualification requirements listed in Table 1-1 for the GD2 binding, CDC, and ADCC potency assays are currently (b) (4)%, and "similar to reference", respectively. These criteria are too wide or undefined, to support the prevention of drift in the potency of commercial material. The requalification protocol will need to contain updated acceptance criteria for potency. We recommend acceptance criteria no wider than (b) (4)% activity.

c. You should provide additional information on how reference standard activity will be routinely monitored on stability through an absolute measurement, such as through curve parameters (e.g., EC50 values). This could include requalification testing as well as routinely monitoring curve parameters during release and stability testing.

d. If stability testing of the reference standard uses "compares to reference standard" criteria, this will need to be defined. Specifically, you should describe how conformance to reference standard will be determined when the reference standard itself is being evaluated.

e. Commit to providing the remaining primary reference standard stability data to the BLA in annual reports as the data becomes available.

13. We recommend that a two tiered reference standard system be used (i.e. primary and secondary reference standards). Protocols covering future reference standards, including future primary and secondary reference standards should be submitted to the BLA. The protocols should include information on manufacturing, qualification, and requalification. When a Reference Standard protocol is agreed upon, that protocol must be followed; update the BLA accordingly. If reference standard protocol(s) cannot be submitted and agreed upon during the current review cycle, the protocol(s) can be submitted to the BLA as a PAS; in this case, section 3.2.P.6 should be updated to reflect that no reference standard will be implemented until its use is approved by FDA.

14. Provide information and data on the reference standards used prior to drug product lot S110601.

Regards,

Norma S. Griffin
Senior Regulatory Health Project Manager
CDER / OHOP / DOP2
Email Norma.Griffin@fda.hhs.gov Telephone 301.796.4255

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/s/

NORMA S GRIFFIN
08/06/2014

Griffin, Norma

From: Griffin, Norma
Sent: Wednesday, August 06, 2014 7:23 AM
To: 'nbyrd@unither.com'
Cc: Davis, Gina
Subject: BLA 125516 - United Therapeutics Corporation - Unituxin - FDA STATS Information Request

Importance: High

Good Morning Dr. Byrd,

On behalf of your RPM, Gina Davis, I am covering your BLA submission this week while Gina is unexpectedly out of the office.

The STATS review team has the following information request. In addition, our STATS review team would like to schedule a T-con with you and would request to also include United Therapeutics STATS Reviewer on Thursday, August 7, 2014 from 11 AM until 12 NOON. This T-Con is regarding the statistical analysis, and FDA would like to discuss and verify the methods/process simultaneously during the T-con. We will be working from our laptops during the TCON so that United Therapeutics can walk us through the process.

Please see the 4 comments and information request below. Kindly respond to confirm receipt of this email and to confirm the date and time for the TCON tomorrow. Please also provide me a toll-free conference call in number for the TCON.

1. Please clarify the discrepancy noted in the below table regarding the total number of events and 3-year survival rates for OS efficacy analysis for 30 June 2012 data cutoff.

	Sponsor's OS results		**FDA Reviewer's OS results**	
	Immuno+RA n=114	**RA alone n=114**	**Immuno+RA n=114**	**RA alone n=114**
No of events	(b) (4)		31 (27.19%)	48 (42.11%)
3-yr survival rates			79.52% (72.05- 86.99%)	67.25% (58.45- 76.05%)
p-val (2-sided; Unstratified logrank test)			0.0165	

The above results were derived using (b) (4)

2. Please provide the definitions of Period-01 and Period -02 since the treatment variables (TRTP, TRTPN) in the analysis datasets for the 30 June 2012 data cutoff were derived using the treatments planned in Period-02(TRT02P). However, the define file describes the TRTP, TRTPN variables were derived from ADSL.TRT01P. Also, please clarify as which treatment variable is more appropriate to perform the efficacy analysis.

3. It is unclear from your define files and SAS program files as which tabulation datasets were used to derive the analysis\legacy ADTTE datasets for the 30 June 2012 data cutoff. The SAS programs, submitted in Sequence-0013, for deriving the efficacy results used libraries referring the paths to local drives and hence it was difficult to verify and reproduce your results.

4. The response submitted in sequence-0023 with regards to the clarification on calculating interim stopping boundaries was received; however, we still could not duplicate the table using EAST version-6.2. It is expected that using the newer version should derive the same/similar results as that of using earlier versions or any other software and hence we request UTC to verify the stopping boundaries using EAST 6 and walk us through the parameters used to calculate the

Please contact me via email if you have any questions.
Regards,

Norma S. Griffin
Senior Regulatory Health Project Manager
CDER / OHOP / DOP2
Email Norma.Griffin@fda.hhs.gov Telephone 301.796.4255

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NORMA S GRIFFIN
08/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 29, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Statistics

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comment and request for information.

> In response to your submission of calculating interim monitoring boundaries (eCTD: 0017 SN-18; submission date: July 16, 2014), we were unable to download the software specified (www.biostat.wisc.edu/Software/landemets/index.html) and verify the stopping boundaries. Hence, we request UTC to submit the EAST software output for the reproduction of stopping boundaries and sample size calculations. In your submission please include the snapshots of EAST software explaining step-by-step the parameters included in computing the interim monitoring boundaries and sample size.
>
> Since the two tables submitted in the document (using EAST Version-5 and the software) are identical, could you clarify that whether the result in the Table-2 could be reproduced by EAST? If yes, please also provide all snapshot.

Please provide a response to the aforementioned request as soon as possible. Your submission is still under review and additional comments and requests for information may be forthcoming.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 28, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

> Your July 22, 2014 response to our July 17, 2014 request for information indicates that six patients were incorrectly included as part of the safety population in the safety related analyses and datasets for DIV-NB-301 and the integrated summary of safety submitted to the BLA. Submit revised and accurate versions of the safety analyses and datasets that were impacted by this error.

Please provide a response to the aforementioned requests as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 21, 20145

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

Drug Substance
3.2.S.2.1 Manufacturers

1. Update section 3.2.S.2.1 to include the assays performed at each testing facility.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

2. Provide clarification on the current (b) (4) lifetimes that are being used.

3.2.S.2.3 Control of Materials

3. Provide the information on the (b) (4) of the MCB.

4. Additional information is required to support the clonality of your master cell bank. It is noted that you performed (b) (4) on the master cell bank. You should provide summary information on this cloning procedure, (b) (4) . In addition, you should provide summary information on any additional cloning steps that were performed prior to this.

5. Provide available information on the qualification and/or validation of the (b) (4) used for the master cell bank.

6. Update this section of the BLA with information on how stability of the master cell bank is monitored.

7. Provide a risk assessment of the raw material used in the drug substance manufacturing process.

8. Update the information on the raw materials to indicate whether they are compendial or non-compendial in grade. For compendial materials, indicate the specific grade that is used (i.e. NF. EP, USP, etc.). For non-compendial materials, provide information on the specifications that are used.

3.2.S.2.4 Controls of Critical Steps and Intermediates

9. It is indicated in Table 1-1 that (b) (4) is tested for (b) (4) . Only the data for (b) (4) are provided in 3.2.A.2. Provide the complete testing results for the (b) (4).

10. Provide a justification for the assays included in the (b) (4) studies (DEV-11-5063 and DEV-12-5118). For example, we note (b) (4)

11. It is noted that you have included (b) (4) Provide clarification on how these (b) (4) are implemented during routine manufacturing. For example, (b) (4) Under what conditions would a (b) (4) be acceptable?

12. Update the (b) (4) listed in tables 1-3 and 1-4 to indicate the (b) (4) temperatures and that the times listed in the table are the (b) (4)

3.2.S.2.5

13. Provide the protocols and data supporting the (b) (4) lifetimes to the BLA or indicate where this information can be found.

14. For each element listed in Section 11 " Specific Performance Qualification Requirements" of the master validation plan (VMP-106), confirm that all results have been submitted to the BLA and provide specific information on where the results can be found (e.g. the document identification number and page numbers). Alternatively, submit the final validation report to the BLA with a summary of where the specific information on these elements can be found.

3.2.S.2.6 Manufacturing Process Development

15. It is noted that for certain assays in the comparability assessment used NCI and UTC drug product in the same [redacted] (b) (4). You should provide a justification for this approach. Specifically, that analytical differences observed due to formulation differences do not represent product quality differences that could impact safety and efficacy.

16. Additional information is required to support that the NCI and UTC lots have comparable ADCC activity. Specifically,

    a. Provide the ADCC results from TEC 12-5014 expressed as a percentage of the reference standard.

    b. It has been suggested that sialic acids may have an impact on FcγRIIIa binding and ADCC activity (Scallon BJ et al. (2007) Mol. Immunol. 44, 1524-1534.). Provide a risk assessment with regard to the potential for differences in sialic acid levels between UTC and NCI material to impact ADCC activity.

    c. Provide a comparison of [redacted] (b) (4) in UTC and NCI lots.

    d. Multiple target and effector cells are used for the ADCC assays used in the comparability assessment. Provide the information on these cells.

17. Provide a justification for the assays included in the forced degradation studies.

18. Explain why the recovery of [redacted] (b) (4) is very low and highly variable in the amino-acid analysis.

19. Provide a risk assessment for the differences observed in [redacted] (b) (4) between NCI and UTC lots.

20. Different x- and y-axis were used for the electropherograms of cIEF in the forced degradation studies. Provide the electropherograms with the same axis in order to assess the comparability.

21. Explain how the limit for [redacted] (b) (4) was determined.

3.2.S.4.2 Analytical Procedures

22. Provide the detailed information on how the coverage of the HCP assay was evaluated.

23. Provide the updated information on the development of an improved HCP assay.

3.2.S.4.2 and 3.2.S.5.2 Analytical Procedures

24. Update section 3.2.4.2 and 3.2.P.5.2 to reflect the current assays being used in DS and DP specifications.

3.2.R.

25. Provide the master batch records for drug product and drug substance as well as the executed drug substance batch records.

5.3.1.4 BAL-12-070-039 Validation of a Cell Based NAb Assay for the Detection of Neutralizing Antibodies to the Drug product ch14.18 in Human Plasma

26. Provide the raw data used for the determination of the MRD and the cut point.

27. Provide the rationale to use plasmas that contain (b) (4).

28. Provide the rationale for why the data needs to be normalized in this assay by the negative control.

29. We note that the normalization of the data is performed by dividing the sample data by the average of the data for the negative control. This approach, however, may not adequately account for the true background of the assay, such as a buffer control (i.e.. absorbance in the absence of serum, but in the presence of all other assay components). There are concerns that this could lead to an underestimation of the neutralizing antibody response for samples with low signals. Provide a justification for this approach. If normalization is needed, we recommend that you consider normalizing as follows: (the test samples subtracted by the true plate background) divided by (the average of the negative control subtracted by the true plate background). Alternately, you can provide information to support that accounting for the true plate background is not expected to impact your reported neutralizing antibody results.

5.3.1.4 BAL-13-070-056 Validation of an Electrochemiluminescent Assay for the Detection of Anti-ch14.18 Antibodies in Human Plasma

30. Provide the raw data used for the determination of the MRD, screening assay cut point, confirmatory cut point and titration cut point.

Please provide a response to the aforementioned requests by close of business August 1, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 21, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. Submit the [redacted] (b) (4) bioburden limits which will be used for the [redacted] (b) (4) until the establishment of the [redacted] (b) (4) bioburden limits.

2. Submit the interim bioburden and endotoxin limits for the ' [redacted] (b) (4)

3. Submit the hold time validation study data of the [redacted] (b) (4) to BLA after completing the studies.

4. Please commit to submit the established bioburden and endotoxin limits for the end of [redacted] (b) (4) after trending the data from 10 batches.

Deficiencies

3.2.S.4.3. Validation of Analytical Procedures

5. Bioburden

   a. [redacted] (b) (4) Please clarify the discrepancy.

   b. The bioburden method qualification report, "TEC-11-5050, Bioburden and Endotoxin Interference (Qualification) [redacted] (b) (4) does not provide the following information: lot numbers of the [redacted] (b) (4) used for the bioburden method qualification, summary results, incubation conditions and acceptance criteria. Please provide the missing information.

c. Bioburden method qualification of the [redacted] was performed using [redacted] samples. The sensitivity of the testing is higher with a larger sample size. Please provide the rationale for not using a large sample size, for example [redacted]).

d. The bioburden assay method qualification study of the [redacted], and drug substance should be completed using two additional batches.

6. Endotoxin

a. Please submit the following information: the lot numbers of [redacted] used for the endotoxin qualification study.

b. Please explain and include your MVD calculations.

c. Include the inhibition/enhancement evaluation data for [redacted] with the following details:

- the dilutions tested for each [redacted]
- No of replicates, positive and negative controls
- Standard curve.

d. The endotoxin assay method qualification for the drug substance and [redacted] should be completed using two additional batches.

7. Endotoxin masking studies: TEC-14-5025R and TEC-14-5027

a. Please provide the source of endotoxin used for spiking the drug substance [redacted] and submit the protocol used to execute this study.

b. Endotoxin spiking studies are performed using drug substance storage and sampling containers. You have used [redacted] for the endotoxin spiking studies. Please clarify if these [redacted] are the endotoxin sampling containers or the drug product containers. In addition, clarify if the endotoxin spiking studies were performed using [redacted] used for storing the drug substance.

c. Please provide an update on the evaluation of endotoxin/pyrogen test for drug product with regard to the low endotoxin recovery.

Please provide a response to the aforementioned requests by close of business August 1, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 18, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Non-clinical information

---

Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. Provide additional clarification on whether ch14.18 can elicit an effective ADCC response in the presence of effector cells from mouse, dog, or monkey origin.

2. Provide in vitro study results, or assist us in finding specific literature that would answer this question.

Please provide a response to the aforementioned requests by August 15, 2014. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
07/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 18, 2014

From: Gina Davis, Senior Regulatory Health Project Manager, CDER/OHOP/DOP2

Subject: Agenda for Midcycle Communication - Unituxin (dinutuximab)

Meeting Date/Time: Friday, July 18, 2014 from 12:00 PM – 1:00 PM

Application Number: BLA 125516
Product Name: Unituxin (dinutuximab)
Indication: Treatment for Patients with High Risk Neuroblastoma
Applicant Name: United Therapeutics Corporation
Meeting Chair: Suzanne Demko
Meeting Recorder: Gina Davis

FDA TENTATIVE ATTENDEES

Patricia Keegan, M.D., Director, OHOP/DOP 2
Suzanne Demko, P. A. – C., Medical Team Lead, OHOP/DOP 2
Martha Donoghue, M.D., Medical Officer, OHOP/DOP 2
Gina Davis, M.T. Senior Regulatory Health Project Manager, OHOP/DOP 2
Dubravka Kufrin, Ph.D., Nonclinical Reviewer, OHOP/DHOT
Whitney Helms, Ph.D., Nonclinical Supervisor, OHOP/DHOT
Sirisha Mushti, Ph.D., Statistical Reviewer, OB/DB V,
Kun He, Ph.D., Statistical Team Lead, OB/DB V
Jingyu (Jerry) Yu, Ph.D., Clinical Pharmacology Reviewer, OCP/ DMP
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, OCP/DCP V
Liang Zhao, Ph.D., Clinical Pharmacology Team Lead, OCP/DMP
Laurie Graham, Ph.D., CMC Team Lead, OBP/DMA
Chikako Torigoe, Ph.D., CMC Reviewer, OBP/DMA
Patricia Hughes, Ph.D., CMC Microbiology Team Lead, OMPQ/BMAB
Lakshmi Narasimhan, Ph.D., CMC Microbiology Reviewer -DS, OMPQ/BMAB
Colleen Thomas, Ph.D., CMC Microbiology Reviewer – DP, OMPQ/BMAB
Naomi Redd, Pharm.D, OSE/DRISK
Frances Fahnbulleh, Pharm.D, OSE/PMS
Patrick J. Zhou, Eastern Research Group

SPONSOR ATTENDEES

Dr. L. Mary Smith, Associate Vice President, Product Development
Mr. Dean Bunce, Executive Vice President, Compliance and Regulatory Affairs
Dr. Noah Byrd, Associate Director, Regulatory Affairs
Mr. Rex Mauthe, Associate Vice President, Regulatory Affairs
Dr. Rita Lee, Regulatory Scientist, Regulatory Affairs
Mr. Mark Farquharson, Senior Director, Biologic Process Development and Manufacturing
Dr. David Meh, Director of Process Development
Mr. Sam Mancuso, Associate Vice President, Quality
Mr. Patrick Poisson, Senior Vice President, Manufacturing, Sterile Products and Biologics
Mr. Thomas Higgs, Director, Quality Control
Dr. Allison Lim, Associate Manager, Product Development
Mrs. Jody Cleveland, Director, Biostatistics
Mr. David Pressley, Senior Manager, Clinical Data Programming
Dr. Elizabeth Garrard, Senior Director, Safety Risk Management
Dr. Stephen Godin, Nonclinical Scientist
Mrs. Hilary Hafeken, Associate Director, Regulatory Informatics
Dr. David Zaccardelli, Chief Manufacturing Officer and EVP Pharmaceutical Development, Manufacturing

Introductions

FDA and United Therapeutics Corporation

Introductory Comments

Suzanne Demko, Cross-Discipline Team Leader

Significant Review Issues

Clinical/Statistics

1. Interim EFS analyses:
   FDA statistical review of the reported efficacy results is ongoing, and there are unresolved issues regarding the statistical analyses leading up to termination of randomization in Study DIV-NB-301. We have not yet been able to verify the alpha spending calculations and interim efficacy boundaries submitted because the number of interim analyses and the number of events for the final analysis of EFS were not specified in the protocol. In the absence of such information, we may elect not to include the p-value for the reported EFS in labeling. Also, since there was no statistical procedure in the protocol for adjusting multiple secondary endpoints, the p-value for the reported OS may not be included in labeling.

2. Contributions of IL-2 and GM-CSF to treatment effect:
The BLA contains minimal clinical information to support the proposed combination of ch14.18 with IL-2 and GM-CSF. Therefore, the relative contributions of IL-2 and GM-CSF to the observed treatment effect and toxicities are uncertain. This uncertainty will be communicated in our published review of the BLA and information regarding use and dosing of IL-2 and GM-CSF in product labeling will be limited to the information that we consider necessary to ensure patient safety.

3. Safety of UTC-produced product:
Additional safety analyses comparing the incidences of adverse events observed with the UTC product as compared to the NCI product is being requested for inclusion in the 120-day safety update.

4. Inspections:
Inspections of the clinical sites, CTEP, and manufacturing site were concluded this week. Final results of these inspections are pending; however, preliminary communications with FDA auditors indicate that it is unlikely that deficiencies uncovered during these audits will result in material delay in reviewing this BLA.

Nonclinical

5. ADCC response:
Additional clarity is needed on whether ch14.18 can elicit an effective ADCC response in the presence of effector cells from mouse, rat, dog, or monkey origin.

6. Possible PMR:
An additional animal study may be required to assess sub-chronic toxicity and recovery from neuropathic pain.

Clinical Pharmacology/Pharmacometrics

7. PK comparability assessment:
Additional clarity is needed on why noncompartmental analysis (NCA) for PK comparability assessment was not conducted for the DIV-NB-201 study.

CMC/Microbiology

8. Microbial retention study
The microbial retention study was performed with (b) (4) . The microbial retention study should be performed with (b) (4)
Please repeat the microbial retention study with (b) (4). The batch volume, contact time, and pressure for the microbial retention study should be worst-case compared to production.

9. Sterilization validation data
Sterilization validation data for the [redacted] is not included in [redacted] DMF [redacted]. Provide [redacted] data for the [redacted]. If this information is located in [redacted] DMF, provide a Letter of Authorization which clearly indicates the location of the information within the DMF. In addition, provide data from the last three quarterly dose audits performed at the [redacted] contract sterilization site.

10. Rabbit pyrogen test data
Rabbit pyrogen test data as required in 21CFR610.13(b) was not provided for the drug product. The rabbit pyrogen test should be performed at least once with three different lots of product to confirm that the product does not contain pyrogenic substances other than bacteria endotoxin. Provide rabbit pyrogen test data for three different lots of the drug product.

11. Low endotoxin recovery study
Additional information is needed regarding the low endotoxin recovery study. An information request will be sent. When sufficient information has been provided, a path forward for endotoxin control and testing will be discussed.

12. Hold time validation study
When the hold time validation study for [redacted] is completed, submit the data to the BLA.

13. Additional IRs for DS and DP
Review of the product quality microbiology information for the drug substance and drug product is ongoing, and additional information requests will be sent.

Product Labeling

14. Initial labeling revisions
Thank you for your recently submitted revisions to the proposed package insert for dinutuximab. The Division may solicit additional revisions from UTC prior to initiation of formal labeling negotiations and is also likely to propose additional extensive changes to product labeling during formal labeling negotiations. Negotiations for the PI will occur no later than November 10, 2014.

Information Requests

The following information requests are outstanding as of today. Please submit the requested information as per the timeline stated in the individual information request.

Clinical/Statistics

15. With the 120-day safety update, provide an analysis of the incidence of adverse events (AEs) observed with the UTC-produced ch14.18 product in comparison with those observed with the NCI product for study DIV-NB-201. In this analysis, include comparison of the per-patient incidences of AEs by CTCAE grade (Grade 3 and above and less than Grade 3), serious adverse events, and target toxicities. Additionally, provide a preliminary analysis of the incidences of these AEs observed from the time of the switch to the UTC product for DIV-NB-302, in comparison with the AE profile observed with the NCI product prior to the switch. This information was requested on July 17, 2014.

16. For Study 301, please confirm that the following patients were randomized and received study treatment. The subject level (ADSL) dataset contains treatment start and end dates that are identical for each of these patients [who are included in the safety population (SAFFL = 'Y')]:

    - 726098 (RA)
    - 743151 (immunotherapy)
    - 762851 (RA)
    - 778342 (RA). Please note that the preliminary results of our site audit indicate that this withdrew prior to starting treatment.

    Additionally, please confirm that patient 714449 (immunotherapy) received study treatment. The preliminary results of our site audit indicate that this patient did not receive study therapy. This information was requested on July 17, 2014.

CMC/Microbiology

17. An information request regarding drug product manufacturing was sent on June 25, 2014. A response is requested by July 17, 2014.

18. An information request regarding post-dilution storage time for the drug product was sent on July 2, 2014. A response is requested by August 11, 2014.

Major Safety Concerns/Risk Management Update

19. Review of the application is ongoing; however, at this time the review team believes that a REMS may not be necessary to mitigate the risks associated with dinutuximab treatment.

Advisory Committee Meeting Plans

20. Currently there are no plans for an advisory committee meeting; however, the Division will seek advice from external Special Government Employees with expertise in neuroblastoma during the review of this BLA.

Proposed Date for Late-Cycle Meeting

21. The proposed date for the late cycle meeting is October 6, 2014, from 12:00 PM – 1:00 PM.

PMC/PMRs

22. Negotiations for PMCs/PMRs will occur no later than November 10, 2014.

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/s/

GINA M DAVIS
07/18/2014

Monthly Team Meeting
July 18, 2014

BLA 125516/IND 110494

Product:	Unituxin (dinutuximab)
Submission Date:	April 11, 2014
Received Date:	April 11, 2014
Sponsor:	United Therapeutics Corporation

Proposed Indication: For the treatment of Pediatric Neuroblastoma

Current Review Team for BLA 125516:
Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS)
Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Officer
Suzanne Demko, C-P.A. Medical Team Lead (TL and CDTL)
Sirisha Mushti, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Xianhu Cao, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Dubravka Kurfin, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Chikako Torigoe, Ph.D., CMC
Laurie Graham, Ph.D., CMC
Lyndsey Hennessey, DMA RPM
Melinda McLawhorn- OPDP professional reviewer
Mathilda Fienkeng- OPDP consumer reviewer
Olga Salis – OPDP RPM

This monthly team meeting was converted to a post mid-cycle meeting, via teleconference, with United Therapeutics Corporation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 17, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

---

Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. With the 120-day safety update, provide an analysis of the incidence of adverse events (AEs) observed with the UTC-produced ch14.18 product in comparison with those observed with the NCI product for study DIV-NB-201. In this analysis, include comparison of the per-patient incidences of AEs by CTCAE grade (Grade 3 and above and less than Grade 3), serious adverse events, and target toxicities. Additionally, provide a preliminary analysis of the incidences of these AEs observed from the time of the switch to the UTC product for DIV-NB-302, in comparison with the AE profile observed with the NCI product prior to the switch.

2. For Study 301, please confirm that the following patients were randomized and received study treatment. The subject level (ADSL) dataset contains treatment start and end dates that are identical for each of these patients [who are included in the safety population (SAFFL = 'Y')]:

   - 726098 (RA)
   - 743151 (immunotherapy)
   - 762851 (RA)
   - 778342 (RA). Please note that the preliminary results of our site audit indicate that this withdrew prior to starting treatment.

   Additionally, please confirm that patient 714449 (immunotherapy) received study treatment. The preliminary results of our site audit indicate that this patient did not receive study therapy.

Please provide a response to the aforementioned requests as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/17/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125516/0

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

United Therapeutics Corporation
55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

ATTENTION: Noah Byrd, PhD, RAC
Associate Director, Regulatory Affairs

Dear Dr. Byrd:

Please refer to your Biologics License Application (BLA) dated April 11, 2014, received April 11, 2014, submitted under section 351(a) of the Public Health Service Act, for Dinutuximab, 3.5 mg/mL.

We also refer to your April 15, 2014, correspondence, received April 15, 2014, requesting review of your proposed proprietary name, Unituxin.

We have completed our review of the proposed proprietary name, Unituxin and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your April 15, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Gina Davis, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
07/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 10, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical Pharmacology

---

Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

1. Submit an analysis report for PK comparability assessment using non-compartmental analysis (NCA) based on study DIV-NB-201 data, following the NCA approach specified in page 92 of your protocol titled "DIV-NB-201 (NCI protocol number 9347) Protocol Amendment 4; 27 Dec 12".

Please provide responses to the aforementioned request by close of business July 17, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 2, 20145

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Statistics

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

1. The number of patients for June 2012 data cut off is mentioned as 228 (114 per arm) in the CSR. However, subsetting the ADSL data from 302 study for ITTFL and RANDFL results in only 227 subjects. Please clarify the difference.

2. Please submit the censoring rules used for the efficacy analysis.

3. Please submit the SAS programs used to perform the primary efficacy analysis.

4. Please provide the number of EFS events for the final analysis when calculating the sample size using 0.05 (one-sided alpha) in the original protocol. Please clarify whether 23 events is 20% as stated *"after 20% (23) of the planned events have occurred"* in page 49 of the original protocol. Please also provide the total number of events used after increasing the sample size, and also provide the details of procedure, including software, version and all parameters used (HR, power, etc), in calculating the boundary for the interim analyses (Table 11.6 in DSMC page 137 of 142).

Please provide response to the aforementioned requests by noon, July 7, 2014 or sooner. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 2, 20145

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently, your submission is under review and we have the following comments and requests for information.

1. Please refer to the CMC comment in the 74-day letter regarding microbiological studies to support the 24 hour post-dilution storage time. As discussed in *Guidance for Industry: ICH Q8 Pharmaceutical Development*, the conditions for microbiological challenge studies should simulate conditions during patient use. To better understand the microbiological risks associated with the long infusion time, please include the infusion time at room temperature in the growth promotion study. The study should include storage at 2-8°C for twice the maximum storage time indicated by the label followed by storage at room temperature for a period exceeding the maximum infusion time (twice the maximum infusion time or appropriate safety margin).

2. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The study should use the label-recommended diluent and bags. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

Please provide a response to the aforementioned requests by close of business August 11, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 2, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516/0; United Therapeutics Corporation; Request for Teleconference Post Mid-cycle Meeting

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

The Division of Oncology Products 2 respectfully requests a teleconference with United Therapeutics Corporation to discuss the highlights of the July 9, 2014, mid-cycle meeting. We have reserved the date of July 18, 2014, from 12:00 PM – 1:00 PM to speak with you and your team. The following information will be discussed with you and your team.

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for the late-cycle meeting
- Updates regarding plans for the AC meeting (if an AC meeting is anticipated)
- Other projected milestones dates for the remainder of the review cycle

Please provide call-in information regarding this teleconference no later than 1 week prior to the scheduled teleconference. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 2, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Labeling - dinutuximab

---

Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

We also refer to our June 24, 2014, letter listing the deficiencies identified in the package insert (PI) for dinutuximab. For ease of review we have enclosed the dinutuximab PI, containing the deficiencies noted in the June 24, 2014 letter as well as additional deficiencies not listed in the letter.

Please address the deficiencies outlined in the PI by July 8, 2014 and submit revised content of labeling in structured product labeling (SPL) format as described at: http://www.fda.gov/oc/datacouncil/spl.html.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
FDA proposed labeling

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GINA M DAVIS
07/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 8, 2014

From: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products

Subject: Designation of Review for Original BLA Submission

Sponsor: United Therapeutics Corporation

Product: Unituxin (dintuximab)

Indication: For the treatment of Pediatric Neuroblastoma

To: BLA 122516/0

The review status of this file is designated to be:

Standard (12 month review – PDUFA V) _____

Priority (8 month review - PDUFA V) ____X_____

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/s/

GINA M DAVIS
06/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 25, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information

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Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. Clarify whether [redacted (b) (4)].

2. The sample volume for [redacted (b) (4)]. Provide justification for the smaller sample volume.

3. Provide a response to the following comments regarding integrity testing of the [redacted (b) (4)].

   a. Indicate the [redacted (b) (4)] used for pre-use and post-use integrity tests.

   b. Indicate the acceptance criterion for pre-use integrity testing.

   c. Provide the pre-use and post-use integrity test results for the process validation lots.

   d. If integrity testing is performed with [redacted (b) (4)]. If integrity testing is performed with [redacted (b) (4)]

4. Provide a response to the following comments regarding [redacted (b) (4)] and microbial retention.

   a. Clarify whether the production [redacted (b) (4)] is a [redacted (b) (4)] as described in the [redacted (b) (4)] validation report.

b. Indicate the [redacted] step during production.

c. The microbial retention study was performed with [redacted] The microbial retention study should be performed with [redacted] by the same method used for the production [redacted]. Please repeat the microbial retention study with [redacted] The batch volume, contact time, and pressure for the microbial retention study should be worst-case compared to production. Indicate when the study data will be submitted to the BLA.

5. Provide a response to the following comments regarding the [redacted] If the information is located in the supplier's DMF, provide a Letter of Authorization which clearly indicates the location of the information within the DMF.

a. Provide a copy of the Certificate of Analysis.

b. Provide a diagram which illustrates the [redacted]

c. Describe the [redacted] test performed by the supplier, indicate the test method sensitivity in terms of detectable [redacted] and summarize the method validation data.

6. Provide a response to the following comments regarding [redacted].

a. [redacted] validation data for the [redacted] is not included in [redacted] DMF [redacted]. Provide [redacted] data for the [redacted]. If this information is located in [redacted] DMF, provide a Letter of Authorization which clearly indicates the location of the information within the DMF.

b. Provide data from the last three quarterly dose audits performed at the [redacted] contract sterilization site.

7. Rabbit pyrogen test data as required in 21 CFR 610.13(b) was not provided for the drug product. The rabbit pyrogen test should be performed at least once with three different lots of product to confirm that the product does not contain pyrogenic substances other than bacteria endotoxin. Provide rabbit pyrogen test data for three different lots of the drug product. If the study is scheduled but not yet completed, indicate when the study data will be submitted to the BLA.

Please provide a response to the aforementioned requests by July 17, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
06/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125516/0

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 TW Alexander Drive, P. O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your Biologics License Application (BLA), dated April 11, 2014 received April 11, 2014 submitted under section 351(a) of the Public Health Service Act for dinutuximab.

We also refer to our filing notification letter dated June 10, 2014.

During our filing review of your application, we identified the following potential review issues:

Statistics

1. You have not provided the SAS programs that were used to perform the efficacy analysis. Please submit these to the BLA within one week of receipt of this letter.

2. You have not provided the censoring rules used in defining the time-to-event endpoints. Please submit these to the BLA within one week of receipt of this letter.

Chemistry Manufacturing and Controls (CMC)

3. There is inadequate information to support the proposed post-dilution storage time described in the product labeling. Submit microbiological studies in support of the 24 hour post-dilution storage time within one month of receipt of this letter. In lieu of this data, the product labeling can indicate a post-dilution storage period of not more than 4 hours at 2-8°C.

   In your response, describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The study should be conducted at the worst-case storage temperature, use the label-recommended diluent, and be conducted for 48 hours (twice the recommended storage period). Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of potential issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

General comments:

4. Throughout the label, use command language and active voice whenever possible, instead of phrases such as "are recommended."

5. Throughout the label, delete the term "(b) (4)" because it is promotional. Use different wording, such as "dinutuximab arm" or "dinutuximab group."

Highlights (HL) of Prescribing Information

6. There appears to be more white space between the end of the Warnings and Precautions section and the beginning of the Adverse Reactions section compared to the white space between other sections. Please make the amount of white space between sections consistent throughout Highlights (HL).

7. The use of periods prior to the referenced section number is not consistent in the Dosage and Administration and Warnings and Precautions sections. Please use periods thoroughout HL.

8. Please include the following required Patient Counseling Information statement in HL: "See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling."

9. In the product title, please change "(b) (4) to "UNITUXIN (dinutuximab) injection, for intravenous infusion." (b) (4). Additionally, the dosage form should not be in title case, the route of adminstration should be preceded by a comma.

10. The dosage form for Unituxin should be listed under "Dosage Forms and Strengths" as follows: "Injection: 17.5 mg/5 mL (3.5 mg/mL) single use vial."

11. Modify the HL indication statement to clearly state that that dinutuximab is used in combination with GM-CSF, 13-cis RA, and IL-2 (b) (4)

9. Include a description of the most common serious adverse reactions in the Adverse Reactions section of HL.

10. Eliminate information regarding (b) (4), restricting this information to the adverse event and clinical studies sections.

Full Prescribing Information

Indications and Usage

11. We recommend that you refrain from using the term (b) (4) because it may be misleading due to its imprecise use and variable definition. (b) (4) (b) (4).

Dosage and Administration

12. We recommend bulleting the instructions in this section, starting with clear instructions to administer as an intravenous infusion only, not as an intravenous push or bolus.

13. Provide information on the recommended starting rate based upon data from clinical trials of dinutuximab and instructions for titration of rate based on tolerability. (b) (4) Provide

justification for these recommendations as comments to FDA in the revised version of the label.

14. [redacted] refer to the Clinical Studies section for information regarding the dosage regimen for these agents in Study 1.

15. Specify the storage temperature of the diluted solution – Unituxin in 0.9% Sodium Chloride Injection, USP.

Warnings and Precautions

16. In section 5.1 provide clear instructions for monitoring for signs and symptoms of [redacted] reactions with a time frame for observation (i.e., during infusion and for a period of time following completion of the infusion based upon data from clinical studies) Also state that dose interruption/modification is required for signs and symptoms of an [redacted] reaction.

17. In section 5.5, provide information on average opioid dose requirements.

18. In section 5.6, provide information regarding duration and reversibility of peripheral neuropathy.

19. In section 5.7, provide information regarding duration [redacted] of ocular signs/symptoms and recommendations regarding surveillance for neurologic disorders of the eye.

Adverse Reactions

20. Include descriptions of the most common serious adverse reactions (SAEs) such as infection and hypotension. Use the high level term (HLT) for pain when expressing the per-patient incidence (PPI) of pain SAEs.

21. In section 6.1, Table 4 should be comprehensive and include those adverse reactions described in the Warnings and Precautions section that meet the specified criteria for inclusion in the table. Additionally, include the per-patient incidence of pain using the HLT for pain with a footnote listing the preferred terms (PT's) included in this HLT.

22. After Table 4, provide a brief description of the DIV-NB-302 and DIV-NB-303 studies and the adverse reactions observed in these studies. If the adverse reaction profile was similar in these studies to those observed in DIV-NB-301, state this. If not, provide a description of adverse reactions seen in these studies that were not observed in the DIV-NB-301 study. Also provide a table summarizing the laboratory abnormalities observed in DIV-NB-303 (i.e., derived from laboratory dataset not the adverse event dataset).

23. Use a separate section, i.e. 6.2, to describe immunogenicity testing results including assays used with any limitations and the number of patients tested as well as clinical impact. (Note: you will also need to add section 6.2 to the FULL PRESCRIBING INFORMATION: CONTENTS section of the package insert,)

Clinical Studies

24. Please include the efficacy results in table format, using the example below.

Table #: Efficacy Results for Study-xxx

		[redacted] (b) (4) + RA n=113	RA alone n=113
EFS	No. of Events (%)	xxx (%)	Xxx (%)
	Median (<units>) (95% CI)	xx (xx, xx)	xx (xx, xx)
	Hazard ratio (95% CI)[a]	xx (xx, xx)	
	P-value	xxx †	
OS	No. of Events (%)	xxx (%)	xxx (%)
	Median (<units>) (95% CI)	xx (xx, xx)	xx (xx, xx)
	Hazard ratio (95% CI)[a]	xx (xx, xx)	
	P-value	xxx †	

(b) (4)

25. Provide results of updated overall survival (OS) analysis including HR, 95% CI, and nominal p-value.

We request that you resubmit labeling (in Microsoft Word format, clean and redline versions) that addresses these issues by July 8, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed,

professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
06/24/2014

Filing Meeting Summary
May 9, 2014

BLA 125516/IND 110494

Product:	Unituxin (dinutuximab)
Submission Date:	April 11, 2014
Received Date:	April 11, 2014
Sponsor:	United Therapeutics Corporation

Proposed Indication: For the treatment of Pediatric Neuroblastoma

Current Review Team for BLA 125516:

Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS)
Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Officer
Suzanne Demko, P.A.- C Medical Team Lead (TL and CDTL)
Sirisha Mushti, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Xianhua Cao, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Dubravka Kurfin, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Jingyu (Jerry) Yu, Ph.D., Pharmacokinetics, Primary Reviewer
Liang Zhao, Ph.D., Pharmacokinetics (TL)
Chikako Torigoe, Ph.D., CMC
Laurie Graham, Ph.D., CMC (TL)
Lakshmi Narasimhan, Ph.D., Facility/ Drug Substance Reviewer
Colleen Thomas, Ph.D., Facility/ Drug Product Reviewer
Patricia Hughes, Ph.D., Micro/Facility (TL)
Frances Fahnbeullah, PharmD. – OSE RPM
Jeffery Summers, M.D., OHOP Safety Deputy Director
Lyndsey Hennessey, DMA RPM
Naomi Redd, PharmD
Carole Broadnax - OPDP professional reviewer
Mathilda Fienkeng- OPDP consumer reviewer
Olga Salis – OPDP RPM

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

Agenda Items:

1. Discuss Filing Issues by Discipline:

   a. Clinical - There are clinical issues with the quality of the data. The application has been enrolled in the jump start program. There is no definitive difference with respect between the two products with respect to the safety data.

      - Clinical site inspections selected/tentative dates of inspections (OSI)

   b. Nonclinical

   c. Clinical Pharmacology

   d. CMC

      - Facility inspections

   e. Stats

   f. Pharmacometrics

   g. Regulatory

      - Please bring a copy of your Filing review (draft) and any interim deliverables needed. Please note your filing review will need to be uploaded and signed off on in DARRTs prior to day 60 (June 10, 2014).

2. **Review Status:**
   - Priority Review requested - Priority review granted (8 month PDUFA V clock)
   - Orphan Drug Designation - granted December 20, 2010
   - Requested full waiver of pediatric studies
   - Categorical Exclusion Requested
   - UTC requested to be awarded a rare pediatric disease priority review voucher – April 18, 2013
   - UTC claims seven year marketing exclusivity
   - Proprietary name request submitted on April 15, 2014
   - The clinical development of Unituxin was conducted under IND 110494

3. **Dates Milestone Letters Must Issue**: **PDUFA V dates**

Milestone	6 month review
Acknowledgment Letter	April 25, 2014
Filing Action Letter •Do we have any filing issues that we should discuss today? •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	June 10, 2014
Deficiencies Identified Letter (74 Day Letter)	June 24, 2014
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	November 10, 2014 (subject to change)
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 19, 2014
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off*** ***Compliance Check List (BLA)***	 September 13, 2014 September 17, 2014 November 19, 2014 November 30, 2014 December 10, 2014 November 12, 2014
Compile and circulate Action Letter and Action Package	November 19, 2014
FINAL Action Letter Due	December 10, 2014

4. **Potential Consults/Collaborative Reviewers Needed:**

OPDP	Carole Broadnax – professional reviewer Mathilda Fienkeng- consumer reviewer Olga Salis – RPM
OSE	Frances Fahnbulleh-OSE RPM Sean Bradley – OSE *DMEPA/DDMAC to review carton/container Naomi Redd, PharmD Risk Management Plan – submitted with the application
Maternal Health	Erica Wynn – Reviewer Denise Pica-Branco - RPM
Facility	Lakshmi Narasimhan Drug Substance Reviewer Colleen Thomas / Drug Product Reviewer
QT-IRT	Consult submitted to address the data sent to the ECG warehouse.
OSI	Lauren Iacono-Connor assigned sites to be selected.
Pediatric Page/PeRC	**Full Waiver Requested/Orphan Drug Designation
Patient Labeling Team	N/A
SEALD - Labeling	Questions to be submitted via email communication – no consult required.

5. **Upcoming/ Internal Team Meetings**:

- **Filing Meeting:** Scheduled for May 9, 2014.
  Please bring Filing review (TL signature) and Interim Deliverables

  a. Please be prepared to identify significant filing issues for day 74 letter. The template is available on the 21st Century website. http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm

- **Mid-Cycle Meeting Date:** July 9, 2014

- **Late-Cycle Meeting Date:** TBA – Once the decision is made regarding ODAC.

- **Labeling Meetings:** TBA **(suggested sections for review)**

  a. TBA (Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions)

  b. TBA (Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References)

  c. TBA (Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Clinical Pharmacology, Nonclinical Toxicology)

  **Include OSE/CMC during this labeling meeting to review carton and container.

  d. TBA (Highlights, Indications and Usage, Patient Counseling Information)

  Labeling included:
  - Draft Carton Labels
  - Draft Vial Labels
  - Draft Labeling (PI)

  Monthly Team Meetings:
  - June 10, 2014
  - June 13, 2014 (DRISK meeting with clinical and nonclinical)
  - July 11, 2014
  - August 5, 2014
  - September 10, 2014
  - October 3, 2014
  - November 4, 2014

  PMC/PMR Meetings

  - **TBD**

6. **Application Orientation Presentation:** United Therapeutics respectfully declined our offer of an Application Orientation Meeting for their product Unituxin (dintuximab) on April 28, 2014.

UPDATE – The Division of Oncology Products 2 has contacted United Therapeutics Corporation and requested an Application Orientation Meeting scheduled for June 5, 2014.

7. **ODAC –** To be determined no later than May 20, 2014.

UPDATE - The Division of Oncology Products 2 decided that the an ODAC meeting was not necessary for this application.

The team has determined that the marketing application submitted by United Therapeutics Corporation will be filed.

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/s/

GINA M DAVIS
06/10/2014

Planning Meeting Summary
April 25, 2014

BLA 125516/IND 110494

Product:	Unituxin (dinutuximab)
Submission Date:	April 11, 2014
Received Date:	April 11, 2014
Sponsor:	United Therapeutics Corporation

Proposed Indication: For the treatment of Pediatric Neuroblastoma

Current Review Team for BLA 125516:
Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS)
Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Officer
Suzanne Demko, C-P.A. Medical Team Lead (TL and CDTL)
Sirisha Mushti, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Xianhu Cao, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Dubravka Kurfin, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Chikako Torigoe, Ph.D., CMC
Laurie Graham, Ph.D., CMC
Lyndsey Hennessey, DMA RPM
Melinda McLawhorn- OPDP professional reviewer
Mathilda Fienkeng- OPDP consumer reviewer
Olga Salis – OPDP RPM

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss

Agenda Items:

1. **Review Status:**
   - Priority Review requested - will this be a standard review or priority review
   - Orphan Drug Designation - granted December 20, 2010
   - Exempt from Pediatric Research Requirements
   - Categorical Exclusion Requested
   - UTC requested to be awarded a rare pediatric disease priority review voucher – April 18, 2013
   - UTC claims seven year marketing exclusivity

2. **Dates Milestone Letters Must Issue**: **PDUFA V dates**

Milestone	6 month review	
Acknowledgment Letter	April 25, 2014	
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	June 10, 2014	
Deficiencies Identified Letter (74 Day Letter)	June 24, 2014	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	November 10, 2014 (subject to change)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 19, 2014	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off*** ***Compliance Check List (BLA)***	 September 13, 2014 September 17, 2014 November 19, 2014 November 30, 2014 December 10, 2014 November 12, 2014	
Compile and circulate Action Letter and Action Package	November 19, 2014	
FINAL Action Letter Due	December 10, 2014	

3. Potential Consults/Collaborative Reviewers Needed:

OPDP	Melinda McLawhorn- professional reviewer Mathilda Fienkeng- consumer reviewer Olga Salis – RPM
OSE	Frances Fahnbulleh-OSE RPM *DMEPA/CMC/DDMAC to review carton/container, and patient labeling *Risk Management Plan – submitted with the application Proprietary Name Review- request for proprietary name review submitted on April 15, 2014 - Unituxin (dintuxumab)
Maternal Health	? TBD
Facility	? TBD
QT-IRT	Consult will be submitted to address the data sent to the ECG warehouse.
OSI	Lauren Iacono-Connor assigned sites to be selected.
Pediatric Page/PeRC	**Full Waiver Requested/Orphan Drug Designation
Patient Labeling Team	*Patient Information Included
SEALD	TBD
SGE's or Patient Representatives	TBD

Are there any additional consults we need?

All consults will be requested by April 30, 2014.

4. Upcoming/TBD Internal Team Meetings:

- **Filing Meeting:** Scheduled for May 9, 2014.
  Please bring Filing review (TL signature) and Interim Deliverables

  a. Please be prepared to identify significant filing issues for day 74 letter. The template is available on the 21st Century website. http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm

- **Mid-Cycle Meeting Date:** TBD - no later than July 11, 2014 - Priority

- **Late-Cycle Meeting Date:** TBD (by filing meeting)
- **Labeling Meetings:** To be announced (by filing meeting)
- **Internal Meetings:** TBA (by filing meeting)
    - **Monthly Team Meetings?** TBD (by filing meeting)
    - **PMC/PMR Meetings?** (at least one PMR per the pre-BLA Meeting)
    - **No REMS** (per the pre-BLA Meeting)

5. **Application Orientation Presentation:** Awaiting response from sponsor – close of business April 25, 2014.

6. **ODAC - To be determined.**

7. **Miscellaneous Items or Issues:**

- OSI inspections are needed, when does clinical/stats team need to pick the sites that will be inspected? The OSI reviewer will work with the medical officer and identify sites to be inspected by the filing meeting.
- Environmental Analysis: Request for Categorical Exclusion (Assistance from Lyndsey Hennessey – CMC RPM)
- Was ECG data submitted to the warehouse? ECG data was submitted to the warehouse, the Division of Cardiac and Renal Products will be provided with the information.
- No toxicology reproductive data.
- Clinical I/R will go out next week.

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/s/

GINA M DAVIS
06/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125516/0

FILING NOTIFICATION

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 TW Alexander Drive, P. O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your Biologics License Application (BLA), dated April 11, 2014, received April 11, 2014, submitted under section 351(a) of the Public Health Service Act for dinutuximab.

We also refer to your amendments dated April 15, May 5, May 8, May 12, May 15, May 19, June 3 and June 7, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is December 10, 2014.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 10, 2014. In addition, the planned date for our internal mid-cycle review meeting is July 9, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

While conducting our filing review, we have identified potential review issues which we will communicate to you on or before June 24, 2014.

If you have any questions, please contact Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
06/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 31, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information

---

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comment and request for information.

> In the protocol it mentions that in addition to obtaining IRB approval a web based training is required, and can be found in power-point on the study page of the children's oncology group website. We are unable to locate the web based training. Please direct us to its location in your submission.

Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/31/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 22, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516 – United Therapeutics Corporation – Unitixin (dintuximab) Application Orientation Science

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Dear Dr. Byrd,

You were contacted by The Division of Oncology Products 2 on May 14, 2014, requesting that United Therapeutics Corporation schedule an Application Orientation Meeting for the Biologics License Application (BLA) Unituxin for the treatment of neuroblastoma.

Per our May 16, 2014, teleconference, United Therapeutics has agreed to an Application Orientation Meeting for June 5, 2014 from 3:00 PM – 4:00 PM (EST).

Please send me the names of all staff members that will be present at this presentation. I am including a foreign visitor form to be filled out by all non-US citizens. Please send this information to me by Friday, May 30, 2014.

I have also included a form that will assist your team with your presentation. We ask that your team consist of no more than 10 members. If you have any questions or concerns please contact me.

All the best,
Gína

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Foreign Visitor Form
OHOP General Advice and Application Orientation Presentation Meetings

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

OHOP's General Advice for Application Orientation Presentation Meetings

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OHOP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

Administrative:

1. Sponsor attendees

2. Presentation outline or Agenda. Should list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.

4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.

5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.

6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.

7. Regulatory history, including the following:
    - Orphan Drug designation, Fast Track designation
    - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
    - Key Outcomes from FDA Interactions
        - EOP2 Meeting

- Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
- Pre-NDA/BLA meeting
- Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

Summary Content of NDA/BLA/Efficacy Supplement Sections:

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

   You should also present results of the following, as appropriate:
   - Clinical study sites (foreign or domestic)
   - Biomarker development for population selection (if applicable)
   - Assay validation (if applicable)

   120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data

10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
    - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.

11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities

12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, $t_{1/2}$, ADME, PK in special populations, drug-drug interactions).

13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU).

14. Risk/benefit profile for drug/biologic

15. Summary

16. Q & A

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/s/

GINA M DAVIS
05/22/2014

From: Noah Byrd
Sent: 4/28/2014 8:46:50 AM
To: Davis, Gina
Subject: RE: BLA 125516 - Application Orientation - Unituxin

Good Morning Gina,

Thank you for the memo regarding the optional Application Orientation Meeting. United Therapeutics respectfully declines this opportunity. We do; however, plan to take the Division up on any post-approval meetings to discuss the review process and experience upon completion.

Best Regards,
Noah

Noah Byrd, PhD, RAC
Associate Director, Regulatory Affairs
United Therapeutics Corporation
55 TW Alexander Drive
PO Box 14186
RTP, NC 27709
Direct: 919.425.8143
nbyrd@unither.com

From: Davis, Gina [mailto:Gina.Davis@fda.hhs.gov]
Sent: Friday, April 25, 2014 9:02 AM
To: Noah Byrd
Subject: BLA 125516 - Application Orientation - Unituxin
Importance: High

Good morning Dr. Byrd,

Enclosed is a memo regarding your recent submission to the Division of Oncology Products 2. Please review the memo and respond accordingly.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Gina.Davis@fda.hhs.gov
301-796-0704 (office)
301-796-9849 (fax)

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/s/

GINA M DAVIS
05/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 22, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – CMC

Dear Dr. Byrd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

1. Please provide a diagram showing the proposed microbiological sampling locations, the locations of the [(b) (4)], and the [(b) (4)] in the manufacturing process.

2. Please clarify if culture purity is monitored at the [(b) (4)]

3. Please clarify how long the [(b) (4)] is held before [(b) (4)] Please provide the bioburden data from the [(b) (4)] at the end of the hold time.

4. Please clarify if [(b) (4)]

5. Please implement [(b) (4)] bioburden and endotoxin sampling and establish bioburden and endotoxin limits for [(b) (4)]

6. Please clarify how long the [(b) (4)] before being used for manufacturing drug product.

3.2.S.2.3. Control of Materials

7. Table 1-5 in section 3.2.S.2.3 Control of Materials states that the [redacted] (b) (4) . Please provide microbiological data supporting this hold time.

3.2.S.2.4 Controls of Critical Steps and Intermediates

8. You state in section 3.2.S.2.4 that the [redacted] (b) (4)

3.2.S.2.5 Process Validation and/or Evaluation

9. [redacted] (b) (4) result tables (Table1-2, Table1-7, Table1-9 Table1-11 Table1-13 Table1-15 and Table1-17) do not include the bioburden and endotoxin data of the process validation batches for any of the manufacturing steps. Please update the tables with microbial control data and the established limits.

10. Please clarify if the effectiveness of the [redacted] (b) (4) was assessed from a microbial control perspective.

3.2.S.4.1 Control of Drug Substance: Specification

11. The bioburden release specification [redacted] (b) (4) is high and [redacted] (b) (4) . Please tighten the bioburden release specification to [redacted] (b) (4) .

Please provide responses to the aforementioned requests by close of business June 2, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/22/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 14, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Application Orientation Presentation

---

Dear Dr. Bryd,

The Division of Oncology Products 2 respectfully requests that United Therapeutics Corporation present their product ch 14.18 (proposed name Unituxin), for the treatment of high risk pediatric neuroblastoma to the Office of Hematology and Oncology Products via an Application Orientation Meeting.

Please contact me as soon as possible so that we can schedule a meeting with your team. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
05/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 13, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical

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Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. The Study Data Reviewer's Guide for the integrated summary of safety (ISS) indicates that the safety data submitted from Study DIV-NB-201 has a data cutoff or February 5, 2013, but the minutes for our February 19, 2014 pre-BLA meeting indicate that preliminary safety data from DIV-NB-201 using a data cutoff date of December 31, 2013 would be used for the ISS and the statistical analysis plan (DIV-NB ISS) submitted with the BLA indicates that the data cut would be as of February 5, 2014 for the BLA submission. Please clarify. Additionally, according to the clinical overview submitted to the BLA, the last subject completed study DIV-NB-201 in February 2014. When will an updated analysis of safety from this study be available?

2. Provide a mechanism from existing datasets or a new safety dataset for Study DIV-NB-201 that permits analysis of adverse events broken down by ch14.18 product received proximal to the adverse event (i.e., UTC vs. NCI product).

3. Please provide case report forms for all deaths and premature discontinuations from study therapy for patients enrolled in Study DIV-NB-201. Provide narratives for all serious adverse events or premature discontinuations from study therapy that occurred in this study.

4. Please confirm that analysis of the primary endpoint of EFS from Study DIV-NB-301 was based upon local investigator assessment. The schedule of events indicates that copies of tumor imaging assessments were required to be submitted to the Quality Assurance

Review Center (QARC) for central review at enrollment and at study end. Is information available regarding concordance of the investigator assessments of tumor imaging with central review of tumor imaging performed by QARC? We are aware of the technical reports dated April 11, 2013 and February 26, 2013, but these reports do not address this question.

5. Please provide case report forms for all subjects in the immunotherapy group in Study DIV-NB-301 and DIV-NB-302 who prematurely discontinued study therapy for reasons coded as unknown, withdrawal by subject, or corticosteroid use.

6. According to the study report and annotated case report form for DIV-NB-301, adverse events were graded using CTCAE criteria. However, in many of the case report forms submitted to the BLA, toxicities are instead characterized using the terms "mild," "moderate," or "severe." Please explain the discrepancy. If toxicity grades are included in the case report forms supplied but have been overlooked by the reviewer, please describe where this information is located in the CRF. If case report forms did not include grading using CTCAE criteria, how were toxicity grades derived for the adverse event datasets?

7. The folder entitled "Protocol Deviations" in Section 5.3.5.1 and Section 5.3.5.2 contains the "Listing of Eligibility Criteria" (16.2.2.1 and 16.2.2.2; 16.2.2) for DIV-NB-301 and DIV-NB-302, respectively. Please explain and correct.

8. As outlined in the appendix to the minutes for the February 19, 2014 pre-BLA meeting , Please include the following information in a tabular format in the BLA for Studies DIV-NB-301, DIV-NB-302, DIV-NB-303, and DIV-NB-201:

    a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

    b. Name, address and contact information of all Contract Research Organizations (CROs) used during the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously submitted to FDA.

    c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

9. For Study DIV-NB-301 and DIV-NB-302, please explain how the TRTEDT variables were derived and the location of this information in the case report forms.

10. In the CE datasets for Study DIV-NB-301 and DIV-NB-302, please explain the differences between the terms ZZ_DEATH and DEATH, and if these terms were taken from different locations in the CRFs, please explain.

11. Please explain the meanings of the variables AECAT and AESCAT, and how the data for these variables were obtained.

12. Why is age missing for 295 of 1,092 patients in the DIV-NB-302 ADSL dataset? If this information is available, please submit a new ADSL dataset that includes the missing patient ages.

13. For Study 302, please explain the discrepancy between the assignment of treatment actual arm in the DM and EX and ADSL datasets for the following patients: 767629, 778176, and 785522. These patients had an actual arm designated as Regimen A in the DM datasets but received immunotherapy according to the EX and ADSL datasets.

14. For Study 302, the following subjects are missing in the DM dataset but appear in other datasets. Please explain.
    - 832285 (in the CO and MH datasets)
    - 830940, 832320, 838742, 839044 (in EG and SUPPEG datasets)
    - 800112 (in PC and SUPPPC)

15. For the laboratory datasets for Study 301 and Study 302, are the rows containing the result "1" in the AVISITN column all baseline results? If not, please explain how to determine if a result is a baseline value.

16. For Study DIV-NB-303 (COG Protocol ANBL0931), please provide the location in the submission where the number of patients enrolled by site can be found. Also provide the location of information explaining how the numeric site ID (as in the DM dataset) equates to the alphanumeric site number in Appendix 16.1.4 for this study.

17. Please verify that the list of investigators for Study DIV-NB-201 and Study DIV-NB-301 included as appendices to the Form FDA 3454 for each study comprise all the clinical investigators and sub-investigators who were directly involved in the treatment or evaluation of research subjects in these studies.

Please provide responses to the aforementioned requests by close of business May 19, 2014. Additional comments and requests for information may be forthcoming as your submission is still under review. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 8, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – Clinical Pharmacology

---

Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and requests for information.

1. Please submit the method validation and bioanalytical reports for ch14.18 concentration measured in studies DIV-NB-301, CCG-0935, B89-0005, B90-0014, B93-0009, and B94-0002.

2. For your report "Population PK Report , DIV-NB-201" (Module 5.3.1.2), please submit the following information:

    a. NONMEM control stream files and corresponding input files in CSV format (e.g., CHP1002dat.csv and DIVdat.csv)
    b. NONMEM output files, including all output files (e.g., *.lst) and tables.
    c. Raw, intermediate, final input datasets and SAS code files for your final and secondary BE analysis.

Provide responses to the aforementioned request by Thursday, May 15, 2014. If you have any questions or concerns please contact me. Additional comments and requests for information may be forthcoming.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 8, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information – QT-IRT

Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

> Currently your submission is under review and we note that your QT sub-study is still ongoing. The current dataset has 40 subjects and targets 60. When are you planning to complete the sub-study and submit the results as an amendment to your BLA? Please advise.

Provide responses to the aforementioned request as soon as possible. If you have any questions or concerns please contact me. Additional comments and requests for information may be forthcoming.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 30, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Request for Information - CMC

Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and request for information.

1. The responsibilities of the drug substance and drug product release and stability testing sites are not clearly defined. Please update Table 1 of sections 3.2.S.2.1 and 3.2.P.3.1 to indicate which assays are performed by each testing site (e.g. "sterility testing only" or "all drug product release tests except for sterility").

2. The pre-license inspection will cover dinutuximab drug substance manufacturing and drug product manufacturing (b) (4). To facilitate inspection planning, please provide updated manufacturing schedules for the following:

    a. Dinutuximab drug substance.

    b. Dinutuximab drug product, any other drug product (or placebo) manufactured (b) (4)

Please provide responses to the aforementioned request by Monday, May 5, 2014. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
04/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 30, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Clinical Pharmacology and Cardiac Safety Form

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Dear Dr. Bryd,

Please refer to your April 11, 2014, Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for your product dinutuximab for the treatment of high risk neuroblastoma.

Currently your submission is under review and we have the following comments and request for information.

> Please complete the attached Clinical Pharmacology and Cardiac Safety Form and submit as a formal amendment to your BLA.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Clinical Pharmacology and Cardiac Safety Form

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

GINA M DAVIS
04/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125516/0

BLA ACKNOWLEDGEMENT

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 TW Alexander Drive, P. O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mathue:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: dinutuximab

Date of Application: April 11, 2014

Date of Receipt: April 11, 2014

Our Submission Tracking Number (STN): 125516/0

Proposed Use: For the treatment of high risk neuroblastoma

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Gina Davis at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
04/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 25, 2014

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: BLA 125516; United Therapeutics Corporation; Application Orientation Presentation

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Dear Dr. Bryd,

The Division of Oncology Products 2 is offering United Therapeutics Corporation an opportunity of an Application Orientation for the product ch 14.18 (proposed name Unituxin) for the treatment of high risk pediatric neuroblastoma.

Please note you are not required to conduct an Application Orientation. Should you and your team decide to conduct an Application Orientation for your product we request that you notify us of your intentions by 10:00 AM Monday, April 28, 2014.

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
04/25/2014

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125516/0

LATE-CYCLE MEETING MINUTES

United Therapeutics Corporation
Attention: Noah Byrd, Ph.D.
Associate Director, Regulatory Affairs
55 TW Alexander Drive, P.O. Box 14186
Research Triangle Park, NC 27709

Dear Dr. Byrd:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Unituxin (dinutuximab) 17.5 mg/m^2/day, Injection for Intravenous Use.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 6, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: `
Application Number: BLA 125516
Product Name: Unituxin (dinutuximab)
Applicant Name: United Therapeutics Corporation
Meeting Chair: Suzanne Demko
Meeting Recorder: Gina Davis

FDA ATTENDEES

Office of Hematology and Oncology Products
Richard Pazdur, M.D., Director

Division of Oncology Products 2
Patricia Keegan, M.D., Director, DOP 2
Jeffery Summers, M.D. Deputy Director for Safety, DOP 2
Suzanne Demko, P.A. – C., Clinical Team Lead, DOP 2
Martha Donoghue, M.D., Medical Officer, DOP 2
Amy Barone, M.D. Medical Officer, DOP 2
Denise Casey, M.D. Medical Officer, DOP 2
Karen Jones, Chief, Project Management Staff, DOP 2
Gina Davis, M.T., Senior Regulatory Health Project Manager, DOP 2
Ruth Maduro, Ph.D., Regulatory Health Project Manager, DOP 2

Division of Hematology Oncology Toxicology (DHOT)
Whitney Helms, Ph.D., Supervisor, DHOT
Dubravka Kufrin, Ph.D., Toxicology Reviewer, DHOT

Division of Clinical Pharmacology V (DCP V)
Jingyu Yu, Ph.D., Clinical Pharmacology Reviewer, DCP V
Hong Zhao, Ph.D., Team Lead, DCP V
Liang Zhao, Ph.D., Team Lead, DCP V

Division of Biometrics V (DB V)
Kun He, Ph.D., Team Lead, DB V
Sirisha Mushti, Ph.D., Statistical Reviewer, DB V

Division of Monoclonal Antibodies (DMA)
Laurie Graham, Ph.D., CMC Team Lead, DMA
Chikako Torigoe, Ph.D., CMC Reviewer, DMA

Office of Biotechnology Products (OBP)
Colleen Thomas, Ph.D., CMC Reviewer, OBP
Lakshmi Rani Narasimhan, Ph.D., CMC Reviewer, OBP
Patricia F. Hughes, Ph.D., Team Leader, OBP
Jibril Abdus-Samad, Pharm.D., Regulatory Director, OBP

Office of Scientific Investigations (OSI)
Lauren Iacono-Connor, PhD, OSI Reviewer

Office of Surveillance and Epidemology (OSE)
Naomi Redd, Pharm.D., Risk Management Analyst
Frances Fahnbeullah, Pharm.D., Senior Regulatory Project Manager
Otto Townsend, Pharm.D., CMC Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Eastern Research Group
Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES
Dr. L. Mary Smith, Senior Director, Product Development
Dr. Noah Byrd, Associate Director, Regulatory Affairs
Dr. Rita Lee, Regulatory Scientist, Regulatory Affairs
Mr. Dean Bunce, Executive Vice President, Compliance and Regulatory Affairs
Mr. Rex Mauthe, Associate Vice President, Regulatory Affairs
Dr. Allison Lim, Senior Clinical Research Scientist
Mrs. Jody Cleveland, Associate Director, Biostatistics
Mr. David Pressley, Senior Manager, Clinical Data Programming
Dr. Elizabeth Garrard, Senior Director, Safety Risk Management
Dr. Stephen Godin, Nonclinical Scientist
Dr. Wendy London, Associate Professor of Pediatrics, (b) (6) and Statistician COG

BLA 125516/0 was submitted on April 11, 2014 for Unituxin (dinutuximab)

Proposed indication: For the treatment of high risk neuroblastoma

PDUFA goal date: December 10, 2014

FDA issued a Background Package in preparation for this meeting on September 24, 2014.

2.0 DISCUSSION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team

Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

Discussion of Substantive Review Issues

Clinical/Statistics

1. Based upon our statistical review of the data submitted to the BLA, the results of the event-free survival (EFS) analysis leading up to cessation of randomization in Study ANBL0032 did not meet the pre-specified stopping boundary. To convey this information, the calculated p-value for EFS may be compared with the allocated alpha for the interim analysis of EFS in the product labeling. Also, because there is no pre-specified analysis plan for the analysis of overall survival (OS), the calculated p-value will be omitted in the product labeling.

   UTC Response: For consideration, a formal Statistical Analysis Plan for Study ANBL0032 was not generated; however, as standard practice for Children's Oncology Group studies, the Statistical Considerations section of the protocol outlines the statistical plan for the study. Specifically, with regards to the analysis for overall survival, ANBL0032 protocol amendment #9, section 11.71 [Statistical Considerations; Objective 1.1, 1.21, and 1.22], details the additional plans for the analysis of overall survival. Specifically, the protocol states: "The final analysis of EFS (in the stage 4 subset (b)) and of OS (overall (a) and in the stage 4 subset (b)) will be performed on a data snapshot taken two years after the last randomized patient was enrolled, i.e., early 2012". Ultimately, the analysis occurred in June 2012. This analysis as described in the DIV-NB-301 CSR showed that the OS as of June 2012 demonstrated a statistically significant improvement [p = 0.0193] for subjects randomized to the ch14.18 immunotherapy arm vs RA alone [81.9 % vs. 68%, respectively].

   Discussion during the meeting: United Therapeutics presented their response but acknowledged FDA's comments on the lack of a pre-specified analysis plan for formal testing of OS. No additional discussion occurred.

2. As discussed during the July 18, 2014 post mid-cycle teleconference, the BLA contains minimal clinical information regarding the relative contributions, if any, of IL-2 or GM-CSF to the observed treatment effect. This uncertainty will be communicated in our published review of the BLA. Information regarding dosing of IL-2 and GM-CSF in

product labeling will be limited to that necessary to mitigate risks to patients and provide an accurate description of the clinical trial.

UTC Response: UTC has no preliminary comments at this time and looks forward to interaction on this issue after UTC has had the opportunity to review FDA's proposed edits to the Unituxin label.

Discussion during the meeting: No discussion occurred.

3. Because recently manufactured lots of drug product and drug substance may have increased antibody dependent cellular cytotoxicity (ADCC) activity compared to earlier lots of material manufactured by UTC, there is a potential safety concern. The BLA does not currently include safety data from patients who have been treated with these lots. Please provide information regarding the number of patients who have received treatment with recently manufactured lots that have higher ADCC activity and a listing of adverse events that have been reported for these patients. Include a narrative description for all serious adverse events including a description of the adverse event, the temporal relationship between the onset of the adverse event (including treatment cycle) and treatment with dinutuximab, concomitant therapies, intervention needed, and outcome of the adverse event. If this information is not readily available, please provide an estimated timeframe for when United Therapeutics will be able to provide it.

   Depending upon the amount of clinical data available from patients treated with newer lots of dinutuximab, a potential PMR may need to be considered for the provision of updated safety data from ongoing clinical trials of dinutuximab to assess whether variations in ADCC activity in different lots of dinutuximab result in increased toxicity to patients.

   UTC Response: The clinical information on the use of recent UTC lots is not readily available. UTC, in Sequence No. 0027 to BLA 125516, provided the clinical safety data from study ANBL0032 [DIV-NB-302] for one lot (lot 1200021) of UTC manufactured material which was the only lot in use as of the most recent data cut of March 2014 (120-day safety update). As the FDA is aware, the transition from NCI- to UTC-manufactured material for the on-going NCI-sponsored studies occurred in January 2014.

   In order to provide the most data for evaluation, UTC proposes that once the ANBL0032study is closed to enrollment (likely early 2Q15), UTC will request a data transfer from the COG 6 months after the last subject has enrolled. Given the timing of the data transfer and the generation of tables and listings it is likely that data will not be available to the FDA until April 2016. At the present time, UTC-manufactured drug product Lots1200021, 1200041 and 1600001 are currently in use clinically, and it is anticipated that at least one or two additional UTC-manufactured lots will also be used in Study ANBL0032before the study is closed to enrollment.

   Discussion during the meeting: UTC stated that safety data from patients who have received recent UTC lots cannot be provided because UTC needs to obtain this

information from the Children's Oncology Group (COG). FDA stated that a more detailed request for safety information and exposure information from patients treated with recently manufacturing lots of dinutuximab, i.e., released since January 2014, will be sent to UTC, but that in the meantime UTC should make arrangements with COG to facilitate acquisition of these data.

Chemistry, Manufacturing and Controls

4. Available information suggests that recently manufactured lots of drug product (DP) and drug substance (DS) have increased antibody dependent cellular cytotoxicity (ADCC) activity compared to earlier lots of material manufactured by UTC, including the early UTC manufactured lots used in the comparability assessment and the PK clinical trial. Additional information to support the safety of lots with increased ADCC activity is needed, such as determining if there is a correlation between safety signals and ADCC activity.

   Final specifications for DS and DP still need be agreed upon. It appears that many of the acceptance criteria in specifications are based upon manufacturing and stability data without consideration for clinical experience. In addition, based uponthe proposed updated specifications received on September 12, 2014, it appears that drug substance lots CHL11006 and 1500045 as well as DP validation lot 1200041 would fail cIEF release criteria. Specifications will need to be updated. FDA strongly recommends that consideration be given to establishing end of shelf-life specifications for DP based upon available information on clinical experience. This may necessitate altering your proposed shelf-lives for both DS and DP.

   UTC Response: The drug substance and drug product specifications are currently being re-examined based on clinical experience gained using NCI-manufactured and UTC manufactured material. UTC commits to submitting the updated specifications to the BLA for review.

   Discussion during the meeting: No discussion occurred.

Product Quality Microbiology

5. Microbial retention data is needed for the (b) (4)

   UTC Response: A study is in progress at the vendor. UTC remains on schedule to provide a final report by 31 October 2014.
   Discussion during the meeting: FDA acknowledged UTC's response to Substantive Review issue #5. No discussion occurred.

6. Additional (b) (4) validation data is needed for the (b) (4).

   UTC Response: UTC addressed this request in Sequence No. 0057 to the BLA submitted on 29 September 2014.

Discussion during the meeting: FDA acknowledged UTC's response to Substantive Review issue #6 and receipt of this amendment to the BLA; No discussion occurred.

7. The LAL kinetic chromogenic method for drug product release testing was replaced with the rabbit pyrogen test. As a result, new testing sites were added to the BLA file.

   UTC Response: UTC confirms that the testing site for rabbit pyrogen testing was submitted to the BLA in Sequence No. 0053.

   Discussion during the meeting: FDA acknowledged UTC's response to Substantive Review issue #7 and receipt of this amendment to the BLA; no discussion occurred.

Information Requests

The following information requests are outstanding as of September 17, 2014:

Clinical Pharmacology

8. Please submit the results of the long-term storage stability of PK samples. The storage time in a long-term stability evaluation should equal or exceed the time between the date of first sample collection and the date of last sample analysis (Bioanalytical Method Validation guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/UCM368107.pdf).

   UTC Response: UTC has addressed this request in Sequence Nos. 0047 and 0055 to the BLA submitted on 10 and 19 September 2014, respectively.

   Discussion during the meeting: FDA acknowledged UTC's response to information request (a) and receipt of this amendment to the BLA; No discussion occurred.

Office of Biotechnology Products

9. General Comment for Container Label and Carton Labeling
   In response to our September 10, 2014 Information Request – Carton and Container, it appears you removed the bolding from the strength per total volume. In the previous submissions, the strength per total volume "17.5 mg/5 mL" was appropriately more prominent than the strength per milliliter "3.5 mg/mL". Revise the strength presentation to appear as:

   17.5 mg/5 mL
   (3.5 mg/mL)

UTC Response: This revision has been completed and will be reflected in final carton labeling.

Discussion during the meeting: FDA stated that "(3.5 mg/mL)" should not be bolded. UTC acknowledged FDA's response and will ensure that "(3.5 mg/mL)" does not appear in bold type on the carton and container.

Product Quality Microbiology

10. UTC indicated that October 2014 is the expected submission date for the repeat microbial retention study for the (b) (4). Provide an update on the expected submission date. Additional product quality microbiology information requests will be sent prior to the late cycle meeting.

    UTC Response: A study is in progress at the vendor. UTC remains on schedule to provide a final report by 31 October 2014.

    Discussion during the meeting: No discussion occurred.

11. The (b) (4) hold time qualification data are pending and UTC committed to submit the (b) (4) hold time data by September 30, 2014 and (b) (4) hold time qualification data by October 31, 2014.

    UTC Response: The (b) (4) study was submitted in Sequence No. 0056. The (b) (4) hold time supplemental study is on schedule to be submitted by the indicated date.

    Discussion during the meeting: No discussion occurred.

Upcoming Advisory Committee Meeting

FDA confirmed that an Advisory Committee meeting is not planned for this new molecular entity.

REMS or Other Risk Management Actions

No new issues which require additional risk management actions or require a REMS have been identified to date. FDA has not reached final agreement on product labeling, which is a component of United Therapeutic's risk management plan.

Discussion during the meeting: No discussion occurred.

Postmarketing Requirements/Postmarketing Commitments

Postmarketing Requirements (PMR)

Nonclinical

12. To further investigate the potential for long term neuropathy and neuropathic pain as well as to further explore the toxicity of dinutuximab as a monotherapy.

    UTC Response: UTC requests additional discussion on this topic to understand the FDA's expectations with regard to this study.

    Discussion during the meeting: FDA stated that full details cannot be provided at this time. A 13-week study in juvenile animals, most likely monkeys, will be requested and that the study protocol should require histopathologic evaluation of tissues. More detailed comments will be provided at a later date.

Clinical Pharmacology

13. To conduct an assessment of neutralizing antibodies response to dinutuximab with a validated assay (under CMC PMC m) capable of sensitively detecting neutralizing antibodies responses in the presence of dinutuximab levels that are expected to be present at the time of patient sampling. The neutralizing antibodies response and its clinical impact will be evaluated in all available samples from ANBL0032 [DIV-NB-301 and DIV-NB-302], DIV-NB-303, and DIV-NB-201 studies.

    UTC Response: UTC has no preliminary comments at this time and looks forward to discussion with the Division.

    Discussion during the meeting: FDA acknowledged UTC's response and asked UTC to provide information regarding immunogenicity samples in Studies ANBL0032, (DIV-NB-301and DIV-NB-302) and DIV-NB-303 and DIV-NB-201. UTC stated that archived samples from Studies DIV-NB-301, DIV-NB-302, and DIV-NB-303 have been evaluated for immunogenicity and the assessment is considered complete. FDA stated that the issue is that the neutralizing antibodies (NAb)_ assay is considered to be relatively insensitive. The FDA stated that a sensitivity of 500 μg/mL would definitely be considered adequate to ensure detection of NAb. UTC expressed concern (b) (4) FDA stated that they understood the concern, however the current NAb assay is too insensitive to characterize the incidence of NAb and that an assay with improved sensitivity is required to adequately characterize this aspect of product quality. The FDA further stated that UTC should either develop a new assay or optimize the current assay to improve assay sensitivity. FDA stated that UTC should use the archived samples collected under Study ANBL0032 and available samples from DIV-NB-303 and DIV-NB-201. If there are insufficient samples available for assessing neutralizing antibody response, UTC should conduct a new study in which immunogenicity will be assessed.

Postmarketing Commitments (PMC)

CMC

In addition to the PMCs below, the FDA informed UTC that other PMCs were being considered. Specifically, the FDA indicated that two additional PMCs had been identified: to perform studies on the compatibility of the drug product with IV bags and infusion sets of different materials of construction and to include osmolality in DP specifications.

14. To re-assess drug substance (DS) and drug product (DP) specifications based upon additional clinical experience with material manufactured with the commercial process in ongoing trials and/or additional characterization information on product critical quality attributes.

    UTC Response: UTC commits to re-assessing drug substance and drug product stability specifications based on additional clinical experience gained with UTC-manufactured ch14.18.

    Discussion during the meeting: FDA acknowledged UTC's response and commitment to obtain these data under an agreed-upon post-marketing commitment (PMC). No discussion occurred.

15. To manufacture, qualify, and implement a new reference standard. This new reference standard will also be entered into a requalification program.

    UTC Response: UTC agrees to manufacture, qualify and implement a new reference standard, which will be entered into a requalification program. (b) (4)

    Discussion during the meeting: FDA acknowledged UTC's response. (b) (4)

16. To validate an improved assay for the detection of host cell proteins. DS specifications will be updated to include the improved assay.

    UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

    Discussion during the meeting: UTC acknowledged FDA's response and will address this issue under an agreed-upon PMC.

17. To validate a (b) (4) assay for the detection of (b) (4). The assay will be included in DS and/or DP specifications.

UTC Response: UTC acknowledges this request. UTC has determined that a (b) (4) in the ch14.18 material and will be substituting the (b) (4) for this purpose.

Discussion during the meeting: FDA acknowledged UTC's response and no discussion occurred.

18. 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.

UTC Response: UTC acknowledges this request. For clarification, UTC will perform end of production cell testing and do a comparability assessment (b) (4)

Discussion during the meeting: stated that UTC must repeat full testing of end of production cells at commercial scale as a part of the qualification of the working cell bank.

19. To provide additional testing to confirm the monoclonality of the master cell bank.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: FDA acknowledged UTC's response agreement to conduct additional testing to confirm monoclonality of the master cell bank. UTC asked that the FDA provide additional information on what type of information would be needed to support clonality. The FDA indicated that single cell clones of the current master cell banks could be tested to assess clonality. However, the acceptability of this approach would require sufficient information to support that the methods used are appropriate and sufficiently sensitive to detect non-clonality. In this case, data supporting the statistical validity of the number of clones analyzed should be provided.

20. To perform studies to support acceptable product quality and shipper performance during shipping of Unituxin. This should include consideration for worst case shipping routes, including routes to testing sites.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

21. 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.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: FDA acknowledged UTC's response and asked UTC to provide further detail on their plans. UTC stated that no current plans are available to share with FDA.

22. To perform commercial scale (b) (4) lifetime studies.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

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

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

24. To re-assess validation of the SEC-HPLC, cSDS, and cIEF assays with regards to accuracy and sensitivity for purity, and for the performance of the assays for the detection of the applicable product related impurities included the final drug substance and drug product specifications.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

25. To reassess the performance of the ADCC assay, to include the range of activities expected to be observed in DS and DP lots during release and stability testing. If applicable, an optimized assay will be incorporated into DS and DP specifications.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

26. 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

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

Product Quality Microbiology

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

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

28. Conduct studies to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product.

UTC Response: UTC acknowledges this request. Until such time that a suitable endotoxin release test is developed, validated, and implemented, it is UTCs position that the current testing of endotoxin on drug substance and manufacturing controls mitigate the patient risk of performing the rabbit pyrogen test rather than an endotoxin test for release testing of drug product.

Discussion during the meeting: FDA acknowledged UTC's response to retain the rabbit pyrogen test until an alternative endotoxin testing method is developed and validated.

29. Conduct the bioburden method qualification studies for the [redacted] (b) (4) using 2 additional batches and for the drug substance using 3 different drug substance lots. [redacted] (b) (4) The results should be submitted.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: No discussion occurred.

30. Submit the final established [redacted] (b) (4) after trending the data from 10 drug substance batches.

UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

Discussion during the meeting: FDA acknowledged UTC's response and noted that studies are ongoing.

Major Labeling Issues

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

- The revised label submitted to the BLA on July 8, 2014 did not address all of the FDA comments and questions that were communicated in the June 24, 2014 Filing Letter and the memorandum sent on July 2, 2014. Issues that were not adequately addressed include but are not limited to issues relating to attribution of adverse reactions to dinutuximab (as opposed to IL-2 and GM-CSF), communication of dose modification instructions for dinutuximab, and differentiating allergic reactions from infusion reactions in product labeling. Additionally, FDA is considering the potential inclusion of additional adverse reactions such as (b) (4) and infusion reactions in the boxed warning of product labeling for dinutuximab.

  UTC Response: UTC requests additional clarification on this topic, specifically related to the attribution of AEs to dinutuximab (as opposed to IL-2 and GM-CSF).Dinutuximab was given in combination with IL-2 and GM-CSF in the ANBL0032 study; the data regarding attribution was collected but was not specifically assigned to a particular component of therapy. However, in the ANBL0931 study, investigators did attempt to assign attribution to a particular

component. This information is summarized in the DIV-NB-303 CSR, specifically table 14.3.2.1.1 displays a summary of treatment emergent attributable (to ch14.18) AEs by SOC. UTC could potentially use data from this study to summarize ch14.18-related events. UTC would like to understand if this is FDA's expectation with regards to this topic.

Discussion during the meeting: FDA acknowledged UTC's response and stated that FDA is considering inclusion of a table in the Adverse Reactions section of the Unituxin package insert that presents the per-patient incidence of adverse reactions in cycles containing GM-CSF with the per-patient incidence of adverse reactions in cycles containing IL-2 to provide additional information regarding the contribution of each of these cytokines to the risk of adverse reactions observed in patients treated with ch14.18 in the randomized portion of Study ANBL0032.

- (b) (4) . Provide revised laboratory datasets for Study DIV-NB-303 that include CTCAE grading of laboratory data and a revised table of laboratory abnormalities that categorizes abnormal laboratory values using CTCAE grading. For an example of the desired format for communication of laboratory abnormalities in product labeling, please see the pembrolizumab package insert.

  UTC Response: UTC has no preliminary comments at this time and looks forward to discussions with the Division.

  Discussion during the meeting: FDA acknowledged UTC's response. UTC stated that revised laboratory datasets, to include the NCI CTCAE grading of laboratory abnormalities will be provided the week of October 13 – 17, 2014.

Review Plans

Review of BLA 125516 is ongoing and FDA plans to hold a wrap-up meeting on November 10, 2014.

Discussion during the meeting: No discussion occurred

Inspections

The pre-license inspection of the United Therapeutics site located in Silver Spring, MD was conducted in June 2014. The final recommendation is pending.

Discussion during the meeting: No discussion occurred

Wrap-up and Action Items

Discussion during the meeting: No discussion occurred

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

GINA M DAVIS
11/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125516

LATE CYCLE MEETING
BACKGROUND PACKAGE

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 TW Alexander Drive, P. O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mathue:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Unituxin (dinutuximab).

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 6, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	October 6, 2014, 12:00 PM – 1:30 PM
Meeting Location:	Teleconference
Application Number:	BLA 125516
Product Name:	Unituxin (dinutuximab)
Indication:	For the treatment of high risk neuroblastoma
Sponsor/Applicant Name:	United Therapeutics Corporation

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical/Statistics

1. Based upon our statistical review of the data submitted to the BLA, the results of the event-free survival (EFS) analysis leading up to cessation of randomization in Study ANBL0032 did not meet the pre-specified stopping boundary. To convey this information, the calculated p-value for EFS may be compared with the allocated alpha for the interim analysis of EFS in the product labeling. (b) (4)

2. As discussed during the July 18, 2014 post midcycle teleconference, the BLA contains minimal clinical information regarding the relative contributions, if any, of IL-2 or GM-CSF to the observed treatment effect. This uncertainty will be communicated in our published review of the BLA. Information regarding dosing of IL-2 and GM-CSF in

product labeling will be limited to that necessary to mitigate risks to patients and provide an accurate description of the clinical trial.

3. Because recently manufactured lots of drug product and drug substance may have increased antibody dependent cellular cytotoxicity (ADCC) activity compared to earlier lots of material manufactured by UTC, there is a potential safety concern. The BLA does not currently include safety data from patients who have been treated with these lots. Please provide information regarding the number of patients who have received treatment with recently manufactured lots that have higher ADCC activity and a listing of adverse events that have been reported for these patients. Include a narrative description for all serious adverse events including a description of the adverse event, the temporal relationship between the onset of the adverse event (including treatment cycle) and treatment with dinutuximab, concomitant therapies, intervention needed, and outcome of the adverse event. If this information is not readily available, please provide an estimated timeframe for when United Therapeutics will be able to provide it.

   Depending upon the amount of clinical data available from patients treated with newer lots of dinutuximab, a potential PMR may need to be considered for the provision of updated safety data from ongoing clinical trials of dinutuximab to assess whether variations in ADCC activity in different lots of dinutuximab result in increased toxicity to patients.

Chemistry, Manufacturing and Controls

4. Available information suggests that recently manufactured lots of drug product (DP) and drug substance (DS) have increased antibody dependent cellular cytotoxicity (ADCC) activity compared to earlier lots of material manufactured by UTC, including the early UTC manufactured lots used in the comparability assessment and the PK clinical trial. Additional information to support the safety of lots with increased ADCC activity is needed, such as determining if there is a correlation between safety signals and ADCC activity.

   Final specifications for DS and DP still need be agreed upon. It appears that many of the acceptance criteria in specifications are based upon manufacturing and stability data without consideration for clinical experience. In addition, based upon the proposed updated specifications received on September 12, 2014, it appears that drug substance lots CHL11006 and 1500045 as well as DP validation lot 1200041 would fail cIEF release criteria. Specifications will need to be updated. FDA strongly recommends that consideration be given to establishing end of shelf-life specifications for DP based upon available information on clinical experience. This may necessitate altering your proposed shelf-lives for both DS and DP.

Product Quality Microbiology

5. Microbial retention data is needed for the [redacted] (b) (4)

6. Additional sterilization validation data is needed for the [redacted] (b) (4).

7. The LAL kinetic chromogenic method for drug product release testing was replaced with the rabbit pyrogen test. As a result, new testing sites were added to the BLA file.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No new issues which require additional risk management actions or require a REMS have been identified to date. FDA has not reached final agreement on product labeling, which is a component of United Therapeutic's risk management plan.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

- The revised label submitted to the BLA on July 8, 2014 did not address all of the FDA comments and questions that were communicated in the June 24, 2014 Filing Letter and the memorandum sent on July 2, 2014. Issues that were not adequately addressed include but are not limited to issues relating to attribution of adverse reactions to dinutuximab (as opposed to IL-2 and GM-CSF), communication of dose modification instructions for dinutuximab, and differentiating allergic reactions from infusion reactions in product labeling. Additionally, FDA is considering the potential inclusion of additional adverse reactions such as [redacted] (b) (4) and infusion reactions in the boxed warning of product labeling for dinutuximab.

- [redacted] (b) (4)
  Provide revised laboratory datasets for Study DIV-NB-303 that include CTCAE grading of laboratory data and a revised table of laboratory abnormalities that categorizes abnormal laboratory values using CTCAE grading. For an example of the desired format for communication of laboratory abnormalities in product labeling, please see the pembrolizumab package insert.

LCM AGENDA

1. **Introductory Comments** – 5 minutes: Welcome, Introductions, Ground rules, Objectives of the meeting (RPM/CDTL)
2. **Discussion of Substantive Review Issues** – 10 minutes.
3. Each issue will be introduced by FDA and followed by a discussion.

   Product Quality Microbiology

   - Endotoxin release test strategy for the drug product.
   - [redacted] (b) (4)
   - New testing site for pyrogen testing.

   CMC

   - Specifications
   - Discussion of increasing ADCC activity in recent lots.

4. **Discussion of Minor Review Issues** – 5 minutes

   CMC

   FDA anticipates another information request to address minor review issues.

5. Additional Applicant Data – Time to be determined (Applicant)

6. Information Requests – 10 minutes

   The following information requests are outstanding as of September 17, 2014:

Clinical Pharmacology

a. Please submit the results of the long-term storage stability of PK samples. The storage time in a long-term stability evaluation should equal or exceed the time between the date of first sample collection and the date of last sample analysis (Bioanalytical Method Validation guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf).

Office of Biotechnology Products

b. General Comment for Container Label and Carton Labeling

In response to our September 10, 2014 Information Request – Carton and Container, it appears you removed the bolding from the strength per total volume. In the previous submissions, the strength per total volume "**17.5 mg/5 mL**" was appropriately more prominent than the strength per milliliter "3.5 mg/mL". Revise the strength presentation to appear as:

17.5 mg/5 mL
(3.5 mg/mL)

Product Quality Microbiology

c. UTC indicated that October 2014 is the expected submission date for the repeat microbial retention study for the (b) (4). Provide an update on the expected submission date. Additional product quality microbiology information requests will be sent prior to the late cycle meeting.

d. The (b) (4) hold time qualification data are pending and UTC committed to submit the (b) (4) hold time data by September 30, 2014 and (b) (4) hold time qualification data by October 31, 2014.

7. The following Postmarketing Requirements/Postmarketing Commitments to be discussed with United Therapeutics Corporation – 20 minutes

Postmarketing Requirements (PMR)

Nonclinical

a. To further investigate the potential for long term neuropathy and neuropathic pain as well as to further explore the toxicity of dinutuximab as a monotherapy.

Clinical Pharmacology

b. To conduct an assessment of neutralizing antibodies response to dinutuximab with a validated assay (under CMC PMC m) capable of sensitively detecting neutralizing antibodies responses in the presence of dinutuximab levels that are expected to be present at the time of patient sampling. The neutralizing antibodies response and its clinical impact will be evaluated in all available samples from (b) (4) DIV-NB-302], DIV-NB-303, and DIV-NB-201 studies.

8. Postmarketing Commitments (PMC)

CMC

a. To re-assess drug substance (DS) and drug product (DP) specifications based upon additional clinical experience with material manufactured with the commercial process in ongoing trials and/or additional characterization information on product critical quality attributes.

b. To manufacture, qualify, and implement a new reference standard. This new reference standard will also be entered into a requalification program.

c. To validate an improved assay for the detection of host cell proteins. DS specifications will be updated to include the improved assay.

d. To validate (b) (4) he assay will be included in DS and/or DP specifications.

e. 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.

f. To provide additional testing to confirm the monoclonality of the master cell bank.

g. To perform studies to support acceptable product quality and shipper performance during shipping of Unituxin. This should include consideration for worst case shipping routes, including routes to testing sites.

h. 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.

i. To perform commercial scale (b) (4) lifetime studies.

j. To conduct studies to determine the root cause of the (b) (4) observed in drug product stored under recommended

conditions. Based on a risk assessment of the results, appropriate corrective and preventative actions will be implemented.

k. To re-assess validation of the SEC-HPLC, cSDS, and cIEF assays with regards to accuracy and sensitivity for purity, and for the performance of the assays for the detection of the applicable product related impurities included the final drug substance and drug product specifications.

l. To reassess the performance of the ADCC assay, to include the range of activities expected to be observed in DS and DP lots during release and stability testing. If applicable, an optimized assay will be incorporated into DS and DP specifications.

m. 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.

Product Quality Microbiology

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

o. Conduct studies to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product.

p. Conduct the bioburden method qualification studies for the (b) (4) using 2 additional batches and for the drug substance using 3 different drug substance lots. (b) (4) The results should be submitted.

q. Submit the final established (b) (4) after trending the data from 10 drug substance batches.

8. Major labeling issues – 20 minutes

9. Status of Inspections – 2 minutes

BMAB

- The pre-license inspection of the United Therapeutics site located in Silver Spring, MD was conducted in June 2014. The final recommendation is pending.

EES

- EER – Status of EER.

10. Review Plans – 1 minute

Review of BLA 125516 is ongoing and FDA plans to hold a wrap-up meeting on November 10, 2014.

11. Wrap-up and Action Items – 1 minute

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

/s/

GINA M DAVIS
09/24/2014