

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125516Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	125516
Product Name:	Unituxin
2878-10 PMC Description:	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 submitted in the subsequent BLA annual reports. The WCB qualification report will be submitted in a prior approval supplement.

PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission:	03/ 2016
	Other:	_____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4)



2. Describe the particular review issue and the goal of the study.

(b) (4)



3. [OMIT – for PMRs only]

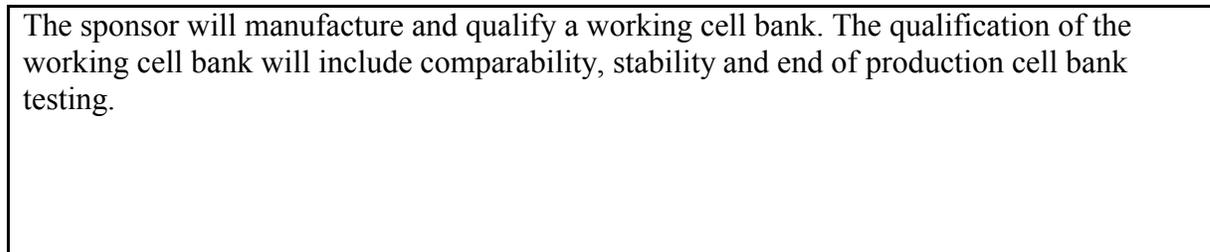
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will manufacture and qualify a working cell bank. The qualification of the working cell bank will include comparability, stability and end of production cell bank testing.



5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	125516
Product Name:	Unituxin
2878-11 PMC Description:	Conduct studies to further characterize the Unituxin master cell bank (MCB) and to confirm the monoclonality of the MCB.
PMC Schedule Milestones:	Final Protocol Submission: <u>06/2015</u>
	Study/Trial Completion: <u>12/2015</u>
	Final Report Submission: <u>01/2016</u>
	Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
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1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Substance (DS) and Drug Product (DP) release specifications approved under the BLA are sufficient to ensure adequate quality and safety of Unituxin for the initial marketed product. Assurance of the monoclonality of the Unituxin producing master cell bank (MCB) will reduce the risk of the generation of product variants and ensure the consistency of Unituxin product quality throughout the product life cycle.

2. Describe the particular review issue and the goal of the study.

The study will provide additional assurance of product quality consistency through additional testing to support the monoclonality of the MCB.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Additional characterization of the Unituxin master cell bank (MCB) to support the monoclonality of the MCB.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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NDA/BLA #	125516
Product Name:	Unituxin
2878-12	
PMC Description:	Conduct validation studies to confirm acceptable product quality and shipper performance during shipping of dinutuximab drug product. This should include consideration for worst case shipping routes, including routes to testing sites. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for drug product quality [e.g., opalescence, protein concentration, purity by SEC-HPLC, cSDS (reduced and non-reduced), cIEF, WCX, sub-visible particulates, and potency of dinutuximab], and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission:	06/2015
	Other:	_____

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- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
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- Theoretical concern
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- Other

The results of studies provided in the BLA support that Unituxin should remain stable during transportation. However, the shipping qualifications studies provided in the BLA did not include product quality data and the conditions used were not the same as those that will be used for the commercial shipping of Unituxin. Additional shipping validation studies are needed.

2. Describe the particular review issue and the goal of the study.

Data is needed to support the performance of the commercial shipping configurations and to confirm that there is no adverse impact of shipping on product quality. The shipping validation studies should be performed under representative conditions for commercial shipping of Unituxin. All relevant product quality attributes that may be potentially impacted during shipping should be evaluated.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Shipping validation studies using commercial shipping conditions will be performed to evaluate the performance of the commercial shippers and to assess the impact of shipping on product quality.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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The results of extractable studies for Unituxin support that there is a low risk for leachables to impact Unituxin product quality.

The preliminary results from extractables studies indicate that the presence of leachates from the Unituxin commercial container closure systems do not appear to be a safety issue. However, the real-time leachate studies were not performed to the end of the drug product shelf life. A real-time leachable study through the end of drug product expiry period would provide a more comprehensive assessment of the levels of leachates that can be introduced into the drug substance and drug product under recommended storage conditions.

2. Describe the particular review issue and the goal of the study.

Leachable studies for Unituxin are currently incomplete. The performance of real-time leachable studies to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of the drug product shelf life and a toxicological evaluation of the levels of leachates detected in the drug product would provide a better assessment of the risk to patients from any leachates that are potentially present in the drug substance and drug product by the end of the expiry period.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

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- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Conducting a leachate study using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals present at the end of drug product shelf life.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?

- Are the objectives clear from the description of the PMC?
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NDA/BLA #	125516
Product Name:	Unituxin
2878-14	
PMC Description:	Conduct a study 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).

PMC Schedule Milestones:	Final Protocol Submission:	03/2015
	Study/Trial Completion:	11/2017
	Final Report Submission:	12/2017
	Other:	

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- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The (b) (4) lifetime studies in the BLA were performed using (b) (4). The results support that the (b) (4) maintain consistent performance over their lifetimes. Data obtained at commercial scale would provide higher assurance of the (b) (4) over their lifetimes.

2. Describe the particular review issue and the goal of the study.

It was not clear whether the scale-down models used to support the (b) (4) lifetimes are sufficiently representative of the manufacturing-scale (b) (4). The studies at commercial scale will confirm the (b) (4) lifetimes.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Studies assessing the performance of the (b) (4) over their lifetimes will be conducted at commercial scale.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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NDA/BLA # 125516
Product Name: Unituxin

2878-15
PMC Description: Conduct a study 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, risk assessment reports, and proposed corrective and preventive actions will be submitted as a prior approval supplement.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 03/2016
Other: _____

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- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4) was observed during the long-term storage of Unituxin drug product. However, drug product specifications provide assurance that (b) (4) will remain within clinical experience.

2. Describe the particular review issue and the goal of the study.

The levels of (b) (4) during drug product stability studies for lots manufactured with the commercial process. The reason for (b) (4) is not clear. To provide increased assurance of product quality, (b) (4) should be investigated and a safety and efficacy risk assessment provided for the root cause(s). Corrective and preventative actions should be implemented based on the results of the investigation.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The root cause of (b) (4) in Unituxin drug product under the long-term storage conditions will be investigated and a risk assessment of the results provided along with appropriate corrective actions.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

The validation of the SEC-HPLC assay did not include evaluations of accuracy or sensitivity for the purity assessments. In addition, the assay was not validated with respect to the impurities that are included in the final DS and DP specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The SEC-HPLC assay will be validated for accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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CHIKAKO TORIGOE
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LAURIE J GRAHAM
03/13/2015

The validation of the reduced cSDS assay did not include evaluations of accuracy or sensitivity for the purity assessments. In addition, the assay was not validated with respect to the impurities that are included in the final DS and DP specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The reduced cSDS assay will be validated for accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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The validation of the non-reduced cSDS assay did not include evaluations of accuracy or sensitivity for the purity assessments. In addition, the assay was not validated with respect to the impurities that are included in the final DS and DP specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The non-reduced cSDS assay will be validated for accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
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NDA/BLA #	125516
Product Name:	Unituxin
2878-19 PMC Description:	Conduct a study to confirm validation of the cIEF assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications.
PMC Schedule Milestones:	Final Protocol Submission: <u>06/2016</u>
	Study/Trial Completion: _____
	Final Report Submission: <u>12/2016</u>
	Other: _____

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- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current neutralizing anti-drug antibody (ADA) assay is capable of detecting the presence of neutralizing ADA. However, the sensitivity of the assay to detect ADA in the presence of drug levels expected to be present in clinical samples is low. Based on the risk/benefit of the approval of Unituxin for the neuroblastoma indication, the lack of an appropriate neutralizing ADA assay does not preclude approval. The development of an improved neutralizing ADA assay will allow for a more accurate estimation of the effect of neutralizing antibodies on efficacy.

2. Describe the particular review issue and the goal of the study.

In the presence of drug levels expected to be present in clinical samples, the assay to detect neutralizing anti-drug antibodies has relatively poor sensitivity. There may, therefore, have been an underestimation of the percentage of patients that developed neutralizing antibodies. A more accurate assessment of neutralizing antibody responses will allow for an improved assessment of the impact of neutralizing antibodies on efficacy. Therefore, it is recommended that a neutralizing ADA with improved sensitivity in the presence of expected levels of Unituxin at the time of sample collection be developed and validated. This improved assay will be used as a component of a post-marketing requirement to assess neutralizing antibodies in clinical samples.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will develop and validate an assay with improved sensitivity for the detection of neutralizing ADA.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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NDA/BLA #	125516
Product Name:	Unituxin
2878-20	
PMC Description:	Develop, validate/qualify and implement an osmolality assay for the drug product release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion should be submitted as a Changes Being Effected in 30 Days (CBE-30) supplement.

PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission:	05/ 2015
	Other:	_____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The lack of osmolality testing in drug product specifications was considered acceptable for the initial marketed product as available data indicates that there is adequate control over the final formulation to ensure that osmolality will be acceptable. However, including osmolality testing in drug product specifications will support consistency of the drug product formulation throughout continued commercial manufacturing.

2. Describe the particular review issue and the goal of the study.

The current specifications include some methods for evaluating formulation, such as levels. The addition of osmolality will provide monitoring of the remaining formulation components.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will develop and validate an osmolality assay that will be implemented in the drug product release specifications.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125516
Product Name: Unituxin

2878-21
PMC Description: Conduct a study to confirm compatibility of drug product with intravenous infusion (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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 11/ 2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL*. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Data provided in the BLA support the compatibility of Unituxin drug product with IV bags and infusion sets. However, there was no information provided on the materials of construction of the IV bags and infusion sets used in the compatibility studies. Drug product compatibility studies should be performed with IV bags and IV administration sets of different materials of construction to ensure product quality attributes are not impacted by various infusion systems.

2. Describe the particular review issue and the goal of the study.

The compatibility studies reported in the BLA did not document the specific infusion bags and infusion sets that were used. In order to confirm that the drug product is compatible with infusion bags and sets of different materials of construction, additional drug product compatibility studies will need to be performed.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will perform studies that confirm the compatibility of the Unituxin drug product with infusion systems of different materials of construction.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125516
Product Name: Unituxin

28787-22
PMC Description: Conduct a study 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 11/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

There are concerns regarding microbial control due to the long infusion time (20 hours) associated with the administration of Unituxin. However, no clear adverse events have been directly linked to the long infusion time. It was recommended by the Agency that an in-line filter be used during administration. Data will need to be provided demonstrating that product quality is not adversely impacted by the use of in-line filters.

2. Describe the particular review issue and the goal of the study.

An in-line filter during administration was recommended by the Agency due to microbial control concerns. The compatibility of the Unituxin drug product with in-line filters should be demonstrated to confirm there is no adverse impact on product quality.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will perform the studies that confirm the compatibility of the Unituxin drug product with in-line filters used for the administration.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

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NDA/BLA #	125516
Product Name:	Unituxin
2878-23	
PMC Description:	Conduct a study to re-evaluate dinutuximab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission:	06/2017
	Other:	_____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL*. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDA A A OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Substance release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of Unituxin for the initial marketed product. *Additional* manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Unituxin drug substance release and shelf-life specifications are based on clinical and manufacturing experience *provided in the BLA and assessed* during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125516
Product Name: Unituxin

2878-24
PMC Description: Conduct a study 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 06/2017
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL*. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Product release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of Unituxin for the initial marketed product. *Additional* manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Unituxin Drug Product release and shelf-life specifications are based on clinical and manufacturing experience *provided in the BLA and assessed* during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

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NDA/BLA # 125516
Product Name: Unituxin (dinutuximab)

2878-25
PMC #25 Description: 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 07/2015
Other: _____

2878-26
PMC #26 Description: 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/2018
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 21 CFR 314.101 OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The endotoxin testing issue is appropriate for PMCs because the sponsor's interim plan for drug product release testing complies with the regulations. The sponsor will use rabbit pyrogen testing for drug product release until a more suitable *in vitro* assay is developed. 21 CFR 610.13(b) states that "each lot of final containers of any product intended for use by injection shall be tested for pyrogenic substances by intravenous injection into rabbits." The rabbit test requirement is waived if a method equivalent to the rabbit test is demonstrated in accordance with 21 CFR 610.9.

2. Describe the particular review issue and the goal of the study.

The LAL kinetic chromogenic test method under-reports the amount of endotoxin spike solution added to undiluted drug product (low endotoxin recovery). The goals of the PMC studies are as follows: (1) to determine whether low endotoxin recovery in the product corresponds to non-pyrogenicity *in vivo* and (2) to develop, if possible, a more suitable *in vitro* release test method for endotoxin.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will perform a comparison study of the LAL endotoxin test method and the rabbit pyrogen test. The drug product will be spiked with an endotoxin standard and then tested by both methods at specified time points.

The sponsor will explore alternative *in vitro* test methods and work on development of a more suitable *in vitro* test with the goal of replacing the rabbit pyrogen test with an *in vitro* test.

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Team Leader)

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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/s/

COLLEEN THOMAS
03/12/2015

PATRICIA F HUGHES TROOST
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125516
Product Name: Unituxin (dinutuximab)

2878-27

PMC #27 Description: 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 06/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor provided data from microbial ingress and dye ingress tests that demonstrated container closure integrity. However, only the dye ingress method will be used for stability testing, and validation of the dye ingress test method is incomplete.

2. Describe the particular review issue and the goal of the study.

The dye ingress method validation study performed by the contract testing laboratory did not specifically validate the method for the dinutuximab container closure system. The study was performed with empty vials rather than liquid-filled vials, which could impact the sensitivity of the method. Therefore, the sensitivity of the method has not been determined. The goal of the study is to determine the method sensitivity in terms of the defect size that is detectable. The defect size for the assay positive control (defective vial) will be determined based on the method sensitivity.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The dye ingress method will be validated for the dinutuximab container closure system. The dye ingress method will be updated with an appropriate positive control.

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Team Leader)

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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COLLEEN THOMAS
03/12/2015

PATRICIA F HUGHES TROOST
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

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BLA # STN 125516
Product Name: Unituxin (dinutuximab)
2878-28
PMC #28 Description: Conduct a study, including the bioburden method qualification analyses, for the (b) (4) using 2 additional batches and for the bulk drug substance using 3 different drug substance lots. Submit the results.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 04/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The bioburden assay method qualification studies have been performed using samples from one lot of the (b) (4) and drug substance. To demonstrate the consistency, samples from three lots are required to complete the qualification study.

2. Describe the particular review issue and the goal of the study.

The bioburden assay method qualification studies have been completed using samples from only one lot for (b) (4) and drug substance. Additionally, a consistent approach was not employed in qualifying the bioburden assay method qualification study of the (b) (4) and drug substance. The completion of this study will meet the qualification requirement of using samples from 3 lots with a consistent method qualification approach of the bioburden assay for all the (b) (4) materials.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will perform the bioburden method qualification studies for the (b) (4) using two additional batches and for the drug substance using 3 different drug substance lots. (b) (4)

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Team Leader)

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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LAKSHMI RANI NARASIMHAN
03/13/2015

PATRICIA F HUGHES TROOST
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

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BLA # STN 125516
Product Name: Unituxin (dinutuximab)
2878-29
PMC #29 Description: Conduct a study to determine the final established (b) (4)
 after trending the data from 10 drug substance batches.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

These (b) (4) sampling points have been newly introduced during the review and currently being monitored with no established limits. The data from 10 drug substance batches during routine manufacturing will be trended to establish the limits for these sampling points and this cannot be completed prior to BLA approval.

2. Describe the particular review issue and the goal of the study.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The Sponsor will be submitting the final established (b) (4)

 after trending the data from 10 drug substance
 batches.

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Team Leader)

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

LAKSHMI RANI NARASIMHAN
03/13/2015

PATRICIA F HUGHES TROOST
03/13/2015

In the presence of drug levels expected to be present in clinical samples, the assay to detect neutralizing anti-drug antibodies has relatively poor sensitivity. There may, therefore, have been an underestimation of the percentage of patients that developed neutralizing antibodies. A more accurate assessment of neutralizing antibody responses will allow for an improved assessment of the impact of neutralizing antibodies on efficacy. Therefore, it is recommended that a neutralizing ADA with improved sensitivity in the presence of expected levels of Unituxin at the time of sample collection be developed and validated. This improved assay will be used as a component of a post-marketing requirement to assess neutralizing antibodies in clinical samples.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will develop and validate an assay with improved sensitivity for the detection of neutralizing ADA.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	125516
Product Name:	Unituxin
2878-6 PMC Description:	Conduct a study to re-assess drug substance and drug product 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.

PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission:	06/2017
	Other:	_____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The DS and DP release and shelf-life specifications approved under BLA are sufficient to ensure adequate safety and efficacy of Unituxin for the initial marketed product. Additional product characterization information or clinical experience gained with material that is representative of the commercial manufacturing process can generate improved specifications.

2. Describe the particular review issue and the goal of the study.

There is limited clinical experience using Unituxin manufactured with the commercial process. At the time of approval, there were on-going clinical trials using commercial lots of Unituxin. Clinical experience with these lots, along with additional product characterization data, will provide a more robust set of data for refining drug substance and drug product specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Data from on-going clinical trials using lots representative of the current commercial manufacturing process and/or additional process characterization studies will be used to evaluate drug substance and drug product specifications. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

The reference standard, used for release and stability testing of drug substance and drug product, represents a link to clinical experience. A new reference standard needs to be qualified and implemented (b) (4). In addition, the stability of the new reference standard needs to be monitored using a requalification protocol.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The reference standard qualification and requalification protocols and the qualification report for the new reference standard will be submitted in a prior approval supplement.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125516
Product Name: Unituxin

2878-8
PMC Description: 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 submitted in a prior approval supplement.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 10/2015
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current assay and acceptance criterion for the assessment of host cell proteins (HCP) in the drug substance release program are sufficient to ensure adequate quality and safety of Unituxin for the initial marketed product. However, the improvement and implementation of a process-specific assay for HCP will provide better control of HCP levels in DS.

2. Describe the particular review issue and the goal of the study.

The current Unituxin DS release specifications include an ELISA for evaluating HCP levels. This method detects various proteins (b) (4) that are used for manufacturing of Unituxin. However, this method is not optimal in terms of the coverage of HCP. The implementation of an improved, process-specific HCP assay will provide more accurate control of the HCP levels in DS.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Development and validation of a process-specific HCP assay with improved sensitivity and capability to detect a wider range of HCP.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	125516
Product Name:	Unituxin
2878-9 PMC Description:	Validate an assay for the detection of dinutuximab (b) (4) and implement this assay in the drug substance and drug product 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.

PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission:	04/2016
	Other:	_____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current DS and DP release and stability specifications are adequate to ensure adequate safety and efficacy of Unituxin for the initial marketed product. The implementation of an assay that can sensitively detect (b) (4) will provide for an improved control strategy.

2. Describe the particular review issue and the goal of the study.

The results of forced degradation studies suggest (b) (4) may be one of the potential modifications that can impact Unituxin potency. While there are assays in place that can detect changes in (b) (4), there is currently no assay specific for (b) (4). The implementation of an assay that can sensitively detect product (b) (4) will provide an improved control strategy, including potentially more clinically meaningful specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Development and validation of an assay to sensitively detect the (b) (4) of Unituxin. The validated assay will be used to provide updated specifications to the BLA.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHIKAKO TORIGOE
03/13/2015

LAURIE J GRAHAM
03/13/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: BLA 125516/Unituxin (dinutuximab)

2878-1

PMR#1 Description: Conduct a study to compare exposure and safety data from approximately 220 patients who complete treatment with dinutuximab, pooling across dinutuximab lots and by individual lot, 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 risk serious infusion reactions and neuropathy, and the overall safety and tolerability of the marketed product, Unituxin. In addition, assess whether variations in antibody-dependent cell-mediated toxicity across dinutuximab lots alter the safety and tolerability of dinutuximab.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>9/2015</u>
	Study/Trial Completion:	<u>6/2016</u>
	Final Report Submission:	<u>12/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Currently available efficacy and safety data are sufficient to support approval of Unituxin (dinutuximab) as (b) (4) treatment of patients with high risk neuroblastoma, a serious and life threatening illness. However, most of the data supporting approval is derived from use of investigational product manufactured by SAIC and supplied by the National Cancer Institute. Safety data from use of the United Therapeutics product are limited and there is a theoretical concern that variability in antibody dependent cell mediated cytotoxicity could impact the safety profile of dinutuximab. Therefore, collection and analyses of additional safety data from use of dinutuximab in this expanded access trial are warranted in order to determine if there are clinically meaningful differences in the safety profile of Unituxin that would require a change in product labeling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The data from this ongoing trial will be used to further characterize safety and tolerability of Unituxin (dinutuximab) for the (b)(4) treatment of patients with high risk neuroblastoma.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR is for provision of additional study data and a final study report for an ongoing open-label, multi-center expanded access clinical trial of dinutuximab in patients with high risk neuroblastoma. This study will be amended to include additional safety data from patients exposed to dinutuximab and the final study report will include comprehensive analyses comparing the safety and tolerability of dinutuximab with ch14.18 produced by SAIC (used to treat patients enrolled in this clinical trial prior to January 2014).

Required

- Observational pharmacoepidemiologic study
 Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See above explanation.
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- x Does the study/clinical trial meet criteria for PMRs or PMCs?
- x Are the objectives clear from the description of the PMR/PMC?
- x Has the applicant adequately justified the choice of schedule milestone dates?
- x Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

MARTHA B DONOGHUE
03/10/2015

JEFFERY L SUMMERS
03/11/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: BLA 125516/Unituxin (dinutuximab)
2878-2
PMR # 2
Description: Conduct a study to analyze 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, re-challenge information, and an assessment of whether the clinical presentation and laboratory data obtained were consistent with an allergic reaction or an infusion reaction. In addition, submit datasets used for safety analyses of the laboratory data.

PMR/PMC Schedule Milestones: Analysis Plan Submission: 4/2016
Final Report Submission: 3/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Currently available efficacy and safety data are sufficient to support approval of Unituxin (dinutuximab) as (b) (4) treatment of patients with high risk neuroblastoma, a serious and life threatening illness. Available safety data suggest that the majority of adverse reactions coded as anaphylaxis, hypersensitivity, or allergic reactions in the clinical trials submitted to the BLA were infusion reactions; additional information is needed to more accurately characterize the risk of anaphylaxis and allergic reactions and inform product labeling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Available safety data suggest that the majority of adverse reactions coded as anaphylaxis, hypersensitivity, or allergic reactions in the clinical trials submitted to the BLA were infusion reactions; additional information is needed to more accurately characterize the risk of anaphylaxis and allergic reactions, provide more informed dose adjustment or discontinuation guidelines to healthcare providers and better inform product labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Provision and analysis of clinical and laboratory data from a completed multicenter open label clinical trial of dinutuximab in patients with high risk neuroblastoma.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Provision and analysis of laboratory data collected in a completed open label clinical trial needed to better characterize the risk of infusion and allergic reactions, including anaphylaxis.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- x Does the study/clinical trial meet criteria for PMRs or PMCs?
 - x Are the objectives clear from the description of the PMR/PMC?
 - x Has the applicant adequately justified the choice of schedule milestone dates?
 - x Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

MARTHA B DONOGHUE
03/10/2015

JEFFERY L SUMMERS
03/11/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125516
Product Name: Unituxin (dinutuximab)
2878-4

PMR # 4 Description:

To conduct a study to assess the neutralizing anti-drug antibody responses to dinutuximab with a validated assay capable of sensitively detecting neutralizing antibody responses in the presence of dinutuximab levels that are expected to be present in the blood at the time of patient sampling. The clinical impact of the neutralizing antibody response should be evaluated in at least 300 patients to include an interim report analyzing data from Studies DIV-NB-302, DIV-NB-303 and DIV-NB-201 and a final report analyzing data from Study NANT2011-04.

PMR Schedule Milestones:

Interim Report Submission:	<u>09/2016</u>
Final Report Submission:	<u>06/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sensitivity of neutralizing antibody (Nab) assay is low based on CMC review of the BLA submission and there is lack of immunogenicity information on the to-be marketed product manufactured by the applicant (UTC).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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 as described above is recommended. The goal is to evaluate the neutralizing antibody response and its clinical impact.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Assessment of immunogenicity in clinical trials.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Test neutralizing antibodies in patients' samples using a sensitive assay.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

JINGYU YU
03/10/2015

HONG ZHAO
03/10/2015
I concur.

JEFFERY L SUMMERS
03/11/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 125516
Product Name: UNITUXIN

2878-5

PMR # 5 Description: To conduct a 5-month repeat-dose juvenile animal toxicology study in cynomolgus monkeys that will measure the chronic toxicity of dinutuximab, particularly its 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: 01/2017
Study/Trial Completion: _____
Final Report Submission: 05/2018
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a long history of clinical experience with this drug in a serious and life-threatening illness that occurs primarily in children. The drug, however, has been investigated primarily in combination with other drugs in clinical trials and has had an unusual development process, so chronic studies have not been performed in any species. There are concerns about long term effects on the nervous system due to the mechanism of action of the drug, though given the seriousness the disease in the intended treatment population these concerns should not prevent approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Because of the unusual clinical development of this monoclonal antibody, there is limited data on single agent toxicity related to dinutuximab administration and outstanding concerns about the potential long term neurotoxic effects of the drug. An additional nonclinical toxicology study is proposed to help address these outstanding issues.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 will be performed to investigate potential longer term single-agent effects of the antibody on the peripheral and central nervous system.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

DENALI D KUFRIN
03/10/2015

WHITNEY S HELMS
03/11/2015

JEFFERY L SUMMERS
03/11/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 125516/0

Application Type: New BLA

Name of Drug/Dosage Form: Unituxin (dinutuximab) - 17.5 mg/5 mL (3.5 mg/ML)

Applicant: United Therapeutics Corporation

Receipt Date: April 11, 2014

Goal Date: December 10, 2014

1. Regulatory History and Applicant's Main Proposals

On July 1, 2010, United Therapeutics Corporation (UTC) entered a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute based on the results of Study ANBL0032 to collaborate on the late stage development and regulatory submission of the investigational product ch14.18 for the treatment of patients with high risk neuroblastoma under IND 110494.

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.

On January 27, 2011, UTC informed the Division of Oncology Products 2 that UTC would assume manufacturing responsibilities for the product ch 14.18 and would demonstrate the comparability between ch14.18 produced by NCI and ch 14.18 produced by UTC.

The CMC pre-BLA meeting was held on January 14, 2014 and the pre-BLA all discipline meeting was held February 19, 2014 to finalize the content and format of the BLA submission.

UTC submitted their complete BLA for Unituxin (dinutuximab)[also known as ch14.18] on April 11, 2014, requesting priority review of the application.

The proposed indication for Unituxin (dinutuximab) is high risk neuroblastoma [REDACTED] (b) (4) treatment, in combination with GM-CSF, IL-1 and RA.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

RPM PLR Format Review of the Prescribing Information

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

Highlights – General Format

1. *There is more white space between the end of the Warnings and Precautions section and the beginning of the Adverse Reactions section. It should be consistent throughout HL. (# 5)*
2. *The use of periods prior to the referenced section number is not consistent. Please use periods throughout the HL section.*

Highlights – Product Title in Highlights

3. *Patient Counseling Information Statement does not appear in highlights (# 7).*
4. *Patient Counseling Information Statement does not appear under highlights (#23).*

Highlights – Details

5. *Only the established name should be in parentheses, not [REDACTED] ^{(b) (4)}. The dosage form should not appear in title case and the route of administration should be preceded by a comma - should be "injection for intravenous use" -UNITUXIN (dinutuximab) injection, for intravenous use. (# 10)*

Dosage Forms and Strengths

6. *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) for intravenous infusion. (#20)*

Patient Counseling Information Statement in Highlights

7. *HL does not contain the required statement: See 17 for PATIENT COUNSELING INFORMATION. (#23)*

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 8, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is more white space between the end of the Warnings and Precautions section and the beginning of the Adverse Reactions section. It should be consistent throughout HL.*

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: The use of periods prior to the referenced section number is not consistent. Please use periods throughout the HL section.

- NO** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: The required appropriate Patient Counseling Information Statement does not appear in highlights.

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- NO** 10. Product title must be **bolded**.

Comment: Only the established name should be in parentheses, not (b) (4). The dosage form should not be in title case and the route of administration should be

Selected Requirements of Prescribing Information

preceded by a comma - should be "injection for intravenous use" -UNITUXIN (dinutuximab) injection, for intravenous use.

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment: *BW not submitted by UTC, therefore, BW not applicable at this time.*

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment: *See comment for # 12.*

- N/A** 14. The BW must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment: *See comment for # 12.*

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “***See full prescribing information for complete boxed warning.***”).

Comment: *See comment for # 12.*

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *Original BLA submission.*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment: *See comment for #16.*

Selected Requirements of Prescribing Information

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: See comment for #16.

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- NO** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: 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) for intravenous infusion.

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: HL does not contain the required statement: See 17 for PATIENT COUNSELING INFORMATION.

Selected Requirements of Prescribing Information

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: *BW not submitted by UTC, therefore, BW not applicable at this time.*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *No recent major changes - original BLA.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment: *BW not submitted by UTC, therefore, BW not applicable at this time.*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment: *BW not submitted by UTC, therefore, BW not applicable at this time.*

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment: *Contraindications are listed in the label.*

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *Unituxin has not been approved.*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]
[section (X.X)]

[m/year]
[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

GINA M DAVIS
03/06/2015

Internal Consult

****Pre-decisional Agency Information****

To: Gina Davis, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Date: February 19, 2015

Re: **Unituxin (dinutuximab) injection, for intravenous use**
BLA 125516
Comments on proposed product labeling (PI and carton/container)

In response to the Division of Oncology Products 2 (DOP 2)'s May 8, 2014, consult request, OPDP has reviewed proposed product labeling (PI and carton/container) for Unituxin (dinutuximab) Injection. The version of the PI used in this review was sent via electronic mail from DOP-2 on February 5, 2015, and is titled, "BLA 125516 – Unituxin Label – pst lb mtg 2 5 15 FDA proposal gd doc.docx." The version of the proposed substantially complete carton/container labeling was sent via electronic mail from DOP 2 on February 19, 2015.

OPDP's comments for the PI are provided directly in the attached document. Please note that OPDP accepted all deletions and formatting changes so our comments are easier to read.

OPDP has no comments at this time on the proposed carton/container labeling.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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

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/s/

CAROLE C BROADNAX
02/19/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs—ODE IV
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

From: Erica L. Wynn, M.D., M.P.H, Medical Officer
Office of New Drugs - ODE IV
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Acting Director, DPMH

To: Division of Oncology Products 2

Drug: BLA# 125516 (UnituxinTM/Dinutuximab)

Applicant: United Therapeutics Corporation (UTC)

Therapeutic Class: monoclonal antibody (mAb) to disialoganglioside-2 (GD2) antigen

Formulation: (b) (4)

Proposed Dosing Regimen: 17.5 mg/m²/day administered as an intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 monthly cycles.

Proposed Indication: Dinutuximab is indicated for high-risk neuroblastoma (b) (4) treatment, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin (RA).

Consult Question: “Please assign a reviewer to attend milestone meetings and to provide labeling comments for this new BLA

Materials Reviewed:

- Division of Oncology Products 2 consult dated May 8, 2014
- Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling dated February 2013
- Information available in the sponsor’s submission dated April 11, 2014

INTRODUCTION

Disease Overview

Neuroblastoma is the most common extracranial pediatric solid tumor.¹ Patients with high-risk disease have poor prognosis despite complex multimodal therapy.¹ Neuroblastoma tumors develop from primordial neural crest cells with primary tumors mostly occurring in the abdominal region. Neuroblastoma accounts for approximately 7% of pediatric malignancies in children less than 15 years of age, with approximately 90% of patients diagnosed by five years of age.² There is a direct correlation between age and site or extent of disease. Children with “high-risk” disease have a three-year survival of approximately 30%.³ Diagnosis of neuroblastoma is based on the presence of characteristic histopathological features of tumor tissue or the presence of tumor cells in a bone marrow aspirate or biopsy accompanied by raised concentrations of urine catecholamines.

Several clinical variables impact patient prognosis. These variables include age at diagnosis, stage of the tumor; histopathological features of the tumor; MYCN oncogene amplification and stage of the tumor in relation to MYCN amplification (patients with stage 4 tumor(s) without MYCN amplification have a better prognosis than patients with MYCN amplification). The most commonly associated biological marker associated with a poor outcome is amplification of the oncogene MYCN.⁴ According to the applicant, patients with high-risk neuroblastoma (stage 4 or MYCN amplified tumors) diagnosed at greater than 18 months of age generally require aggressive multimodality therapy including chemotherapy, radiotherapy, autologous stem cell transplant (ASCT); and isotretinoin (RA).

Clinical Development Overview

Dinutuximab is a disialoganglioside, GD2-binding chimeric monoclonal antibody being proposed for the treatment of high risk neuroblastoma (b) (4) in combination with GM-CSF, IL-2, and RA.

Dinutuximab was studied under the name “Chimeric 14.18 (ch14.18)”. Ch14.18 is a monoclonal antibody composed of the variable region heavy and light chain genes of the murine mAb 14.18 and the human constant region genes for heavy chain immunoglobulin G1 (IgG1) and light chain kappa. Ch14.18 reacts specifically with disialoganglioside (GD2) which is highly expressed on human tumors of neuroectodermal origin such as neuroblastoma and melanoma, but minimally expressed on normal human tissues. The drug was studied in one pivotal Phase III Study conducted by the Children’s Oncology Group (COG) and sponsored by the National Cancer Institute (NCI) under NCI IND 4308. Results of the study (which assessed dinutuximab immunotherapy administered with granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin (RA) were published in the New England Journal of Medicine in September, 2010. Additional information from the study are included below.

Notably, United Therapeutics Corporation (UTC) also developed and studied (under IND 110,494) a commercial-scale ch14.18 similar to the NCI-manufactured product to support the licensure of this product for use in the treatment of neuroblastoma.

Reviewer Comment: There are data suggesting that UTC manufactured lots of the drug product and drug substance have increased antibody dependent cellular cytotoxicity (ADCC) activity.

The Division has requested additional information to support the safety of lots with increased ADCC activity. Final specifications of the drug product and drug substance will be agreed upon while also taking into consideration the clinical experience gained using previously used NCI-manufactured and UTC-manufactured material.

The applicant has received orphan designation for this product. Although 3 Phase studies (DIV-NB-301, DIV-NB-302, and DIV-NB-303) were conducted with this product, 1 study (DIV-NB-301) serves as the “pivotal” trial that will support safety and efficacy of ch14.18 when administered in combination with GM-CSF, IL-2, and isotretinoin. Study DIV-NB-301 was a Phase 3 Randomized Study of Chimeric Antibody 14.18 (ch.14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy an Autologous Stem Cell Rescue. The other two supportive studies were studies were uncontrolled clinical studies (study DIV-NB-302 “Phase III Randomized Study of Chimeric Antibody 14.18 (ch14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue” and study DIV-NB-303 “A Comprehensive Safety Trial of Chimeric Antibody 14.18 (ch14.18) with GM-CSF, IL-2, and Isotretinoin in High-Risk Neuroblastoma Patients Following Myeloablative Therapy”) Additionally, clinical trials/studies in patients with melanoma treated with ch14.18 were included in the application to support the exposure data generated by NCI during drug development. Notably the National Cancer Institute has led the development of ch14.18 for more than 20 years.

Summary of Trial ANBL0032 (DIV-NB-301)

The pivotal study supporting the efficacy of dinutuximab was conducted at 90 institutions in the United States, Canada, and Australia. The majority of sites enrolled only 1 or 2 study participants. Study participants were eligible if they had high-risk neuroblastoma, defined strictly by the Children’s Oncology Group Neuroblastoma Biology Study Committee and local institutions before study enrollment. Each study participant had to complete induction therapy, autologous stem-cell transplantation, and radiotherapy. Patients were also required to achieve at least a partial response at the time of evaluation before autologous stem-cell transplantation; have autologous stem-cell transplantation performed within 9 months after the initiation of induction therapy; enroll between day 50 and day 100 after the final autologous stem-cell transplantation; demonstrate absence of progressive disease; and adequate organ function and a life expectancy of at least 2 months.⁵

Study participants with high-risk neuroblastoma and less than 31 years of age, were randomized in a 1:1 manner to receive standard therapy with isotretinoin alone or immunotherapy in combination with GM-CSF, IL-2, and isotretinoin. Enrollees received standard therapy (six cycles of isotretinoin) or immunotherapy (six cycles of isotretinoin and five concomitant cycles of ch14.18 in combination with alternating GM-CSF and interleukin-2). Notably, randomization was stopped when, during a planned interim analysis, the Data Safety Monitoring Committee determined that ch.14.18 immunotherapy and isotretinoin was superior to standard isotretinoin therapy alone with regards to event free survival (EFS) and therefore the study met early stopping of the randomization criteria. Overall survival (OS) and event free survival (EFS) in International Neuroblastoma Staging System (INSS) stage 4 subjects were measured as secondary endpoints.

The primary intent-to-treat (ITT) analysis concluded that there was a statistically significant

improvement ($p = 0.0115$) in Event Free Survival favoring the newly proposed drug regimen for ch14.18 combination immunotherapy over standard therapy alone. Additionally there was a clinically and statistically significant improvement in the two-year point estimate of overall survival.

Safety was evaluated through adverse event reporting, physical examination, and clinical laboratory assessments. All safety analyses were performed on the safety population, defined as all subjects enrolled into the study who actually received study drug therapy. Pain, hypersensitivity, and fever were among the most commonly reported adverse events. Targeted toxicities required to be reported regardless of severity included drug hypersensitivity, capillary leak syndrome, and peripheral neuropathy (for the primary analysis); and hypotension, hypersensitivity, urticaria, capillary leak syndrome, anaphylactic reaction, dyspnea, cytokine release syndrome, and acute respiratory distress syndrome (for the follow-up analysis).

Overall, the most commonly reported AEs in the ch14.18 combination therapy treatment group included: pyrexia (70%), platelet disorder (64%), lymphopenia (62%), drug hypersensitivity (59%), hypotension (58%), hyponatremia (56%), increased ALT (54%), abdominal pain (54%), low hemoglobin (49%), vomiting (44%), diarrhea (42%), and hypokalemia (42%). The most commonly reported AEs among subjects receiving standard therapy alone included platelet disorder (42%), lymphopenia (36%), increased ALT (31%), pyrexia (28%), and low hemoglobin (21%).

Reviewer Comment: The reader should refer to the primary clinical review for additional information. According to the article by Yu et al., the immunotherapy combination regimen was associated with important treatment-related clinical toxic effects, notably pain, hypotension, capillary leak syndrome, and hypersensitivity reactions.⁵ The authors questioned if some of the signs and symptoms could be attributable to the interleukin-2 component.⁵ Some of the toxic side effects were self-limited and resolved after cessation of treatment.

REVIEW OF LABELING AND DPMH RECOMMENDATIONS

Pediatric Use Labeling

Sections 505A(j) and 505B(g)(2) of the Food, Drug and Cosmetic Act (FDCA) require that data submitted in response to a PREA study requirement be described in the labeling whether the findings are positive, negative, or inconclusive. Likewise, data submitted in response to a Written Request should be described in a similar manner.

Reviewer Comment: PREA is not applicable for this application and a Written Request was not issued. The applicant has been granted US orphan drug designation for this product for this indication. Additionally, "treatment of neuroblastoma" has a "rare pediatric disease" designation as defined in section 529(a)(3) of the FDCA.

The Pediatric Use subsection (8.4) of labeling should clearly describe what is known and what is unknown about the use of a drug in the pediatric population, including limitations of use. This subsection should also highlight any differences in efficacy or safety in the pediatric versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted (see Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling). Additionally, the code of federal regulations (21 CFR 201.57(c)(9)(iv)) describes the appropriate pediatric use statements to include in labeling based on findings of safety and effectiveness in the pediatric population.

DMPH recommendations are based on the January 15, 2015, version of the labeling provided by the Project Manager on January 22, 2015. Additionally DPMH participated in the orientation meeting, mid-cycle meeting, and multiple labeling meetings for this application.

1 INDICATIONS AND USAGE

Unituxin (dinutuximab) is indicated (b) (4)
 [see Clinical Studies (14)].

Reviewer comment: Divisions may choose to define the specific "patient population" for which the indication is appropriate in the labeling of their products. However, neuroblastoma is almost exclusively a disease of children.

8.4 Pediatric Use

The safety and effectiveness of Unituxin as part of ^{(b) (4)} multi-agent, multimodality therapy have been established in pediatric patients with high risk neuroblastoma based on results of an open-label, randomized trial (Study 1) in 226 patients ages 11 months to 15 years (median age 3.8 years). ^{(b) (4)}

(b) (4)

*Clinical Pharmacology**(12) and Clinical Studies (14)].*

Reviewer Comment: DMPH suggested additions are indicated with “underlined text” above. When data support the use of a drug in a pediatric population for a particular indication, a “high-level” summary of this data may be presented in Section 8.4 with a cross reference to pediatric use information in the following sections:

- *Indications and Usage*
- *Dosage and Administration*
- *Contraindications*
- *Warnings and Precautions*
- *Adverse Reactions*
- *Clinical Pharmacology, Pharmacodynamics and Pharmacokinetics*
- *Clinical Studies*
- *Patient Counseling Information*

12.3 Pharmacokinetics

The pharmacokinetics of dinutuximab were evaluated by a population pharmacokinetic analysis in a clinical study of Unituxin in combination with GM-CSF, IL-2, and RA. In this study, 27 children with high-risk neuroblastoma (age: 3.9 ± 1.9 years old) received up to 5 cycles of Unituxin at $17.5 \text{ mg/m}^2/\text{day}$ as an intravenous infusion over 10 to 20 hours for 4 consecutive days every 28 days. The observed maximum ^{(b) (4)} dinutuximab concentration (C_{max}) was 11.5 mcg/mL (20%, coefficient of variation (CV)). The mean volume of distribution at steady state (V_{dss}) was 5.4 L (28%). The clearance was 0.21 L/day (62%) and increased with body size. The terminal half-life was 10 days (56%). No formal pharmacokinetic studies were conducted in patients with renal and hepatic impairment.

Reviewer Comment: The Division may consider starting this section with a summary statement. “Dinutuximab pharmacokinetics were initially reported to be highly variable and characterized by a higher clearance in pediatric patients than in adults and a large volume of distribution. Subsequent studies revealed that dinutuximab clearance is age-dependent and more rapid in younger children.”⁶ DPMH defers final comment on this section to the Clinical Pharmacology reviewer.

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Non-clinical studies suggest that dinutuximab-induced neuropathic pain is mediated by binding of the antibody to the GD2 antigen located on the surface of peripheral nerve fibers and myelin and subsequent induction of CDC and ADCC activity.

Reviewer Comment: Notably according to the “Guidance for Industry and Review Staff, Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling,” if nonclinical toxicology studies in a juvenile animal model have been conducted to support pediatric clinical trials, these studies should also be noted in the Pediatric Use subsection. This reviewer noted that the non-clinical development program for this product consisted of a review of the published literature as well as formal GLP studies including; tissue cross reactivity, cardiovascular and respiratory safety pharmacology in non-human primates and a 28-day repeat-dose toxicity study in rats. The reviewer also notes deletions made to the applicant’s originally proposed language but defers final decision regarding information in Section 13.2 to the nonclinical pharm-tox reviewer.

¹ Heczey A, Louis CU. “Advances in chimeric antigen receptor immunotherapy for neuroblastoma”. *Discovery Medicine*. 2013.16(90):287-294.

² Modak S, Cheung NK. “Disialoganglioside Directed Immunotherapy of Neuroblastoma” 2007. *Pediatric Oncology. Cancer Investigations* 2007; 25:78-77.

³ Friedman GK and Castleberry RP. “Changing Trends of Research and Treatment in Infant Neuroblastoma”. *Pediatric Blood Cancer*. 2007;49:1060-1065.

⁴ Mari JM, Hogarty MD, Bagatel R, and Cohn SL. “Neuroblastoma.” *Lancet*. 2007;369(9579): 2106-2120.

⁵ Yu AL, Gilman AL, Ozkaynak F, London WB, et.al. “Anti-GD2 Antibody with GM-CSF, Interleukin-2 and Isotretinoin for Neuroblastoma. *New England Journal of Medicine*. 2010;363:1324-34.

⁶ Desai AV, Fox E, Smith LM, Lim AP, Maris JM, Balis FM. “Pharmacokinetics of the chimeric anti-GD2 antibody, ch14.18, in children with high-risk neuroblastoma.” *Cancer Chemotherapy and Pharmacology*. 2014; 74(5):1047-1055.

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/s/

ERICA WYNN
02/06/2015

HARI C SACHS
02/12/2015
I agree with these recommendations.

LYNNE P YAO
02/13/2015



Department of Health and Human Services Division of Monoclonal Antibodies
Food and Drug Administration Office of Biotechnology Products
Center for Drug Evaluation and Research

FINAL LABEL AND LABELING REVIEW

Date: December 5, 2014

Reviewer: Jibril Abdus-Samad, PharmD
Office of Biotechnology Products

Jibril Abdus-samad -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S
Date: 2014.12.05 08:10:12 -05'00'

Through: Chikako Torigoe, PhD
Division of Monoclonal Antibodies

Chikako Torigoe -A
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300430897,
cn=Chikako Torigoe -A
Date: 2014.12.05 08:18:10 -05'00'

Laurie Graham, MS, Team Leader
Division of Monoclonal Antibodies

Laurie J. Graham -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300080688,
cn=Laurie J. Graham -S
Date: 2014.12.05 10:55:58 -05'00'

Application: BLA 125516

Product: Unituxin™ (dinutuximab)

Applicant: United Therapeutics Corp.

Submission Dates: April 11; September 4, 15; November 5, and 25, 2014

Executive Summary

The carton and container labels for Unituxin™ (dinutuximab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, USP 37/NF 32 [12/1/14 – 4/30/15]. The initial labeling deficiencies were identified, mitigated, and resolved. The label and labeling submitted on November 25, 2014 are acceptable.

Background and Summary Description

BLA 125516 Unituxin™ (dinutuximab) was submitted April 11, 2014 with a proposed indication of treatment for high risk neuroblastoma patients. The recommended dose is 17.5 mg/m² via intravenous infusion over 10 hours to 20 hours for 4 days per course for 5 courses. Unituxin™ is administered on Days 4 to 7 during Courses 1, 3, and 5 (each course lasting approximately 24 days) and on Days 8 to 11 during Courses 2 and 4 (each course lasting approximately 28 days). (b) (4)

- Injection: 17.5 mg/5 mL solution in a single-dose vial

Materials Reviewed

- Vial Container Label, 17.5 mg/5 mL
- Carton Labeling, 17.5 mg/5 mL

Start of Sponsor Material

Vial Container Label

(b) (4)

End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *Conforms.*

(2) The name, address, and license number of manufacturer; **does not conform.**

OBP Request: Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t) and 21 CFR 610.60.

Mfd by:
United Therapeutics Corp.
Research Triangle Park, NC 27709
US License Number 1993
Applicant revised as requested.

(3) The lot number or other lot identification; *Conforms.*

(4) The expiration date; *Conforms.*

(5) The recommended individual dose, for multiple dose containers. *Not applicable. Single-Dose container.*

(6) The statement: "Rx only" for prescription biologicals. *Conforms.*

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable, no MG for this product.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. *Applicant confirmed.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35(3)(i)]; *conforms.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms.*

D. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] **does not conform.**

OBP Request: Ensure the proper name, dinutuximab, is at least half as large as the proprietary name, Unituxin™, per 21 CFR 201.10(g)(2). *Applicant revised as requested.*

F. 21 CFR 201.15 Drugs; prominence of required label statements; **conforms, however OBP recommends adding the dosage form.**

OBP Request: 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". *Applicant revised as requested.*

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*

H. 21 CFR 201.25 Bar code; **Does not conform.**

OBP Request: Add a bar code per 21 CFR 610.67. *Applicant revised as requested.*

I. 21 CFR 201.50 Statement of identity; *conforms.*

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms,* **however OBP recommends revising the strength statement.**

OBP Request: 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 ("17.5mg/ 5mL). *Applicant revised as requested.*

K. 21 CFR 201.55 Statement of dosage; **conforms, however OBP recommends revising to create space on the right side of label to include a bar code.**

OBP Request: Revise the sentence "See package insert for full prescribing information for preparation and administration" to read "Usual Dosage: See package insert." *Applicant revised as requested.*

L. 21 CFR 201.100 Prescription drugs for human use; **does not conform. See comments for request to add to carton labeling.** *Applicant revised as requested.*

End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

b) The name, addresses, and license number of manufacturer; **does not conform**.

OBP Request: 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 1993

at
United Therapeutics Corporation
Silver Spring MD 20910
Applicant revised as requested.

- c) The lot number or other lot identification; *conforms.*
- d) The expiration date; *conforms.*
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative". **Does not conform.**

OBP Request: Add the statement "No preservative" to the side panel to comply with 21 CFR 610.61(e).
Applicant revised as requested.

- f) The number of containers, if more than one; *Not applicable.*
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms.*
- h) The recommended storage temperature; *conforms.*
We concur with DMEPA's recommends addition of Fahrenheit.
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; **conforms, however OBP recommends revising.**

OBP Request: 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."
Applicant revised as requested.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *Not applicable.*

k) The route of administration recommended, or reference to such directions in and enclosed circular; **conforms, however OBP recommends revising.**

OBP Request: 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
Applicant revised as requested.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*

m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable.*

o) The adjuvant, if present; *not applicable.*

p) The source of the product when a factor in safe administration; *not applicable.*

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium

and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; **does not conform**.

OBP Request: Add the statement, "No U.S. Standard of Potency." to side panel under the storage and handling information per 21 CFR 610.61(r). *Applicant revised as requested*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Not applicable, no MG*.

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)*] Unituxin™ (dinutuximab) is a specified biologic (monoclonal antibody for in vivo use), thus EXEMPT.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:

"Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. *Not applicable*.

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter; *conforms*.

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] **Does not conform.**

OBP Request: Relocate the NDC from the side panel to the top of the PDP per 21 CFR 207.35(3)(i). *Applicant revised as requested.*

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms.*

H. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] **does not conform.**

OBP Request: Ensure the proper name, dinutuximab, is at least half as large as the proprietary name, Unituxin™, per 21 CFR 201.10(g)(2). *Applicant revised as requested.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; **conforms, however OBP recommends revising dosage form and route of administration.**

OBP Requests:

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". *Applicant revised as requested.*

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

Applicant revised as requested.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *Conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; **conforms, however OBP recommends revising the strength statement.**

OBP Request: 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 ("**17.5mg/ 5mL**"). *Applicant revised as requested.*

O. 21 CFR 201.55 Statement of dosage; *Conforms*. We concur with DMEPA's recommendation to revise to include "USUAL DOSAGE". *Applicant revised as requested.*

P. 21 CFR 201.100 Prescription drugs for human use; **does not conform**.

OBP Request: 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). *Applicant revised as requested*

Additionally, we concur with DMEPA's recommendation to revise to include "USUAL DOSAGE". *Applicant revised as requested*

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant revised as requested unless noted otherwise.

A. Container Label

1. 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

The Applicant confirmed there is no text on the top of the ferrule and cap overseal. *Acceptable.*

2. 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.

3. To create space on the label to include a bar code:
 - a. Revise the statement "SINGLE USE VIAL. DISCARD UNUSED PORTION" to Title case "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."

Conclusions

The initial labeling deficiencies were identified, mitigated, and resolved. The label and labeling submitted on November 25, 2014 are acceptable.

Vial Container Label

<\\cdsesub1\evsprod\bla125516\0069\m1\us\draft-vial-labels.pdf>



Carton Labeling

<\\cdsesub1\evsprod\bla125516\0069\m1\us\draft-carton-container-labels.pdf>





DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: October 31, 2014 **Consult Received:** July 10, 2014

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health,
Office of Drug Evaluation IV (ODE IV)

Through: Alyson Karesh, MD Acting Team Leader
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Acting Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Oncology 2

Drug: Unituxin (Dinutuximab), BLA 125516, IND 4308

Subject: Labeling Review of New BLA

Sponsor: United Therapeutics Corporation

Consult Request: “Based on the issues outlined at the mid-cycle meeting the nonclinical team will be including pregnancy category D in the dinutuximab label. DOP 2 respectfully request review of the dinutuximab label.”¹

¹ Dinutuximab (Unituxin), BLA 125516, IND 4308, Consult to DPMH received July 10, 2014 from Gina Davis, RPM, DOP2. DARRTS Reference ID: 3540080

INTRODUCTION

United Therapeutics Corporation (UTC) submitted a new BLA Application on April 11, 2014 for dinutuximab (Unituxin), a monoclonal antibody (mAb) to the disialoganglioside-2 (GD2) antigen. The proposed indication is treatment of high risk neuroblastoma for children of all ages using dinutuximab and isotretinoin (RA), in combination with granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin 2 (IL-2). The BLA for Unituxin was granted a priority review because high-risk neuroblastoma is a rare, often fatal childhood cancer despite currently available treatments. The Division of Oncology 2 (DOP2) consulted Pediatric and Maternal Health Staff - Maternal Health Team (PMHS-MHT)² to revise labeling for dinutuximab.

BACKGROUND

This biological product is being studied as part of the National Cancer Institute's (NCI) childhood cancer therapeutics research which developed this product and submitted the IND in 1991. The patent for this biological product is now owned by UTC.

Neuroblastoma

Neuroblastoma is a cancer of the sympathetic nervous system that causes 12% of all cancer deaths in children less than 15 years of age. It is the most common malignancy in the first year of life. The median age at diagnosis is 23 months with a peak incidence in the first 4 years of life.³ Less than 10% of all patients diagnosed with neuroblastoma are older than ten.⁴ The 5-year survival for patients diagnosed with high-risk neuroblastoma is less than 30%.⁵

Half of all patients with neuroblastoma are classified as high-risk based on their age at diagnosis (over 18 months of age), biological and genomic characteristics of the tumor and staging defined by the International Neuroblastoma Staging System.⁶ The long-term survival for children with high-risk neuroblastoma is about 50%. Treatment for these patients is multimodal and includes chemotherapy, surgical resection, autologous bone marrow transplant, irradiation of the tumor site and maintenance treatment consisting of retinoid and immunotherapy.⁷

Target Population and Waiver of Embryofetal Animal Studies

The target population for this product is children with a median age of 23 months diagnosed with high-risk neuroblastoma.⁸ On this basis, the applicant requested a waiver

² PMHS-MHT has since transitioned to Division of Pediatric and Maternal Health (DHMP), Office of Drug Evaluation IV (ODE IV)

³ Conte M, Parodi S *et al.* Neuroblastoma in Adolescents. *Cancer* 2006;106:1409-1417. DOI 10.1002/cncr.21751

⁴ Franks LM, Bollen A *et al.* Neuroblastoma in Adults and Adolescents. *Cancer* 1997;79:2028 -2035.

⁵ See Parsons *et al.*

⁶ NCI PDQ® Neuroblastoma Treatment. Last Modified August 29, 2014. Accessed Sept 25, 2014. <http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page4#Reference4.8>

⁷ See NCI PDQ.

⁸ Parsons K, Bernhardt B, Strickland B. Targeted Immunotherapy for High-Risk Neuroblastoma — The Role of Monoclonal Antibodies. *Ann Pharmacother* 2013; 47:210-218.

of embryofetal and reproductive toxicology studies which the Agency granted on October 24, 2012,⁹ with the following comment:

*Because of the patient population, embryofetal developmental studies will not be required. However, as development of the drug proceeds, the indication and/or patient population expands, the need for embryofetal development studies will be revisited.*¹⁰

Reviewer's Comment –

DPMH considers the waiver of embryofetal toxicology studies reasonable based on the information above indicating that too few adolescent females will require treatment with dinutuximab. Embryofetal and reproductive toxicology studies may need to be required in the future if the product will be evaluated in females of reproductive potential.

Dinutuximab and its Target Antigen GD2

Dinutuximab is an IgG1 monoclonal immunoglobulin that is chimeric (human-mouse) and is specifically targeted to the GD2 surface antigen. When cells expressing GD2 are bound by dinutuximab they undergo apoptosis by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity.¹¹ GD2 is normally expressed throughout the central nervous system during fetal development.¹² After birth, GD2 is expressed in neurons, peripheral pain fibers and skin melanocytes.¹³ GD2 is also found in several types of cancer including neuroblastoma, retinoblastoma, melanoma, sarcoma, small cell lung cancer and brain.^{14,15} GD2 has also recently been found on breast cancer stem cells.¹⁶

Embryofetal Effects of Monoclonal Antibodies

All of the currently available mAbs are IgG immunoglobulins and have a structure comparable to endogenous immunoglobulins.¹⁷ Animal studies of pregnancy suggest that mAbs are handled similarly to those transferred from the mother during normal gestation.^{18,19} Maternal IgG immunoglobulins cross into the fetal circulation via active

⁹ Dinutuximab (Unituxin), BLA 125516, IND 4308. DARRTS Reference ID: 3208168

¹⁰ Dinutuximab (Unituxin), BLA 125516, IND 4308. DARRTS Reference ID: 3208168

¹¹ Ozkaynak MF, Sondel PM *et al.* Phase I Study of Chimeric Human/Murine Anti-Ganglioside GD2 Monoclonal Antibody (ch14.18) With Granulocyte-Macrophage Colony-Stimulating Factor in Children With Neuroblastoma Immediately After Hematopoietic Stem-Cell Transplantation: A Children's Cancer Group Study. *J Clin Oncol* 2000;18:4077-4085.

¹² Lammie G, Cheung N *et al.* Ganglioside gd(2) expression in the human nervous-system and in neuroblastomas - an immunohistochemical study. *Int J Oncol.* 1993 Nov;3:909-15.

¹³ See Parsons *et al.*

¹⁴ Murray JL, Kleinerman ES *et al.* Phase Ia/Ib trial of anti-GD2 chimeric monoclonal antibody 14.18 (ch 14.18) and rhGM-CSF in metastatic melanoma. *J of Immunotherapy* 1996;19:206-217.

¹⁵ Mahiuddin A, Hu J *et al.* Structure based refinement of a humanized monoclonal antibody that targets tumor antigen disialoganglioside GD2. *Front Immunol* 2014;5:1-6. doi: 10.3389/fimmu.2014.00372

¹⁶ See Mahiuddin *et al.*

¹⁷ Hyrich K, Verstappen S. Biologic therapies and pregnancy: the story so far. *Rheumatology* 2014;53:1377-1385. doi:10.1093/rheumatology/ket409

¹⁸ See Hyrich *et al.*

¹⁹ Sarno M, Mancari R *et al.* Are monoclonal antibodies a safe treatment for cancer during pregnancy? *Immunotherapy* (2013) 5(7), 733–741. 10.2217/IMT.13.64

transport using Fc receptors.²⁰ IgG is the only immunoglobulin class that is transferred in any significant amount and all four subclasses are transferred.²¹ Fc receptors start to be expressed in the placenta at the beginning of the second trimester. Their concentration increases through gestation permitting ever greater quantities of IgG to be transferred to the fetus.²² The greatest transfer of IgG occurs in the last 4 weeks of gestation such that at delivery, the neonate's concentration of IgG1 may be higher than that of the mother's.²³

This reviewer evaluated several currently approved mAbs to understand any potential class effects or possible teratogenicity. The anti-TNF mAbs, infliximab,²⁴ adalimumab²⁵ and golimumab²⁶ are pregnancy category B products. Rituximab, an anti-B cell CD-20 mAb carries a pregnancy category C labeling. Data have shown that second and third trimester exposure to rituximab often leads to low B cell counts in the infants for months after birth.²⁷ Another pregnancy category C product, bevacimab, is an anti-vascular endothelial growth factor (VEGF) mAb used to block angiogenesis in several malignancies.²⁸ Preclinical data for bevacimab demonstrated teratogenicity including gross fetal alterations and increased fetal resorptions.²⁹ Thus, these data suggest that mAbs have varying effects on fetal growth and development which may be difficult to predict based on the mAbs' target alone.³⁰

Monoclonal Antibodies and Human Milk Feeding

If a nursing mother required treatment with dinutuximab the risk of exposure to the product for the nursing neonate or infant would be very small. IgG mAbs are large proteins (> 100 kDa) which makes it unlikely that a significant amount will be present in the milk of a nursing mother. If there were any mAbs present in human milk, both Hale's³¹ and LactMed³² state that IgG mAbs would undergo proteolysis in the nursing neonate or infant's gastrointestinal tract and would not enter the circulation.

²⁰ Firan M, Bawdon R *et al.* The MHC class I-related receptor FcRn plays an essential role in the maternofetal transfer of globulin in humans. *Internat Immunol* 2001;13:993-1002.

²¹ Palmeira P, Quinello C *et al.* IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol* 2012;2012:985646.

²² See Palmeira *et al.*

²³ Saji F, Samejima Y *et al.* Dynamics of immunoglobulins at the feto-maternal interface. *Rev of Reproduc.* 1999; 4: 81-89.

²⁴ BLA 103772

²⁵ BLA 125057

²⁶ BLA 125289

²⁷ See Hyrich *et al.*

²⁸ See Sarno *et al.*

²⁹ See current bevacimab labeling.

³⁰ See Hyrich *et al.*

³¹ Hale's 2012 Medications in Mother's Milk

³² LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women.

DISCUSSION

Possible Embryofetal Effects of Dinutuximab and Pregnancy Category

The Division has proposed assigning pregnancy category D for dinutuximab because of the potential risk that:

1. Dinutuximab will be transferred across the placenta to the fetus beginning in the second trimester just as all other IgG immunoglobulins are.
2. Once in the fetal circulation, dinutuximab may bind to developing neural tissue and induce apoptosis.

Reviewer's Comment

DPMH agrees with Pregnancy Category D for dinutuximab based on the theoretical risks described above.

Waiver of Reproductive and Developmental Toxicology Studies

While the target patient population for dinutuximab therapy currently is young children, the use of anti-GD2 MAbs to treat tumors in non-pediatric populations is reported to be under investigation.³³ As noted by the Division in granting a waiver of reproductive and developmental toxicology studies, the waiver will be reconsidered if the target population changes.

Reviewer's Comment

DPMH agrees with this plan and notes that embryofetal and reproductive toxicology studies may be required in the future if the product is studied for indications that may result in exposure in pregnant women.

Lactation

As discussed above, neuroblastoma is rare in adolescents. Therefore, it is unlikely that there will be pregnant or lactating women who would be receiving this product. Thus, the need for specific additional lactation information to inform this section is not necessary at the present time. However, in the unlikely event that an adolescent female is treated with dinutuximab for neuroblastoma and is breast feeding her infant, the presumed risk to the nursing infant is low for two reasons:

1. The product's large molecular weight would likely prevent transfer to the nursing female's milk; and,
2. If dinutuximab was present in the nursing female's milk, the product would likely undergo proteolytic cleavage in the nursing infant's gastrointestinal tract.

Reviewer's Comment

It is unknown if dinutuximab is present in human milk and if it has serious adverse effects. Therefore the regulatory language required in this labeling, is: "It is not known if dinutuximab is present in human milk. Because many drugs are present in human milk and because the potential for serious adverse reactions in nursing infants, a decision

³³ See Mahiuddin *et al.*

should be made to either discontinue nursing or discontinue drug taking into account the importance of the drug for the mother.”

Duration of Contraception

The recommended duration of effective contraception for females of reproductive potential following completion of therapy with a potential teratogen is generally 5 half-lives, as drug elimination to a negligible level usually occurs between 4 and 5 half-lives. The half-life of dinutuximab is reported to be 10 days;³⁴ therefore, effective contraception is recommended for 50 days or approximately 2 months after completion of therapy.

Reviewer's Comment

DPMH agrees with this plan.

RECOMMENDATIONS

DPMH attended labeling meetings with the Division throughout September and October, 2014 (see approved labeling for final agreements).

DPMH general labeling recommendations include:

- Labeling for the Warnings and Precautions section (5.8) should include information on embryofetal toxicity and women should be advised to use contraception.
- Labeling for the Pregnancy section (8.1) that includes information on embryofetal toxicity.
- Labeling for the Nursing Mothers section (8.3) that includes information on potential serious adverse reactions in nursing infants
- Labeling for the Females and Males of Reproductive Potential (8.8) that includes information on contraception

³⁴ October 8, 2014 labeling meeting with DOP2, Pharmacology Toxicology reported the half-life of dinutuximab is 10 days.

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

- Embryo-fetal toxicity: may cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use effective contraception (5.7, 8.1, 8.8).

5 WARNINGS AND PRECAUTIONS

5.8 Embryofetal Toxicity

Based on its mechanism of action, UNITUXIN may cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. (b) (4)

Advise females of reproductive potential to use effective contraception during (b) (4), and for (b) (4) two months after the last dose of UNITUXIN [see *Use in Specific Populations* (8.1, 8.8)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

Based on its mechanism of action, UNITUXIN may cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no data available in pregnant women and no (b) (4) reproductive studies (b) (4)

Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. (b) (4)

(b) (4)

(b) (4) (b) (4)

8.8 Females and Males of Reproductive Potential

Females

Advise females of reproductive potential to use effective contraception during therapy, and for two months after the last dose of UNITUXIN. (b) (4)

(b) (4)

(b) (4)

17 PATIENT COUNSELING INFORMATION

Advise females of reproductive potential

(b) (4)

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

/s/

CAROL H KASTEN
10/31/2014

ALYSON R KARESH
10/31/2014

LYNNE P YAO
11/03/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 18, 2014

TO: Gina Davis, Regulatory Health Project Manager
Martha Donoghue, M.D., Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125516

APPLICANT: United Therapeutics Corporation

DRUG: Unituxin (dintuximab, ch14.18)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of patients with high-risk neuroblastoma

CONSULTATION REQUEST DATE: May 8, 2014
INSPECTION SUMMARY GOAL DATE: September 13, 2014
DIVISION ACTION GOAL DATE: December 10, 2014
PDUFA DATE: December 10, 2014

I. BACKGROUND:

The National Cancer Institute (NCI) has led the development of chimeric (ch) 14.18 for more than 20 years. Most recently, a randomized, controlled, Phase 3 study conducted by the Children's Oncology Group (COG) (ANBL0032 [DIV-NB-301]) found that when compared to standard therapy, Retinoic Acid (RA) alone, ch14.18 in combination with Granulocyte macrophage colony-stimulating factor (GM-CSF), Interleukin-2 (IL-2), and RA, significantly improved Event-free Survival (EFS) and Overall Survival (OS) estimates in subjects with high-risk neuroblastoma following successful completion of induction therapy, autologous stem cell transplantation (ASCT), and radiotherapy.

In July 2010, United Therapeutics Corporation (United), entered into a Cooperative Research and Development Agreement (CRADA) with the NCI to collaborate on the late-stage development and commercialization of ch14.18. As such, under the CRADA, United has exclusive rights to the clinical study data from all NCI-sponsored ch14.18 studies, including the pivotal Phase 3 Study ANBL0032 as well as the technical information needed to manufacture comparable ch14.18.

United seeks approval to market Unituxin (dintuximab, ch14.18) for the treatment of patients with high-risk neuroblastoma, a serious and life-threatening disease that primarily affects young pediatric patients. The key study supporting this application is Study ANBL0032 (denoted as Study DIV-NB-301 and Study DIV-NB-302 by the Applicant, United, due to use of separate data cut-off points to distinguish the randomized and subsequent single-arm portions of Study ANBL0032). Both DIV-NB-301 and DIV-NB-302 were open label, but DIV-NB-301 was the randomized portion of the ANBL0032 study. Randomization stopped on January 13, 2009. The data cutoff date for the study report for DIV-NB-301 is June 30, 2012.

For the single arm portion of the study (DIV-NB-302), the data cutoff date for the study report is December 31, 2013. Both studies are still ongoing (patients still under follow-up for the randomized portion and patients continuing to be enrolled in the single arm portion of the study). The applicant, United, did not conduct the pivotal study that provides data supporting this application.

According to the applicant, ch14.18 is a monoclonal antibody (mAb) composed of the variable region heavy and light chain genes of the murine mAb 14.18 and the human constant region genes for heavy chain immunoglobulin G1 (IgG1) and light chain kappa. ch14.18 reacts specifically with disialoganglioside (GD2) which is highly expressed on human tumors of neuroectodermal origin such as neuroblastoma and melanoma, and minimally expressed on normal human tissues.

Neuroblastoma is the most common extracranial solid tumor of childhood. It arises from primordial neural crest cells, with primary tumors most commonly occurring in the abdominal region. Patients diagnosed at less than one year of age and patients with localized tumors have a good prognosis; however, children with high-risk disease have a three-year survival of approximately 30%. The diagnosis of neuroblastoma is based on the presence of characteristic histopathological features of tumor tissue or the presence of tumor cells in a bone marrow aspirate or biopsy accompanied by raised concentrations of urine catecholamines. Computed tomography (CT) or magnetic resonance imaging (MRI) are the preferred methods for the assessment of tumor in the abdomen, pelvis, mediastinum, or in paraspinal lesions, respectively. For enhanced detection of tumor, radiolabeled-metaiodobenzylguanidine (MIBG) scintigraphy is used. Other methods are used to detect minimal residual disease such as bone marrow aspirates and biopsy, pathological evaluation and polymerase-chain reaction (PCR)-based techniques to identify GD2 synthase, tyrosine hydroxylase and protein gene product 9.5.

The Phase 3 Study ANBL0032 [DIV-NB-301] evaluated the effect of ch14.18 in conjunction with GM-CSF, IL-2, and RA and found this combination to be superior to standard therapy (RA alone) in subjects with high-risk neuroblastoma following successful completion of myeloablative chemotherapy, ASCT, and radiotherapy. This study forms the basis of primary evidence for the evaluation of safety and efficacy of ch14.18 when administered as described above to subjects with high-risk neuroblastoma. Further data on the use of ch14.18 in subjects with neuroblastoma is provided with data from the ongoing non-randomized portion of the ANBL0032 (DIV-NB-302) study which provided additional safety information.

This study is currently conducted under IND 110494 (Sponsored by United Therapeutics), and was previously conducted under IND 4308 (Sponsored by NCI/CTEP).

Four clinical sites were chosen for inspection: Site 1865 (Dr. Douglas Hawkins, Seattle, WA), Site 1946 (Dr. Maxine Hetherington, Kansas City, MO), Site 1866 (Dr. Leo Mascarenhas, Los Angeles, CA), and Site 1873 (Dr. Frank Balis, Philadelphia, PA), based upon the number of patients enrolled in the randomized and non-randomized portions of ANBL0032. Because of the large number of sites involved in the conduct of ANBL0032, no single site is likely to have driven the efficacy results. A review of protocol deviations, study discontinuations, and incidence of serious adverse events did not uncover a signal to facilitate site selection.

Because this BLA is primarily supported by a single study, assessment of data integrity is crucial to evaluating whether the evidence supporting approval represents substantial evidence of efficacy. Additionally, because the proposed treatment regimen of ch14.18 in combination with IL-2, GM-CSF, and RA has known serious risks (such as capillary leak syndrome and anaphylaxis) audits of representative sites to ensure that the safety data collected from this study were comprehensive and accurate is essential to the risk:benefit assessment of this application.

The original study sponsor, NCI/Cancer Therapy Evaluation Program (CTEP), was also inspected because this application is for a new molecular entity, and the majority of the clinical trial records were held at NCI/CTEP and not the new sponsor, United Therapeutics Corporation.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Douglas Hawkins Seattle Children's Hospital 4800 Sand Point Way Seattle, WA 98105	Protocol: DIV-NB-301 and DIV-NB-302 (ANBL0032) Site Number: 1865:WA061 Number of Subjects : 11 in DIV-NB-301 And 10 in DIV-NB-302	June 10, 2014 – July 2, 2014	Pending Interim classification: VAI
CI#2: Maxine Hetherington Children's Mercy Hospital 2401 Gillham Road Kansas City, MO 64108	Protocol: DIV-NB-301 and DIV-NB-302 (ANBL0032) Site Number: 1946: MO024 Number of Subjects : 9 in DIV-NB-301 And 3 in DIV-NB-302	June 23-27, 2014	Pending Interim classification: VAI
CI#3: Leo Mascarenhas Children's Hospital of Los Angeles USC Keck School of Medicine at CHLA Los Angeles, CA 90027	Protocol: DIV-NB-301 and DIV-NB-302 (ANBL0032) Site Number: 1866:CA009 Number of Subjects : 9 in DIV-NB-301 And 25 DIV-NB-302	June 17, 2014 – July 1, 2014	Pending Interim classification: NAI

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#4: Frank Balis Children's Hospital of Philadelphia 3501 Civic Center Blvd., CTRB-4024 Philadelphia, PA 19104	Protocol: DIV-NB-301 and DIV-NB-302 (ANBL0032) Site Number: 1873:PA076 Number of Subjects : 4 in DIV-NB-301 And 56 in DIV-NB-302	June 12, 2014 – July 7, 2014	Pending Interim classification: VAI
Sponsor: NCI/CTEP 9609 Medical Center Drive Bethesda, MD 20892	Protocol: DIV-NB-301 and DIV-NB-302 (ANBL0032)	June 16, 2014 – July 17, 2014	Pending Interim classification: OAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data appear unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and/or complete review of EIR is pending.

1. CI#1: Douglas Hawkins, M.D. (Site 1865)

- a. What was inspected:** The site initiated study ANBL0032 in 2002. The site screened a total of 56 subjects. Twelve subjects were enrolled in the ANBL0032 DIV-NB-301 study. Subject 730215 was enrolled and randomized to receive the investigational drug however, the family withdrew the consent. Of the eleven subjects who participated in the study, two were randomized to receive the RA only, seven were randomized to receive the investigational drug, and two were enrolled as per the Stratum 7 of the protocol and as such received RA+ anti-disialoganglioside (GD2), (Treatment 02). The subjects assigned to Stratum 7 are defined as having persistent disease documented by biopsy post-ASCT/XRT. According to the Protocol Section 11.0, Statistical Considerations, these subjects are excluded from the analysis of the comparison of the two treatment arms. Of the two subjects enrolled (as per the stratum 7 of the protocol) one subject (779194) discontinued the study drug due to adverse reaction to the study drug ch14.18. Beginning with Amendment 9b, dated April 16, 2009, subjects were no longer randomized. All subjects who enrolled after

this point were given the study drug. Ten subjects were enrolled in the non-randomized study (ANBL0032 DIV-NB-302) to receive the investigational drug. Accrual and follow-up of subjects is ongoing for this study.

The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. A comprehensive review was performed on records for subjects enrolled by 12/31/13. The record audit included informed consent documents, primary endpoint data (event free survival), adverse events (focused mainly on the SAEs, any AEs that are Grade 4 or above, and target toxicities, per FDA headquarters guidance), eligibility, randomization (as appropriate), AdEERS reporting, drug administration records, drug accountability records, laboratory reports, Form FDA 1572s and financial disclosures.

- b. General observations/commentary:** All informed consent documents for all enrolled subjects were reviewed with no issues observed. The IRB approved many versions of informed consent forms depending on the protocol amendments. No discrepancies were observed regarding the ICF elements. The IRB specifically stated in their approval letter whether the subjects must be re-consented. The subjects were re-consented only if they were receiving active drug treatment. All subjects' identification numbers, enrollment dates, randomization dates, study therapy received, treatment start and end dates and last contact dates were verifiable at the site.

The AEs and SAEs are reported in two independent systems, the COG remote data entry system (RDE) system and the AdEERs system. If the baseline toxicity increases during the course of the treatment the toxicity is reported as an AE in the RDE system. For the observed AEs (both targeted and non-targeted toxicities) a grade and attribution is assessed based on the specific protocol requirements in effect at the time. At this site there was no source documentation of the process used to grade and assess attribution for adverse events that occurred in the randomized subjects as reported to AdEERs or RDE. There was no evidence of underreporting of adverse events. Background data listings for AEs, submitted in the application and provided with the assignment, were compared with the source records present at the site for all enrolled subjects. Some of the SAEs were not reported according to the protocol specified timeframe. Seven (Table 1) AEs reported by the site to the sponsor were not part of the data listings provided as inspectional background material.

Table 1. Site reported AEs, not included in the BLA 125516 AE data listings.

Subject #	Event Type	Date onset	Grade	Attribution
825401	Skin and subcutaneous tissue disorders --Urticaria	(b) (6)	Moderate	Probable
825401	Urine output decreased	(b) (6)	Severe	Probable
825401	Urine output decreased	(b) (6)	Severe	Probable
825401	Urine output decreased	(b) (6)	Severe	Probable
825401	Skin and subcutaneous tissue disorders ---Urticaria	(b) (6)	Moderate	Probable
834631	Urine output decreased	(b) (6)	Severe	Probable
834631	Urine output decreased	(b) (6)	Severe	Probable

OSI Reviewer Notes: The protocol specifies that AEs are to be reported only if they are Grade 3 or higher, or if they are one of the targeted toxicities pre-specified in the protocol. Targeted toxicities include allergic reactions and anaphylaxis, hypotension, urticaria, adult respiratory distress syndrome (ARDS), dyspnea, cytokine release syndrome/acute infusion reaction, and capillary leak syndrome. These observations were discussed with the review division Medical Officer Martha Donoghue and she informed that AE reporting was limited as described above and that sites were instructed to report the primary AE and not the secondary related events. For example, decrease in urine output is likely related to hypotension, and urticaria is likely related to an allergic reaction. Subject 825401 AE data listings find that this subject had an AE reported as hypotension on (b) (6). Likewise, Subject 834631 AE data listings find that this subject had AE reported as hypotension on (b) (6) and again on (b) (6). While the site reported these AEs as discrete events, they are likely secondary to a primary AE that was also reported to the sponsor. However, the review division may consider these observations and confirm that they should not affect overall study outcome.

Apart from two possible data discrepancies described below, the primary efficacy endpoint data were verifiable. Briefly, Subject 714449 was enrolled and randomized on July 10, 2002 to receive the study drug but withdrew the consent and was discontinued from this study on (b) (6) (study day (b) (6)). The subject source documents confirm that the subject did not receive the immunotherapy and no data was entered into the COG RDE system. However according to the data listing for derived efficacy parameters this subject had an overall and event free survival in days (3816).

Subject 779194 was enrolled to receive the study drug ch14.18 (Stratum 7, per protocol). The subject experienced bronchospasm within 60 minutes of the first ch14.18 infusion on [REDACTED]^{(b) (6)}. No additional ch 14.18 was given to the patient due to the adverse event related to the drug. Subject 779194 discontinued the immunotherapy and decided to get CIS RA outside of protocol. However, overall (675 days) and event free survival (513 days) was reported for this subject in the data listings submitted to the application.

OSI Reviewer Notes: According to the Protocol Section 11.0, Statistical considerations, Subject 779194 (Stratum 7) is excluded from the analysis of the comparison of the two treatment arms, and is not considered evaluable. The review division may consider the impact of Subject 714449 efficacy data on overall study outcome, and censor as appropriate.

A Form FDA 483 was issued to Dr. Douglas Hawkins citing two inspectional observations. The site failed to report SAEs and disease relapse according to the protocol specified timeframe and lacked records that document the process used to grade and assess attribution of adverse events in randomized subjects.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

1. Serious Adverse Events were not reported to NCI Web-based Adverse Event Expedited Reporting System (AdEERS) within the protocol required time frame.
 - I. Protocol ANBL0032 Amendment 1, dated June 14, 2002 and Amendment 4B dated May 20, 2004 state “an expedited report is to be submitted via AdEERS web-based application within 7 working days of learning of the event.”
 - a) For Subject 744693 grade 3 confusion, grade 2 tremors, chills and edema of face and limbs occurred on [REDACTED]^{(b) (6)}. These events were reported to the NCI Web-based AdEERS on [REDACTED]^{(b) (6)}.
 - b) For Subject 719535 a grade 3 hypoalbuminemia and a grade 4 fever occurred on [REDACTED]^{(b) (6)}. These events were reported to the NCI Web-based AdEERS on [REDACTED]^{(b) (6)}.

OSI Reviewer Notes: These late AE reports do not represent a systemic trend at this site. The vast majority of reportable AEs were reported within the protocol specified timeframes. These events were reported late but are represented in the current application data listings.

- II. Protocol ANBL0032 Amendment 5, dated July 25, 2005 and Amendment 8 dated May 12, 2008 state “an expedited report is to be submitted via AdEERS web-based application within 5 working days of learning of the event.”

- a) For Subject 775336 a grade 3 diarrhea occurred on [REDACTED] (b) (6). It was reported to the NCI Web-based AdEERS on [REDACTED] (b) (6).
- b) For Subject 744693 a grade 3 infection with grade 3 or 4 neutrophils (ANC<1.0 x 10e9/L) catheter related occurred on [REDACTED] (b) (6). It was reported to the NCI Web-based AdEERS on [REDACTED] (b) (6).

OSI Reviewer Notes: These late AE reports do not represent a systemic trend at this site. The vast majority of reportable AEs were reported within the protocol specified timeframes. These events were reported late but are represented in the current application data listings.

2. A relapse report was not submitted in the Children's Oncology Group (COG) Remote Data Entry System (RDE "Within 2 weeks of relapse" for the below mentioned subjects:
 - a) For Subject 779194 the disease relapsed on [REDACTED] (b) (6), but wasn't reported in the COG RDE until [REDACTED] (b) (6).
 - b) For Subject 744693 the disease relapsed on [REDACTED] (b) (6), but wasn't reported in the COG RDE until [REDACTED] (b) (6).
 - c) For Subject 825862 the disease relapsed on [REDACTED] (b) (6), but wasn't reported in the COG RDE until [REDACTED] (b) (6).
 - d) For Subject 813183 the disease relapsed on [REDACTED] (b) (6), but wasn't reported in the COG RDE until [REDACTED] (b) (6).

Observation 2. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically, for the randomized subjects there are no records that document the process used to grade and assess attribution of adverse events. There are no records that document the clinical investigator's review and evaluation of adverse event reports.

OSI Reviewer Notes: The late reporting of AEs and relapses to the sponsor by this site should not importantly impact overall safety and efficacy study outcome. All of these events were reported to the study sponsor and are represented in the application appropriately. The site has since developed corrective actions to minimize the reoccurrence of these inspectional observations moving forward.

Regarding Observation 2, source documentation of the PI/site process for determination of AE grading was lacking. Notwithstanding this inspectional observation, the site staff, in particular, the PI in practice, Dr. Park, determined and entered or had her staff enter AEs with a grade level into the electronic record but the paper/source records were difficult to review because documentation of all factors that might influence the grading and attribution of event were lacking. The FDA field investigation team reported that Dr. Park had reasonably good control over the general conduct of the study over time, and found no evidence that suggests the process of review/grading and reporting of the AEs was corrupt.

According to site staff, the documentation of clinical investigator review and evaluation of AEs and AE reports is an issue that the site has focused significant process improvements on over the past decade. Current practices at this site should minimize the reoccurrence of these inspectional observations moving forward.

Individual Responsibility:

The site methods and documentation for oversight and individual responsibility deviate from established practices typically employed by sponsors and principal investigators in the conduct of clinical research. Typically, each site has a single principal investigator, identified and trained by the sponsor, with overall responsibility for the conduct of the specific study in accordance with 21 CFR 312, and signs the Statement of Investigator, Form FDA 1572 [1572], for the sponsor of the study. The 1572 is typically updated as needed or annually by the PI. Cancer-directed clinical studies sponsored by NCI, more specifically, the Division of Cancer Treatment and Diagnosis [DCTD], NCI, NIH follow a different procedure apparently defined in the DCTD, NCI, NIH Drug Master File (DMF) #2803 Type V. DMF 2803 was established with FDA originally in 1976, has been active since that time, and has been amended numerous times (over 40). The most recent update occurred in February 2014. It is unclear when the procedures regarding study oversight and control at each site were added to the DMF. According to the site NCI studies require that at each research institute that conducts clinical research sponsored by NCI retain a single Principal Investigator who is responsible for all NCI sponsored clinical research at the host institute. The role is referred to as the “COG PI” or “Institutional PI”. The Institutional PI is responsible, among other things, for delegating authority for the conduct of a specific study to another PI at the host institute. The delegate is referred to as the Study PI. The Study PI then proceeds to conduct the study in accordance with GCP as per 21 CFR 312.

However, it should be noted that all persons associated with the conduct of a clinical study under these procedures signs their own 1572 as a PI and files annually with the NCI. There are no sub-investigators, and the 1572 is not study specific, but instead simply states that the signatory is “participating in National Cancer Institute sponsored clinical trials”, under section 7 of the 1572, and under section 9, Commitments, there is no study identified.

Study ANBL0032 was sponsored by the COG/NCI; Dr. Hawkins was identified as the COG PI or institutional PI at SCH. As such, Dr. Hawkins is responsible for all COG studies at the SCH. Dr. Hawkins replaced Dr. Russell Geyer as the hospital’s COG PI in September 2003.

Dr. Hawkins serves in multiple roles at SCH, including:

- Associate Director, Center for Clinical and Translational Research at SCH
- Clinician at SCH
- Professor, University of Washington School of Medicine
- Children's Oncology Group (COG) Principal Investigator (PI) at SCH
- Chair of the COG Soft Tissue Sarcoma Committee
- Chair of the COG Scientific and Discipline Chairs Committee

- The COG Chair of two clinical trials: Ewing sarcoma, and Rhabdomyosarcoma.
- Serves on the following COG steering committees
 - Soft Tissue Sarcoma
 - Bone Tumor
 - Voting Body
- Dr. Hawkins is listed as PI on an extensive listing of clinical studies (COG and Non-COG)

For Protocol ANBL0032 the lead or "study PI" is currently Dr. Julie R. Park. Dr. Park is an attending physician at SCH, associate professor in pediatrics at the University of Washington School of Medicine and an associate in the Clinical Research Division at Fred Hutchinson Cancer Research Center. Dr. Park is an active member of the COG consortium and as Chair of the COG Neuroblastoma Scientific Committee provides leadership for the development of neuroblastoma clinical research within the COG. Her primary research focus has been investigating novel therapies for the treatment of high-risk neuroblastoma.

Dr. Park oversaw each study subject's treatment and overall care while in the clinical trial. She conducts real-time review, or delegates to her sub-investigators, of subject's clinical status (including review of all laboratory data) for all subjects actively receiving ANBL0032 protocol therapy. Dr. Parks also communicates with all sub-investigators and CRAs pertinent patient care information relevant to grade and attribution of toxicities according to the protocol specified CTCAE version. Dr. Parks maintains very good oversight and control of the overall conduct of the study.

Additional observations discussed with the site:

1. There are no records that document the delegation of roles and responsibilities by the Children's Oncology Group Principal Investigator for the conduct of the ANBL0032 Study.
2. Not all sub-investigators, nurse practitioners etc. involved in the study are listed on the FDA 1572 or have signed FDA 1572.
3. Not all personnel involved in the study had signed a financial disclosure statement. However since 2012, all investigators are required to sign financial disclosure.
4. The protocol ANBL0032Amendment No: 9 version dated April 16, 2009 states "Agent Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the lot numbers of drug dispensed to study patients of all commercial supplies of Aldesleukin using the NCI Drug Accountability Record Form (DARF)". No records are maintained of the lot numbers of commercial supplies of Aldesleukin drug dispensed to the study patients from approximately April 2009 to October 2011.
5. No records are maintained by the pharmacy that documents the calculation and preparation of Aldesleukin (interleukin-2, IL-2) doses. The doses were calculated electronically and the dosage calculations are not saved as part of the source documents.

6. No records are maintained by the pharmacy that documents the preparation and filtration (using [REDACTED]^{(b) (4)} syringe filter) of the Chimeric 14.18 infusion in the randomized subjects.
 7. According to the protocol, study drug vials (empty or partially empty) used to prepare each chimeric 14.18 infusion should be retained in the pharmacy and held at 2-8°C in quarantine for one week. The vials should be segregated and labeled with a unique identifier and date of infusion for later reference. If, after one week, the patient has not experienced a Grade 4 serious adverse event (SAE), the vials may be discarded per standard institutional policy. There is no documentation that the vials were segregated and labeled with a unique identifier and date of infusion for later reference. Therefore, this practice could not be verified during the inspection.
 8. Record management issue: For subjects 719535, 740177, 721547, 730215, 754789, 744693, and 733222, the study records were stored on Microfiche. The records on the microfiche are not arranged in a chronological order and there is no index or table of contents for the microfiche, making it very difficult to access and assess subject records stored on Microfiche.
 9. The clinical laboratory reports of the subjects are not reviewed for out of range values by the investigator for their clinical significance.
- c. Assessment of data integrity:** Notwithstanding the inspectional observations noted above, the data for Dr. Hawkins' site, associated with Study ANBL0032 submitted to the Agency in support of BLA 125516, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator(s) and limited review of the EIR. An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

2. CI#2: Maxine Hetherington, M.D. (Site 1946)

- a. What was inspected:** The site initiated study ANBL0032 in 2003. The site enrolled nine subjects into the original protocol through to Amendment 8 of the protocol dated May 12, 2008 (Study DIV-NB-301). Beginning with Amendment 9b, dated April 16, 2009, subjects were no longer randomized. All subjects who enrolled after this point were given the study drug. The site screened and enrolled five subjects into this non-randomized portion of the study (Study DIV-NB-302), two of which were enrolled after the primary analysis data cut-off point of December 31, 2013. Eleven subjects completed all 6 courses of treatment, one subject withdrew early due to progressive disease, two subjects were still undergoing treatment, and three subjects had expired. The non-randomized portion of the study is ongoing with enrollment open at this time.

A comprehensive review was performed on records for all fourteen subjects. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The FDA field investigator reviewed source study records and pertinent medical records and compared them to the data listings submitted to the application. The record audit included informed consent documents, in-patient and outpatient medical records, laboratory reports, pathology reports, imaging and surgical reports, primary endpoint data (event free survival), adverse events (focused mainly on the SAEs, any AEs that are Grade 4+, and target toxicities (per FDA headquarters guidance), eligibility, randomization (as appropriate), AdEERS reporting, and drug accountability and administration records.

- b. General observations/commentary:** The inspection revealed no significant systemic deficiencies. Records and procedures were clear, and generally well organized. Review of data in source documentation matched information provided in the data listings submitted to BLA 125516 with a few exceptions, and most adverse events were accurately reported in accordance with the protocol. The primary efficacy endpoint data were verifiable. However, there were some deficiencies noted regarding protocol deviations and AE reporting. There were no protocol-directed reporting requirements for notifying the sponsor or the local IRB of protocol deviations and no place to enter such events on the CRF. Since there appears to be no systematic site monitoring for GCP compliance and source data verification, the sponsor was not aware of protocol deviations that may have occurred at this or any site, by their own design.

The site was very organized and conscientious; however there was no clear delegation of duties for Sub-Investigators and Co-Investigators or sufficient records to show all that worked on the study were protocol trained. Therefore, AE grading and attribution were inconsistent. The site does not have an internal quality control system to ensure data submitted electronically matches the source documents and there was insufficient monitoring with only 1 true monitoring visit in 12 years of the study.

These site practice issues appear to be due to the NCI/COG sponsor-driven deficiencies in procedures for oversight and control of study conduct. Briefly, there is no site monitoring program, Form FDA 1572s are not complete in that there is no attribution to a particular study, there are no documented sub-investigators on a COG study, no duty delegation logs, and no required documentation of protocol deviations.

Review of source documentation for consent, eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. As with other sites inspected it was noted that the sponsor does not perform monitoring visits at the site for the specific protocol; therefore, monitoring activities were not reviewed. A Form FDA 483 was

issued citing one inspectional observation. In addition, there were a number of items that were discussed with clinical investigator.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator.

Specifically,

There were delinquent reports of SAEs to the IRB and a failure to report targeted toxicities and dose reductions/discontinuations to the sponsor. In addition, you did not have a system, such as a duty delegation/signature log that assures all study personnel are protocol trained and aware of their responsibilities and that Co-Investigators have signed a Form FDA 1572 (1572) for the protocol, thereby attesting to their duty to adhere to the protocol and applicable regulations prior to working on the study.

1. You did not obtain a completed and signed investigator agreement (1572) for (b) (4) until January 7, 2009. Nor was she listed as a Sub-Investigator on the Principal Investigator's 1572 (Dr. Hetherington). (b) (4) was the primary study physician for Subject 779065 who was consented on (b) (4) and was on the non-randomized study regimen B from (b) (4) to (b) (4). (b) (4). (b) (4) also evaluated Subject 774291 on (b) (4) (Course 3, Regimen A).

OSI Reviewer Notes: GCP regulations require all clinical investigators be identified by the sponsor, have their qualifications verified by the sponsor, and have documentation submitted to the sponsor on the Form FDA 1572. This is the process by which a sponsor maintains control over who is conducting investigator specific tasks on a specific clinical research investigation. Briefly, the 1572 has two purposes: 1) to provide the sponsor with information about the investigator's qualifications and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the clinical investigation, and 2) to inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations. Dr. Hetherington provided a written response to the inspection observation and concurs with the seriousness of this violation. She has since developed corrective actions as a follow-up to the inspection and is in the process of implementation.

2. All versions of the protocol required Institutional Review Board (IRB) notification of SAEs. Your IRB required "any adverse events that are serious (SAEs), unexpected, and in any way related to the study" be reported to the IRB Chairperson and sponsor by phone within 24 hours and a written report submitted within 5 working days. Serious was defined "as an event that is fatal or life-threatening, results in permanent disability, requires or prolongs hospitalization, or which results in a congenital anomaly/birth defect in the offspring of a study subject".

- a. Subject 837988 was admitted to the hospital on [REDACTED] (b) (6) during Course 2, Regimen B due to seizures attributed to Posterior Reversible Encephalopathy Syndrome (PRES). The root cause of the PRES was hypertension. The subject remained hospitalized through [REDACTED] (b) (6) and was treated with anti-seizure and antihypertensive medication. The subject was released from the hospital with continuing oral anti-seizure and anti-hypertension medications. The IRB was not notified until [REDACTED] (b) (6).
 - b. In addition to this omission for Subject 837988, on the eCRF submitted to the sponsor, you did not include these additional five days in the hospital or the five days of RA doses that were missed during the SAE/hospitalization. You only reported the four days required for infusion of the study drug.
 - c. Subject 780672 began Course 2 of Regimen A on [REDACTED] (b) (6) and was hospitalized from [REDACTED] (b) (6) for a gram negative rod infection. The SAE report was not created until [REDACTED] (b) (6) and wasn't signed off by the Principal Investigator until [REDACTED] (b) (6).
3. COG required reporting of all targeted toxicities which included capillary leak syndrome. On [REDACTED] (b) (6) Subject 722400 was admitted for infusion of the study drug. While hospitalized she experienced capillary leak syndrome requiring increased intravenous fluids, albumin and a reduction in her infusion time from 5 to 10 hours for the last 3 days of treatment. Capillary leak syndrome was not reported on the Targeted Toxicity report submitted to COG.
 4. Subject 756911 was admitted for Course 4 IL-antibody therapy on [REDACTED] (b) (6) and the first infusion was [REDACTED] (b) (6). On [REDACTED] (b) (6), they reduced the IL dose by 50% due to hypotension and then had to discontinue dosing according to a progress note dated [REDACTED] (b) (6). There is a nurse's note on the dosing chart that states the IL was decreased to 50% on [REDACTED] (b) (6) and prematurely discontinued on [REDACTED] (b) (6). You failed to report the dose reduction on the eCRF.

OSI Reviewer Notes: The site is committed to developing corrective actions to minimize the reoccurrence of these inspectional observations moving forward. Although many of the protocol versions provided instructions for changes in dose/infusion times for study drugs if toxicity was observed and therefore technically not protocol violations, it is concerning to note that two subjects had their infusion time increased or dose reduced in response to such reactions. It is not clear whether this information was communicated or would be important for the review division to be aware of.

Individual Responsibility:

As described above for Clinical Investigator #1, the site methods and documentation for oversight and individual responsibility deviate from established practices typically employed by sponsors and principal investigators in the conduct of clinical research.

Study ANBL0032 was sponsored by the COG/NCI; Dr. Hetherington was identified as the COG PI or institutional PI at the Children's Mercy Hospital (CMH) in Kansas City, MO. As such, Dr. Hetherington is responsible for all COG studies at the CMH. For Protocol ANBL0032 the lead or "study PI" was also Dr. Hetherington.

Additional observations discussed with the site:

1. They did not have an effective system in place to assure everyone working on the study is protocol trained and the FDA 1572s are accurately completed with all relevant individuals included.
 2. Investigational drug accountability records should be maintained within the study file and should account for all used, unused and partial containers of product from receipt to final disposition. For safety and consistency, it is good practice to at least record the lot numbers for comparator drugs in an investigational protocol even when the drug is commercially available.
 3. The firm had not been consistent with obtaining and providing financial disclosures for the physicians on this study.
 4. The site requested a waiver for enrollment of a subject outside the protocol's specifications for granting waivers. Although the sponsor granted the waiver, this was not done per protocol.
 5. The sponsor did not provide regular monitoring of this study and the site did not verify source data was accurately transcribed into the records submitted to the sponsor.
 6. The protocol required grading Adverse Events by the Common Terminology Criteria for Adverse Events (CTCAE) published by NCI. In general, there was inconsistency in grading the AEs and rarely was a CTCAE grade number assigned.
 7. Inconsistent AE grading and assessment resulted in a failure to report what appeared to be Capillary Leak Syndrome in one subject.
 8. The incorrect regimen was assigned to a blood sample sent to the central lab.
 9. The site inaccurately reported subject status in continuing review submissions to the IRB.
- c. Assessment of data integrity:** Notwithstanding the inspectional observations noted above, the data for Dr. Hetherington's site, associated with Study ANBL0032 submitted to the Agency in support of BLA 125516, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and limited review of the EIR. An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

3. CI#3: Leo Mascarenhas, M.D. (Site 1866)

- a. What was inspected:** The site initiated study ANBL0032 in 2003. The site screened 10 subjects into the original protocol through to Amendment 8 of the protocol dated May 12, 2008 (Study DIV-NB-301). Ten subjects were enrolled in that portion of the study with one (Subject 778342) of the ten withdrawing consent when he was randomized to the RA-only (retinoic acid) treatment arm. Beginning with Amendment 9b, dated April 16, 2009, subjects were no longer randomized. All subjects who enrolled after this point were given the study drug. The site screened and enrolled 25 subjects into this non-randomized portion of the study (Study DIV-NB-302) up to the primary analysis data cut-off point of December 31, 2013. This portion of the study is ongoing with enrollment open at this time. A comprehensive review was performed on records for 35 out of 35 subjects enrolled by 12/31/13. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included informed consent documents, primary endpoint data (event free survival) by reviewing all CT scans, bone marrow evaluations, bone scans, MIBG scans and MRIs available for the subjects from enrollment into the study to the reported relapse date or the last contact date (if no relapse occurred), adverse events (focused mainly on the SAEs, any AEs that are Grade 4, and target toxicities (per FDA headquarters guidance), eligibility, randomization (as appropriate), AdEERS reporting, drug administration records, drug accountability records, and laboratory reports.
- b. General observations/commentary:** The source documents consisted of in-patient hospital records and outpatient clinic visit records. These were paper records that were gradually transitioned to the hospital's electronic medical records system beginning in 2006. Records were complete, accurate, and generally organized. There was adequate documentation to ensure that all subjects were alive and available for the duration of their stated participation in the study. There was no evidence of underreporting of adverse events. Primary efficacy endpoint data were verifiable. Review of data in source documentation matched information provided in the data listings submitted to BLA 125516 with a few minor exceptions, and adverse events were accurately reported. A Form FDA 483 was not issued.

Individual Responsibility:

As described above for Clinical Investigator #1, the site methods and documentation for oversight and individual responsibility deviate from established practices typically employed by sponsors and principal investigators in the conduct of clinical research.

Study ANBL0032 was sponsored by the COG/NCI; Dr. Mascarenhas was identified as the COG PI or institutional PI at the CHLA. As such, Dr. Mascarenhas is responsible for all COG studies at the CHLA. Dr. Mascarenhas has been an Attending Physician at the CHLA since 1998. He specializes in

pediatric hematology and oncology and has been involved in research studies since 1998. Dr. Mascarenhas replaced Dr. Paul Gaynon as the hospital's COG PI in April 2008.

Dr. Mascarenhas serves in multiple roles at the CHLA, including:

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For Protocol ANBL0032 the lead or "study PI" is currently Dr. Marachelian.

Noteworthy observations and those discussed with the site included two subjects who discontinued prior to receiving study drug, several late AdeERS reports, misdosing protocol deviations that were reported to the IRB but not the sponsor, some inaccurate laboratory data reporting in the data listings for WBCs due to failure to convert units from that reported by the local laboratory and that reported by the sponsor in the application data listings, and lack of training documentation for site personnel. Briefly,

1. The following protocol deviations in dosing were reported to the IRB but not to the sponsor.
 - a. On [REDACTED], Subject 784320 was infused with 88 mL of an incorrectly prepared dose of the chimeric antibody ch14.18. The patient was to be infused with a bag of GM-CSF (sargramostim) and a bag of the chimeric antibody ch14.18 separately. The pharmacy technician incorrectly mixed the chimeric antibody ch14.18 and the GM-CSF into the same bag for infusion. The bag was labeled as "Ch14.18 in Normal Saline" so it was administered to the patient until the error was identified in the pharmacy. At that point, the subject had been incorrectly infused with 88mL of the mixed product. No adverse events were observed to take place subsequent to this infusion. Additionally, commercial GM-CSF was used by the pharmacy instead of the investigational supply.
 - b. On June 6, 2006, during a clinic visit, it was discovered that Subject 815635 was not being given the correct dose of isotretinoin by her mother. The Subject was to be given 20 mg in the morning and 30 mg in the evening for 14 days. On day 8, the subject was seen in the clinic and it was discovered that the mother was only giving the subject 10 mg in the evening.
 - c. On [REDACTED], Subject 830554 was incorrectly prescribed 100 mg/day of isotretinoin instead of 130 mg/day as required by the protocol. The subject completed his 14-day course with the incorrect dose. On [REDACTED], the subject was started on his Course 3 isotretinoin even though his ALT was six times the normal limit. Per the protocol, ALT must be less than 5 times the normal

limit to begin a course of treatment. The subject completed the 14-day course prior to this discovery by the site.

OSI Reviewer Note: According to the EIR, the FDA field investigator discovered these dosing protocol deviations when reviewing the IRB reportable events. The FDA field investigator queried the site staff on this observation and was told that only major deviations are to be reported to the sponsor and that these were not considered major protocol deviations. However, the site could not produce documented guidance, either within the protocol, or additional sponsor-directed procedural guidance that provides clear reporting requirements for PDs and specifically defines a major PD versus a minor PD. The site staff informed that they do not have any specific directives from the COG on PD reporting, and that there is no reporting mechanism in the eCRFs for reporting PDs to the sponsor.

2. Subject 778342 withdrew consent on Day 1 because he was randomized to RA only therapy. The subject did not undergo any therapy under this protocol; instead, he went to another hospital to enroll in a different study. As such, the EFS date reported for this subject may not properly reflect a study endpoint.
3. Subject 743731 was randomized to RA only therapy. However, the subject passed away before receiving any protocol therapy.
4. The firm had two late AdEERS reports. However, these were the only observed instance of delayed reporting to AdEERS and the IRB, amongst many others that were reported in a timely manner.
 - a. Subject 776291 had a Grade 4 fever without hospitalization on October 8, 2008 for more than 24 hours which was required to be reported within 5 calendar days per the protocol. This was not submitted to NCI until January 20, 2010, more than 14 months after the event. Dr. Marachelian explained that this had been an oversight. She stated that fevers often occur and was an expected toxicity at this point in the treatment and they had just overlooked the reporting requirements.
 - b. Subject 776003 had a Grade 4 anaphylaxis adverse event on (b) (6), which requires reporting to NCI via AdEERS within 5 calendar days. The report was not submitted to NCI until (b) (6) 6 days out of window. This adverse event was not reported to the IRB until (b) (6), which was outside of the 5 calendar day reporting timeframe for unexpected serious adverse events. Dr. Mascarenhas and Dr. Marachelian explained that this was due to a misunderstanding on the part of the research nurse at the time. They stated that she was under the misunderstanding that all information from the event needed to be obtained prior to submitting the report. Dr. Mascarenhas provided a copy of the email correspondence to the study team advising that AdEERS should

always be submitted on time and that supplemental information can be provided later as an amendment to the report.

5. The FDA field investigator observed that a large number of the laboratory data for white blood cells (WBC) was inaccurately reported on the CRFs because a conversion of the values was not done. The data found under WBC in the data listings provided with the assignment reports the WBC in uL. The values listed in the laboratory reports at the site were reported in "K/uL". Most of the WBC data reported by the site did not include the necessary conversion of values and was therefore inaccurately reported.

OSI Reviewer Note: The review division may consider the impact of these WBC unit errors on overall study outcome. Additionally, the division may request the sponsor to amend the datasets where these errors occurred at this site and confirm accurate reporting of WBC units for all sites in the study, as appropriate.

6. With respect to training of study staff the FDA field investigator was unable to determine what training was provided to the site upon study initiation in 2003. The site had no records or documentation of the training. Dr. Mascarenhas and Dr. Marachelian were not involved in the study when it began. However, sign-in sheets and signatures for individuals who were trained in the changes for Amendment #16A dated 12/04/13, were observed. Dr. Marachelian stated that they only recently began using these training tracking forms. Study staff stated that all training would be documented similarly from now on.

OSI Reviewer Note: The FDA field investigator informed that this site and staff, past and present, appear to have generally run the study in accordance with the protocol and sponsor guidelines. However, training of the principal investigator and sub-investigators could not be verified.

7. With respect to Pharmacy access, the hospital pharmacy houses commercial and investigational drugs. It is a restricted access area where only pharmacy personnel can enter without being escorted. However, the storage of investigational drugs is not restricted in access once in the pharmacy area. Anyone in the pharmacy area has access to the investigational drugs. The hospital is limited in space so they have to share storage units with the regular pharmacy. This pharmacy configuration allows for possible use of the investigational drugs by someone who is not involved in research activities. However, no such misuse of study drugs was observed.
8. The site had a delayed submission of Protocol Amendment 4b for IRB Approval. Protocol Amendment 4b, dated May 20, 2004, was posted to the COG website on June 7, 2004. Study staff explained that once an amendment is posted to the COG website, it is the site's responsibility to submit the amendment to their IRB for review and approval. The site did

not submit the amendment to the IRB until September 23, 2004, 3.5 months later. As such, the IRB approval was delayed until October 15, 2004 for the site.

OSI Reviewer Note: While this is clear lack of oversight on the part of study site staff, the changes to the protocol were mostly administrative. The most significant change for study sites was in the eligibility of subjects; however, the change was in the removal of certain restrictions in eligibility and not the addition of any, so the delay in obtaining IRB approval should not have placed subjects at greater risk, or importantly affected study outcome.

- c. Assessment of data integrity:** Notwithstanding the inspectional observations noted above, the data for Dr. Mascarenhas' site, associated with Study ANBL0032 submitted to the Agency in support of BLA 125516, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and limited review of the EIR. An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

4. CI#4: Frank Balis, M.D. (Site 1873)

- a. What was inspected:** The site initiated study ANBL0032 in 2003. The site screened 4 subjects into the original protocol through to Amendment 8 of the protocol dated May 12, 2008 (Study DIV-NB-301). Four subjects were enrolled in that portion of the study. Beginning with Amendment 9b, dated April 16, 2009, subjects were no longer randomized. All subjects who enrolled after this point were given the study drug. The site screened 64 and enrolled 62 subjects into this non-randomized portion of the study (Study DIV-NB-302), six of which were enrolled after the primary analysis data cut-off point of December 31, 2013. One subject was not eligible and failed screening due to progressive disease. Another subject enrolled on another study. This portion of the study is ongoing with enrollment open at this time. Thirty seven subjects completed all 6 courses of treatment, eight subjects completed 5 courses, nine subjects relapsed while on study, three subjects transferred to another COG site, two subjects' physician terminated treatment, six subjects are currently receiving treatment, and one subject refused further therapy.

A comprehensive review was performed on records for four subjects from the randomized portion of the study and 16 subjects enrolled in the non-randomized portion of the study. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included informed consent documents, primary endpoint data (event free survival), adverse events (focused mainly on the SAEs, any AEs that are Grade 4+, and target toxicities (per FDA headquarters guidance), eligibility, randomization (as

appropriate), AdEERS reporting, drug administration records, drug accountability records, and laboratory reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. Review of data in source documentation matched information provided in the data listings submitted to BLA 125516 with a few minor exceptions, and adverse events were accurately reported. The majority of adverse events were reported in accordance with the protocol. There were minor deficiencies noted regarding inclusion/exclusion criteria and AE reporting. There were several Grade 4 AE's for 1 subject that were not reported until the current inspection. There were other Grade 4 AEs that were not promptly reported to the Sponsor. It is noted that that most Grade 4 AE's were laboratory related.

Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. As with other sites inspected it was noted that the sponsor does not perform monitoring visits at the site for the specific protocol; therefore, monitoring activities were not reviewed. A Form FDA 483 was issued citing two inspectional observations. The most notable deficiencies involved not following the protocol, specifically the lack of prompt adverse event reporting to the Sponsor. Additionally, a subject was enrolled that received a stem cell transplant outside the required timeframe. This is allowable if the study chair is notified by day 77. The site notified a committee member, not the chair, on day 91. Lastly, a subject was not re-consented in accordance with the protocol following the change in ch14.18 administration.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

The following procedures as part of study protocols DIV-NB-301 (COG Protocol ANBL0032-Randomized), and DIV-NB-302 (COG Protocol ANBL0032-Non-Randomized), were not always followed. For example:

- a) Subject 814123 experienced grade 4 hyperglycemia with a lab value of 796 mg/dL (74 - 127 mg/dL, normal lab value), grade 4 hypocalcaemia with a lab value of 6.3 mg/dL (8.7 - 9.8, normal lab value), and grade 4 hyponatremia with a lab value of 108 mmol/L (138 - 145 mmol/L, normal lab value) on [REDACTED] (b) (6), during course 2 of the study. These adverse events are required to be reported within 5 calendar days and were not reported to the sponsor until [REDACTED] (b) (6).

OSI Reviewer Note: Dr. Balis responded in writing that this particular set of laboratory values is very likely due to a technical problem with the blood draw. Blood samples are drawn through a central line that has dextrose containing fluids infusing and if the line isn't completely cleared of IV fluids prior the blood draw, the blood sample will be diluted with IV fluids causing this exact type of result. A second sample was drawn approximately 5 hours later, with near normal findings; the glucose final result was 95 mg/dL (within normal limits), the sodium value was 132 mmol/L (grade 1), and calcium value was 7.6 mg/dL (grade 2), all of which were not reportable per protocol. However, all AEs were entered into AdEERS during the current FDA inspection.

- b) Subject 814123 experienced a grade 4 seizure, grade 4 intracranial hemorrhage, grade 4 paralysis, and grade 4 depressed levels of consciousness on [REDACTED] (b) (6), during course 6 of the study. These adverse events are required to be reported within 5 calendar days and were not reported to the sponsor until [REDACTED] (b) (6).
- c) Subject 814123 experienced grade 4 elevated levels of Gamma-glutamyl transpeptidase (GGT) with a lab value of 426 U/L (5 -16 U/L, normal lab value) on [REDACTED] (b) (6), during course 2 of the study. This adverse event is required to be reported within 5 calendar days and was not reported to the sponsor until [REDACTED] (b) (6).
- d) Subject 802513 experienced grade 4 lymphocyte count decrease with a value of 345 ul on [REDACTED] (b) (6). This adverse event is required to be reported within 5 calendar days and was not reported to the sponsor.
- e) Subject 799183 experienced grade 4 elevated levels of Gamma-glutamyl transpeptidase (GGT) with a lab value of 490 U/L (5 -16 U/L, normal lab value) on [REDACTED] (b) (6). This adverse event is required to be reported within 5 calendar days and was not reported to the sponsor until [REDACTED] (b) (6).
- f) Subject 769672 was not enrolled between day 50 and day 77 post- ASCT as required by the protocol. The subject received stem cell infusions on [REDACTED] (b) (6) and [REDACTED] (b) (6). The subject was enrolled on [REDACTED] (b) (6) day 91 post ASCT.

OSI Reviewer Note: Dr. Balis responded in writing that these protocol violations are valid for the most part and that the organization has been instituting process improvements since they began enrolling subjects in 2006. The mis-reported AEs and protocol deviations should be noted by the review division and included in data analysis as appropriate. It is unlikely that these events will importantly impact overall study outcome.

Observation 2. Informed consent was not properly documented in that the written informed consent used in the study was not signed by the subject or the subject's legally authorized representative at the time of consent.

Specifically, Subject 778828 was consented on [REDACTED] (b) (6) using the

informed consent form version from Amendment 8 of the protocol, dated November 2008 and IRB approved on December 9, 2008. An amendment to the protocol, which included an update to the informed consent, was approved by the IRB on April 30, 2009. Subject 778828 was not re-consented in accordance with the protocol.

Individual Responsibility:

As described above for Clinical Investigator #1, the site methods and documentation for oversight and individual responsibility deviate from established practices typically employed by sponsors and principal investigators in the conduct of clinical research.

Study ANBL0032 was sponsored by the COG/NCI; Dr. Balis was identified as the COG PI or institutional PI at the CHOP. As such, Dr. Balis is responsible for all COG studies at the CHOP. However, Dr. Balis informed that each COG study has a specific designated PI for that study. For Protocol ANBL0032 the lead or "study PI" is Dr. John Maris.

Additional observations discussed with the site:

1. Lack of delineation and distinguishing roles and responsibilities during the study. There was no Delegation of Authority log prior to 2012 and Dr. Maris didn't sign the log as a PI until 2014.
 2. Lack of consenting physician's signature for Subject 748582 Informed Consent Form.
 3. Lack of inclusion of all laboratories that would be used during the study.
 4. Lack of documentation of the initial training on the protocol.
- c. Assessment of data integrity:** Notwithstanding the inspectional observations noted above, the data for Dr. Balis' site, associated with Study ANBL0032 submitted to the Agency in support of BLA 125516, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator and limited review of the EIR. An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

5. Sponsor: NCI/CTEP

- a. What was inspected:** The sponsor responsible for much of the conduct of the study was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The National Cancer Institute, a government agency, is part of the National Institutes of Health (NIH). The NCI coordinates the U.S. National Cancer Program and conducts and supports research, training, health information dissemination, and other activities related

to the causes, prevention, diagnosis, and treatment of cancer; the supportive care of cancer patients and their families; and cancer survivorship. Within NCI, the Cancer Therapy Evaluation Program (CTEP) coordinates publicly funded oncology clinical trials globally. The Division of Cancer Treatment and Diagnosis (DCTD) is one of the seven centers/divisions of the NCI and the CTEP is one of six programs under the DCTD. This was the first inspection of NCI, CTEP as a clinical trial sponsor. As such, the firm has no inspectional history.

The inspection, in part, corresponded with an inspection by the European Medicines Agency covering the conduct of the same study. The inspection covered the sponsor's conduct related to selection of clinical investigators and monitors, monitoring procedures, safety and adverse event reporting, data collection, electronic records, and test article control.

- b. General observations/commentary:** This inspection finds that the sponsor of the inspected study uses an atypical approach to managing and providing oversight and control of this and all their clinical studies. The sponsor, NCI, developed and currently uses their own method of maintaining compliance with sponsor GCP regulations. The method employs a generalized approach to clinical investigator identification and agreements (Form FDA 1572 and Financial Disclosure) that are not study specific but instead are sponsor specific. In addition, there are no sub-investigators under the model. The sponsor then proceeds to essentially delegate many sponsor responsibilities to the research group, such as the COG, for any NCI funded study conducted at that particular institute. NCI provides grants to various cooperative groups such as the Children's Oncology Group (COG). The grant for ANBL0032 was given to the COG.

COG was responsible for trial conduct with oversight by NCI/CTEP. Peter A. Abramson, MD, Chair, Children's Oncology Group explained that COG abides by the guidelines of the Cooperative Group Agreement and no additional agreement specific to study ANBL0032 conduct exists. NCI's responsibilities of oversight include protocol review, review of quality control and study monitoring, investigational drug management, and review of compliance with federally mandated regulatory requirements. COG's responsibilities include protocol development and submission, data management and analysis, compliance with regulatory requirements, quality control and study monitoring, and investigational drug management.

The FDA field investigator noted specific compliance violations likely a result, in part, of this sponsor's method of study oversight. Briefly, the sponsor could not produce a complete listing of investigators who assisted in the conduct of the study; site monitoring was not adequate (22 out of 163 study sites have not had data validation performed on any subject enrolled in this study, on-site audits which include source data verification only take place every three years,

and less than 10% of patient cases are reviewed); the Statement of Investigator, Form FDA-1572's were not collected for all investigators prior to their participation in an investigation, and signed Form FDA-1572s obtained from investigators do not identify the study being conducted, and do not include the name and address of all clinical laboratory facilities to be used in the study; and Financial Disclosure documents were not collected from all investigators prior to their participation in this investigation. In addition, the NCI/CTEP did not require investigators working on this protocol to submit financial disclosure data until June 1, 2002, more than three years after the FDA regulation became effective.

With respect to selection and documentation of clinical site investigators, NCI requires that any cooperative group physicians register with NCI prior to participating in any NCI related research. NCI, CTEP registration consists of completing a Form FDA-1572, a Supplemental Investigator Data Form, a CV, and a Financial Disclosure Form. The NCI registration process is not study specific. This practice resulted in compliance violations. Notably the sponsor could not produce a list of investigators who worked on study ANBL0032 over time. A complete list of investigators could not be provided because NCI and COG do not have a procedure or requirement for documenting all physicians (primary and sub-investigators) who participate in a specific trial. Therefore, the FDA field investigator could not determine if there were Form FDA 1572s for all investigators who participated in study ANBL0032. Clinical site inspections for study ANBL0032 found at least 3 clinicians who participated in study related procedures at one COG institution (Children's Mercy Hospitals and Clinics in Kansas City, MO) who were not members of the COG, and had not signed a Form FDA 1572, prior to consenting subjects and performing study visits.

With respect to site monitoring, NCI, CTEP and COG both have procedures which govern the auditing/monitoring processes for NCI studies. However, monitoring visits to COG institutions are not study specific, but instead are focused on the COG institution. Site initiation visits are not performed. When a COG member institution is audited, multiple NCI trials ongoing at the institution are audited. Routine audits are only required per procedures to take place every 36 months. Due to the lack of systematic, on-site and frequent monitoring the FDA field investigator could not reasonably determine that the clinical investigation was conducted in accordance with the investigational plan by all investigators or that the responsibilities of the clinical investigators were carried out according to the FDA regulatory requirements. Based upon inspectional findings, it does not appear the NCI or COG ensures that informed consent is obtained from all subjects in the study.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology which was used during ANBL0032 for adverse event reporting. The CTCAE provides a grading (severity) scale for each adverse

event. All adverse events were to be reported into the Clinical Data Update System (CDUS). If the adverse event was classified as Grade 3 with hospitalization, and/or unexpected, and possibly, probably, or definitely related, the AE would need to be reported within five business days into the Adverse Event Expedited Reporting System (AeEERS). Any Life-threatening or disabling AE (Grade 4) or Death related AE (Grade 5) would also need to be reported whether or not it was expected or determined to be related. Unexpected Grade 4 and 5 events are required to be reported within 24 hours by telephone. The FDA field investigator informed that there was no sponsor procedure for determination of who at a given site determined attribution and grading for AEs reported in eCRFs.

With respect to Financial Disclosure compliance in accordance with Part 54, NCI requires that each investigator provide financial disclosure annually as part of the NCI/CTEP registration process. The registration process includes completing a Form FDA1572, a Supplemental Investigator Data Form, a CV, and a Financial Disclosure Form. However, the Financial Disclosure Form used does not apply to any single drug company or investigational drug study. Problems found relating to financial disclosure reporting include investigators participating in ANBL0032 without a Financial Disclosure Form in place, and NCI not requiring financial disclosure from study investigators until three years after the regulation became effective.

With respect to electronic records, in 1999 COG developed and implemented an electronic case reporting system called the Remote Data Entry 1 (RDE1). This system was used to collect data for study ANBL0032. During the inspection the FDA field investigator was informed by [REDACTED]^{(b)(4)}, COG associate Group Statistician, that validation documentation could not be found for the RDE1 system. Subsequently, Dr. [REDACTED]^{(b)(4)} confirmed that RDE1 system validation had never been performed. Subjects were randomized to the trial using a dynamic randomization algorithm as part of the RDE1 system. Dr. [REDACTED]^{(b)(4)} also informed that the dynamic randomization algorithm was also not validated prior to its implementation. Finally, Dr. [REDACTED]^{(b)(4)} informed that documentation cannot be located for validation of the electronic case report forms, amendments one through six.

During the FDA inspection of Children's Mercy Hospitals and Clinics, Kansas City, MO, the FDA field investigator found that the electronic case report forms for enrolled subjects incorporated changes from all amendments, even if the subject was enrolled prior to the amendment's implementation. Dr. [REDACTED]^{(b)(4)} informed that only the most up to date version of the electronic case report form is retained. He also explained that the electronic case report forms may have had additional questions added or removed when the eCRFs were updated.

Those questions would show up on all subjects' case report forms if they were printed today, even if the question was not part of the CRF at the time the subject was enrolled. In that instance the answer to the question would appear as "no data entered".

In general, records and procedures were inconsistently retained and documented. The sponsor did not maintain continuous and adequate oversight and control over the study. On-site monitoring was very limited and as stated above, not study specific, but instead was directed at all NCI/COG studies active at the host institute. As such, source data verification for subjects in the study was not systematically verified by clinical monitors. A Form FDA 483 was issued citing four inspectional observations.

Observation 1. Investigators who were not qualified by training and experience as appropriate experts were selected to investigate a drug. Specifically,

1. A complete listing of Investigators who assisted in the conduct of the study, or made direct and significant contributions to the data could not be provided.
2. [REDACTED]^{(b) (4)}, was not a registered COG member and did not have a signed Form FDA-1572, Statement of Investigator when he co-consented subject 780672 on [REDACTED]^{(b) (4)}. Documented COG training or training specific to the protocol could not be provided.

Observation 2. Failure to monitor the progress of an investigation conducted under your IND.

Specifically,

- a. Twenty two out of 163 study sites have not had study subject records related to this study reviewed during on-site audits.
- b. On-site audits which include source data verification only take place at COG institutions every three years.
- c. During on-site audits the auditors are only required to review a minimum number of 10 subject records or 12% (whichever is higher) of total patients accrued at a COG institution across all ongoing COG studies.
- d. Specific physicians responsible for audit findings cannot be identified as the Report of Audit findings does not specify the individual who did not follow specific protocol requirements.

Observation 3. Failure to obtain a complete and signed investigator statement, Form FDA-1572, before permitting an investigator to participate in an investigation.

Specifically,

1. You did not obtain a signed Statement of Investigator, FDA-1572 before permitting an investigator to begin participation in an investigation.
 - a. A Form FDA-1572, Statement of investigator was not found for (b) (4), dated prior to January 7, 2009. (b) (4) performed study related procedures for subject 774291 on (b) (4) as part of the randomized portion of ANBL0032 and was listed as the primary study physician by COG for subject 779065 who was consented on (b) (4).
 - b. A Form FDA-1572, Statement of investigator was not found for (b) (4) dated prior to August 20, 2010. (b) (4) assisted in consenting subject 780672 into the study on (b) (4) as part of the randomized portion of ANBL0032.
 - c. A Form FDA-1572, Statement of investigator was not found for (b) (4) dated prior to January 13, 2009. (b) (4) consented subject 779065 in to the study on (b) (4) as part of the randomized portion of ANBL0032.
2. Signed FDA-1572s obtained from investigators do not identify the studies to be conducted by the investigators and do not include the name and address of all clinical laboratory facilities to be used in the study.

Observation 4. Failure to obtain from an investigator sufficient financial information to allow complete and accurate certification or disclosure statements.

Specifically,

1. You did not obtain financial disclosure documents prior to permitting an investigator to begin participation in an investigation.
 - a. (b) (4), (b) (6), MD, signed a Financial Disclosure Form on (b) (4), (b) (6) performed study related procedures for subject (b) (4), (b) (6) on (b) (4), (b) (6) as part of the randomized portion of ANBL0032 and was listed as the primary study physician by COG for subject (b) (4), (b) (6) who was consented on (b) (4), (b) (6).

- b. (b) (4), (b) (6) signed a Financial Disclosure Form on (b) (4), (b) (6). (b) (4), (b) (6) assisted in consenting subject (b) (4), (b) (6) in to the study on (b) (4), (b) (6) as part of the randomized portion of ANBL0032.
- c. (b) (4), (b) (6) signed a Financial Disclosure Form on (b) (4), (b) (6). (b) (4), (b) (6) consented subject (b) (4), (b) (6) in to the study on (b) (4), (b) (6) as part of the randomized portion of ANBL0032.

2. Study ANBL0032 began enrolling patients in October of 2001. The National Cancer Institute, Cancer Therapy Evaluation Program did not require investigators working on this protocol to submit financial disclosure data until June 1, 2002, more than three years after the FDA regulation became effective.

OSI Reviewer Note: These inspectional findings reveal that this sponsor has not maintained adequate oversight and control of their specific study ANBL0032. The violations are largely procedural, albeit required by current 21 Title 312 and 314 regulations. These regulations govern the conduct of clinical research in the United States. If reasonably complied with, the sponsor may anticipate that the data generated by a particular clinical study is highly likely to be reliable and that the rights and welfare of human subject volunteers is highly likely to have been protected.

In this case, the sponsor has not reasonably complied with these regulations, regardless of their unique methods. However, the FDA also inspected four clinical study sites that have conducted this study for many years and have generated a substantial amount of clinical data and extensive study conduct experience. These four sites, that of Dr. 's Hawkins, Hetherington, Mascarenhas and Balis, have a collective total of over 45 study years of performance and experience and over 120 study subjects. Notwithstanding the inspectional observations noted for Dr. Mascarenhas' site, Dr. Hawkins site, Dr. Hetherington's site, and Dr. Balis' site, the data generated by these sites for Study ANBL0032 appear reliable based on available information.

- c. Assessment of data integrity:** The former sponsor of Study ANBL0032 was audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Regulatory violations observed during the inspection of the sponsor responsible for much of the conduct of Study ANBL0032 were primarily procedural and raised concerns about oversight and monitoring of study conduct at sites participating in the study. However, based upon results of the four clinical site inspections linked to the sponsor inspection, the data submitted to the NDA by the sponsor for these sites appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on available information and the review of preliminary inspectional findings for clinical investigators Dr. Douglas Hawkins (Site 1865), Dr. Leo Mascarenhas (Site 1866), Dr. Maxine Hetherington (Site 1946), and Dr. Frank Balis (Site 1873), the Study ANBL0032 data appear reliable.

The preliminary classification for clinical investigators Dr. Douglas Hawkins, Dr. Maxine Hetherington, and Dr. Frank Balis is Voluntary Action Indicated (VAI). The preliminary classification for clinical investigator Dr. Leo Mascarenhas is No Action Indicated (NAI). The preliminary classification for the sponsor, NCI/CTEP is Official Action Indicated (OAI).

Each site had inspectional observations that were reported on a Form FDA 483, with the exception of Dr. Mascarenhas. All clinical sites had additional observations that were discussed with the site staff. Inspectional observations included limited reporting of protocol deviations (due to protocol directives and CRF design), late reporting of AEs, missing or late Form FDA 1572s for study staff, and the Form FDA 1572s used were not study specific. The discussion items included limited documentation of staff training and delegation of duties, missing or inconsistent use of financial disclosure forms, financial disclosure forms did not list a drug product or study sponsor, and site monitoring was extremely limited.

The sponsor inspectional findings suggest that this sponsor has not maintained adequate oversight and control of their specific study ANBL0032 over time. The violations are largely procedural, albeit required by current 21 Title 312 and 314 regulations. These regulations govern the conduct of clinical research in the United States. Although the sponsor has not complied with these regulations, data submitted by the sponsor for Study ANBL0032 in support of this application for the four audited sites appear reliable for use in support of the respective indication.

Note: The observations noted above are based on the preliminary review of information provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

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09/19/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 18, 2014
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: BLA 125516
Product Name and Strength: Unituxin (Dinutuximab) Injection,
17.5 mg/5 mL (3.5 mg/mL)
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: United Therapeutics Corporation
Submission Date: April 11, 2014 and July 8, 2014
OSE RCM #: 2014-854
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review is written in response to a consult from DOP2 requesting DMEPA to assess the proposed Prescribing Information, container labels, and carton labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C – N/A
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified that the proposed container label, carton labeling, and full prescribing information can be improved to provide clarity and important safety and prescribing information.

Additionally, we noted that the proposed container label and carton labeling do not meet the following regulatory requirements:

- The container label lacks a barcode
- Both the container label and carton labeling do not list inactive ingredients
- The National Drug Code (NDC) is located on wrong display panel on the carton labeling.
- Both the container label and carton labeling do not list the license number of the manufacturer

We defer to the Office of Biotechnology Products for their comments and recommendations on these issues.

4 CONCLUSION & RECOMMENDATIONS

We conclude the proposed container label, carton labeling and full prescribing information can be improved to promote the safe use of the product.

4.1 COMMENTS FOR THE DIVISION

Highlights of the Prescribing Information (PI)

Dosage and Administration Section

- 1) Revise the first bullet to include clear communication of the Unituxin treatment schedule, such as including a table:

Course	Days
1, 3, and 5	4 to 7 of the 24-day cycle
2 and 4	8 to 11 of the 32-day cycle

Full Prescribing Information (PI)

Dosage and Administration Section

Section 2.1: Basic Dosing Information

- 1) Spell out the abbreviation, “IV”, as “intravenous” or “intravenously” in this section and throughout the PI.
- 2) Revise dashes (-) to the word that is indicated, such as “to” or “through” (e.g. change Days 2-4 to Days 2 through 4 and change “...over 10-20 hours” to “over 10 to 20 hours”).
- 3) For the third bullet, move this bullet “(b) (4)” to section 2.4 (Premedication and Concomitant Medication Information) so all premedications and concomitant medications are organized and listed in the same Section.
- 4) For the sixth bullet, reformat Unituxin treatment schedule as a table or other presentation that offsets the course and days to improve readability.

For example:

Course	Days
1, 3, and 5	4 to 7 of the 24-day cycle
2 and 4	8 to 11 of the 32-day cycle

- 5) Delete [REDACTED] (b) (4). This information is listed section 2.1 [REDACTED] (b) (4).

Section 2.3: Dose Modifications

- 1) The recommended modified dose or infusion rate needs to be presented in Section 2.3 of the Dosage & Administration Section of the PI, instead of just referring to the Warnings and Precautions Section of the PI, to promote the safe use of Unituxin and to improve readability.

- [REDACTED] (b) (4)
- 1) We note that dosage information for morphine sulfate, acetaminophen, ibuprofen, and lidocaine are presented in parentheses versus dosage information for gabapentin is not in parentheses. We defer to the Review Division for the presentation format regarding this issue.
- 2) For the first bullet, change the spelling of morphine sulfate from “sulphate” to “sulfate”. Additionally, add the route of administration for morphine sulfate (e.g. “morphine sulfate 50 mcg/kg intravenous bolus is given immediately...”).
- 3) For the third bullet, consider revising the statement “When pain is inadequately controlled with [REDACTED] (b) (4)” to “When pain is inadequately controlled with opioid,...” because the first bullet stated that fentanyl or hydromorphone may be used if morphine is not tolerated.
- 4) For the third bullet, revise “0.9% sodium chloride injection” to “0.9% sodium chloride injection, USP” because the normal saline product should meet USP standards.
- 5) We note that the dosage information are presented in the proposed Unituxin PI for [REDACTED] (b) (4) [REDACTED] (b) (4). We defer to the Review Division regarding this issue.
- 6) The proposed Unituxin PI, Section 2.4, fifth bullet, recommends that antihistamine premedication (e.g. [REDACTED] (b) (4) diphenhydramine) must be administered by intravenous injection. However, we note drug reference states that for [REDACTED] (b) (4)

administration “Avoid IV, subcutaneous, or intra-arterial administration”.¹ We defer to the Review Division for the appropriate route of administration regarding this issue.

How Supplied/Storage and Handling

- 1) Delete the word, (b) (4). The abbreviation, NDC stands for National Drug Code;

(b) (4)

4.2 RECOMMENDATIONS (b) (4)

Container Label

The proposed container label lacks required information and could be improved to highlight important safety information.

- 1) According to USP, Unituxin would be classified as a parenteral article in liquid form. As such, the proprietary and proper names should be followed by the word, “Injection”.² The word “Injection” identifies that this product is intended for parenteral administration.

We recommend adding the word “injection” after the proprietary and proper names. For example, “Unituxin (Dinutuximab) Injection”.

- 2) To improve readability of the strength per total volume and strength per milliliter statements, we recommend adding a space between the numerals and corresponding units. For example, change “17.5 mg/5mL (3.5mg/mL)” to, “17.5 mg/5 mL (3.5 mg/mL)”
- 3) According to 21 CFR 201.100(b)(2), the Unituxin container label 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.”

¹ (b) (4)

² *United States Pharmacopeia and National Formulary* (USP 37-NF 32). Vol 39. Rockville, MD: United States Pharmacopeia Convention; 2014:33.

- 4) To maintain consistency with other labels and labeling, we recommend the addition of the equivalent storage temperature range in degrees Fahrenheit (°F).

Carton Labeling

The proposed carton labeling lacks required information and could be improved to highlight important safety information.

- 1) According to USP, Unituxin would be classified as a parenteral article in liquid form. As such, the proprietary and proper names should be followed by the word, "Injection". The word "Injection" identifies that this product is intended for parenteral administration.

We recommend adding the word "injection" after the proprietary and proper names. For example, "Unituxin (Dinutuximab) Injection".

- 2) To improve readability of the strength per total volume and strength per milliliter statements, we recommend adding a space between the numerals and corresponding units.

For example, change "17.5mg/5mL
(3.5mg/mL)"

to, "17.5 mg/5 mL
(3.5 mg/mL)"

- 3) In addition to recommendation number 2 above, ensure bold font is used for the entire dose expression. In the image (see Appendix G) provided in the submission, the numeral "1" does not appear to be presented in bold font.
- 4) 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."

- 5) To maintain consistency with other labels and labeling, we recommend the addition of the equivalent storage temperature range in degrees Fahrenheit (°F).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Unituxin that United Therapeutics submitted on April 11, 2014.

Table 2. Relevant Product Information for Unituxin	
Initial Approval Date	N/A
Active Ingredient	Dinutuximab
Indication	High Risk Neuroblastoma
Route of Administration	Intravenous Infusion
Dosage Form	Injection
Strength	17.5 mg/5 mL (3.5 mg/mL)
Dose and Frequency	17.5 mg/m ² /day intravenously over 10 to 20 hours daily for 4 days.
How Supplied	Single-Use Vials
Storage	Refrigerated

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Unituxin labels and labeling submitted by United Therapeutics on April 11, 2014.

- Container label
- Carton labeling
- Full Prescribing Information

G.2 Label and Labeling Images

Container Label (300%)



1 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

OTTO L TOWNSEND
08/18/2014

CHI-MING TU
08/18/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
BLA# 125516	BLA Supplement # 0	Efficacy Supplement Type SE- N/A
Proprietary Name: Unituxin (proposed) Established/Proper Name: dinutuximab Dosage Form: injection for intravenous infusion Strengths: 17.5 mL/5 mL		
Applicant: United Therapeutics Corporation Agent for Applicant (if applicable): N/A		
Date of Application: April 11, 2014 Date of Receipt: April 11, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: December 10, 2014	Action Goal Date (if different): N/A	
Filing Date: June 10, 2014	Date of Filing Meeting: May 9, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s): For the treatment of high risk neuroblastoma in combination with GM-CSF, IL-2 and isotretinoin.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): INDs 110494, 4308 – DMFs: (b) (4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Proprietary name request submitted on 4.15.14 is under review
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i></p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	United Therapeutics Corporation has requested seven year orphan exclusivity

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	N/A

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Application has orphan designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>BPCA (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proprietary Name request submitted April 15, 2014.
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels			
	<input checked="" type="checkbox"/> Immediate container labels			
	<input type="checkbox"/> Diluent			
	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	QT-IRT consult submitted
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): January 27, 2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): pre-BLA CMC Meeting Minutes issued 1.29.14 Pre-BLA All Discipline Mtg Minutes issued 3.7.14	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 11, 2014 (submit/received date)

BLA/NDA/Supp #: 125516/0

PROPRIETARY NAME: Unituxin

ESTABLISHED/PROPER NAME: dintuximab

DOSAGE FORM/STRENGTH: 17.5 mL/ 5 mL

APPLICANT: United Therapeutics Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of high risk neuroblastoma in combination with GM-CSF, IL-2 and isotretinoin.

BACKGROUND: On July 1, 2010, United Therapeutics Corporation (UTC) entered a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute based on the results of Study ANBL0032 to collaborate on the late stage development and regulatory submission of the investigational product ch14.18 for the treatment of patients with high risk neuroblastoma under IND 110494.

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.

On January 27, 2011, UTC informed the Division of Oncology Products 2 that UTC would assume manufacturing responsibilities of the product ch 14.18 and would demonstrate the comparability between ch14.18 produced by NCI and ch 14.18 produced by UTC.

In addition UTC assumed the responsibilities of all on-going and future studies, in collaboration with NCI (SAIC-Frederick, DBP) with the goal of filing a BLA for use ch14.18 in combination with GM-CSF, IL-2, and RA in patients with high risk neuroblastoma (b) (4)

The CMC pre-BLA meeting was held on January 14, 2014 and the pre-BLA all discipline meeting was held February 19, 2014 to finalize the agreed upon components with respect to the BLA submission.

The BLA was submitted on April 11, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Gina Davis	Y
	CPMS/TL:	Karen Jones	N
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Y
Clinical	Reviewer:	Martha Donoghue	Y
	TL:	Suzanne Demko	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	Xianhu Cao	Y
	TL:	Hong Zhao Lillian Zhang	Y Y
Biostatistics	Reviewer:	Sirish Mushti	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dubravka Kufrin	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:		N/A
	TL:		N/A
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewers:	Chikako Torigoe	Y
	TL:	Laurie Graham	Y
Product Quality (CMC)	Reviewer:	Chikako Torigoe	Y
	TL:	Laurie Graham	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Cikako Torigoe	Y
	TL:	Laurie Graham	Y
Facility Review/Inspection and Micro Team	Reviewer:	Lakshmi Narasimhan Colleen Thomas	Y
	TL:	Patricia Hughes	N
OSE/DMEPA (proprietary name)	Reviewer:	Sean Bradley Frances Fahnbeullah (SRPM)	N Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	LaurenIacono-Connor	Y
	TL:	Janice Pohlman	Y
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Pharmacometrics	Reviewer:	Jingyu (Jerry) Yu	Y
	TL:	Liang Zhao	Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments List comments: 	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: Clinical issues will be communicated in an I/R or 74 day letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? 	<input type="checkbox"/> YES

<p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Date if known:</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason: The application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL</p>	<p><input type="checkbox"/> Not Applicable</p>

<p>(PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Review issues identified - Responses received</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<input type="checkbox"/> Not Applicable

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 9, 2014

21st Century Review Milestones: Filing Action June 10, 2014 – 74 day letter June 24, 2014
Mid-cycle Meeting – July 9, 2014 - PDUFA December 10, 2014

Comments: The following information requests were sent to the sponsor:

1. CMC comments sent to the applicant on April 30, 2014 - response received on May 5, 2014.
2. Clinical Pharmacology comments sent on April 30, 2014 response provided May 8, 2014.
3. QT-IRT comment sent on May 8, 2014 response provided May 12, 2014.
4. Biopharmaceutics/Clinical Pharmacology comments sent on May 8, 2014 response provided on May 15, 2014.
5. Clinical comments sent on May 14, 2014 response provided on May 19, 2014.
6. Request for Application Orientation sent on May 22, 2014.
7. CMC comments sent on May 22, 2014, response provided on June 2, 2014.
8. DRISK requests for information sent on May 31, 2014 response provided on June 7, 2014.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input checked="" type="checkbox"/>	Other <ol style="list-style-type: none"> 1. The team agreed to review the application as a priority review. 2. Standing Monthly Meetings have been scheduled from 3. A separate DRISK meeting has been scheduled with the clinical and nonclinical to discuss potential safety issues identified by with DRISK. 4. Lillian Zhang and Xianhu Cao will not be the primary reviewers for this application per an email received by Hong Zhao. Hong Zhao and Jingyu Yu.

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
06/10/2014