

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125547Orig1s000

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 # STN 125547
Product Name: Portrazza (Necitumumab)

PMC #1 Description: Conduct endotoxin and sterility test method qualification study using two additional batches of Necitumumab drug product manufactured according to the commercial drug substance and drug product manufacturing processes and submit the results in accordance with 21 CFR 601.12.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>06/2016</u>
	Final Report Submission:	<u>09/2016</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: _____

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **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 AA OR WILL BE PUBLICLY 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 sterility and endotoxin test method qualification studies were performed with two non-clinical demonstration//engineering batches of drug product. Therefore, sterility and test method qualification data from two additional commercial batches of drug product are requested as a PMC.

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

The sterility and endotoxin test method qualification studies have been completed using samples from two non-clinical demonstration//engineering batches of drug product. The completion of this study will meet the qualification requirement of using samples from 3 lots of commercial drug product batches.

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:

Lilly will perform and submit the results of endotoxin and sterility method qualification studies using two additional batches of Necitumumab drug product manufactured according to the commercial drug substance and drug product manufacturing processes.

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/

LAKSHMI RANI NARASIMHAN
11/24/2015

Results from endotoxin spiking studies (b) (4) were inadequate. (b) (4)
(b) (4)
(b) (4) Therefore the sponsor will complete hold time studies using three drug substance batches manufactured during a recent campaign. The studies will be completed to determine the maximum hold time prior to completing endotoxin testing.

The studies must be done using an endotoxin standard (RSE or CSE) or with commercially available highly purified LPS calibrated against an endotoxin standard. Studies performed using naturally occurring endotoxin (NOE) will not be accepted.

These studies are not required pre-approval because the test method accurately measures endotoxin (b) (4)
(b) (4)
The data will be available in 2016 which is beyond the review period.

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

Maximum hold times for drug substance samples prior to endotoxin testing have not been adequately established. The sponsor will complete endotoxin spiking studies using recent batches of drug substance determine the maximum hold times for drug substance samples being tested for endotoxin.

The PMC studies may lead to the identification or development of a more suitable endotoxin release test method for this product if the results from the spiking study do not meet acceptance criteria.

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 complete hold time studies using three drug substance batches manufactured during a recent campaign. The studies will be completed to determine the maximum hold time prior to completing endotoxin testing.

The studies must be done using an endotoxin standard (RSE or CSE) or with commercially available highly purified LPS calibrated against an endotoxin standard. Studies performed using naturally occurring endotoxin (NOE) will not be accepted. The sponsor will submit the study report per CFR 601.12. If the results do not meet acceptance criteria, develop an alternative method to detect endotoxin in the drug substance.

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/

CANDACE GOMEZ-BROUGHTON
11/24/2015

PMR/PMC Development Template: Product Quality (CMC)

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NDA/BLA # BLA 125547
Product Name: PORTRAZZA (necitumumab)

PMC #1 Description: PMC wording: "Further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly. "

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study Completion:	<u>12/31/2017</u>
	Final Report Submission:	<u>06/30/2018</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
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- **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

Data provided in the BLA identifies that necitumumab mechanism of activity can include ADCC functionality. Some association between quality attributes (QAs) monitored and ADCC were included in the BLA, and the manufacturing controls are such that the ADCC functionality of necitumumab is controlled. However, some data in the BLA identifies that the QAs used to ensure molecular integrity as related to ADCC are either not consistent under some conditions (b) (4) or it is not clear that those attributes would sufficiently capture changes related to ADCC (b) (4)

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

Data in the BLA identified that the QAs used to ensure molecular integrity as related to ADCC are either not consistently linked with ADCC under some stressed conditions (b) (4) or it has not been shown that control of the attribute would sufficiently control for the changes related to ADCC (b) (4) based on the capabilities of the assay and the acceptance criteria. Therefore, additional studies are needed to further characterize the molecular attributes that should be monitored in order to assure that the ADCC activity is appropriately assessed in those uncommon situations when ADCC does not track with the QAs identified in the BLA.

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:

Characterization of necitumumab quality attributes that are associated with its ADCC activity, and subsequent reassessment of necitumumab control strategy for ADCC.

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/

MISSIRATCH BIABLE
11/23/2015

CHANA FUCHS
11/23/2015

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 # BLA 125547
Product Name: PORTRAZZA (necitumumab)

PMC #1 Description: Reassessment of release and shelf-life specifications for the Drug Substance to allow for better statistical analysis.

PMC wording: “Re-evaluate all necitumumab drug substance lot release and stability data after availability of IEC and CE-SDS release data from 30 lots of drug substance manufactured (b) (4)

(b) (4) Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.”

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study Completion:	<u>12/31/2020</u>
	Final Report Submission:	<u>02/28/2021</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: Reassessment of release and shelf-life specifications for the Drug Product to allow for better statistical analysis.

PMC wording: “Re-evaluate all necitumumab drug product lot release and stability data after availability of IEC and CE-SDS release data from at least 20 lots of drug product manufactured by the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications, based on the available drug substance and drug product data.”

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study Completion:	<u>12/31/2020</u>
	Final Report Submission:	<u>02/28/2021</u>
	Other: _____	<u>MM/DD/YYYY</u>

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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 current release and shelf-life specifications approved in this BLA for the drug substance and drug product are sufficient to ensure adequate quality and safety of necitumumab for the initial marketed product based on the data provided. Increased manufacturing and testing experience gained post licensure can facilitate improved specifications.

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

Necitumumab release and shelf-life specifications were based on clinical and manufacturing experience that were available at the time of BLA submission for a limited number of lots. The re-evaluation of acceptance criteria after manufacturing of additional lots that are made from different campaigns would allow for more robust data to support acceptance criteria. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots or datapoints have been accumulated.

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:

Statistical analysis of release data acquired following manufacture of additional 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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/s/

MISSIRATCH BIABLE
11/23/2015

CHANA FUCHS
11/23/2015



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

FINAL LABEL AND LABELING REVIEW

Date:	September 14, 2015
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus-samad -S 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: 2015.09.14 11:32:06 -0400</small>
Through:	Yan Wang, PhD, Quality Reviewer Division of Biotechnology Review and Research IV Yan Wang -S <small>Digitally signed by Yan Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011514221, cn=Yan Wang -S Date: 2015.09.14 11:52:56 -0400</small>
Application:	BLA 125547/0
Product:	Portrazza™ (necitumumab)
Applicant:	Eli Lilly and Company
Submission Dates:	December 2 2014 and August 31 2015

Executive Summary:

The container label and carton labeling for Portrazza™ (necitumumab) 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), USP 38/NF 33 [August 1, 2015 to November 30, 2015]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on August 31, 2015 acceptable.

Background and Summary Description:

The Applicant submitted BLA 125547 Portrazza™ (necitumumab) on December 2 2014. Table 1 lists the proposed characteristics of Portrazza™ (necitumumab).

Table 1: Proposed Product Characteristics of Portrazza™ (necitumumab).

Proprietary Name:	Portrazza™
Proper Name:	necitumumab
Indication:	Treatment of Squamous Non-Small Cell Lung Cancer for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin
Dose:	800 mg administered as an intravenous infusion over (b) (4) minutes on Days 1 and 8 of each 3-week cycle. Dose can be decreased to 400 mg or 600 mg for skin reactions.
Route of Administration:	Intravenous infusion
Dosage Form:	Injection
Strength and Container-Closure:	800 mg/50 mL in a single-dose vial
Storage and Handling:	Refrigerate at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. DO NOT FREEZE OR SHAKE the vial.

Materials Reviewed:

submitted December 2 2014

- Vial Container Label
- Carton Labeling

Start of Sponsor Material

Container Label



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

Applicant's response in Times New Roman font
OBP decisions in Tahoma italics font.

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; *conforms*.

(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*.

(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*.

(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; *conforms.*

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]; *conforms.*

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

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

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms.*

F. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform.*

OBP Request: Decrease the prominence of “Rx only” by remove the bolding. Consider relocating “Rx only” to the top right corner of the label.

Applicant’s Response August 31 2015: Lilly has revised the PORTRAZZA carton and container labeling to reflect relocation of “Rx only” to the top right corner. Lilly prefers to maintain the existing bolding of “Rx only,” which is consistent with other Lilly products including Cyramza. *Acceptable.*

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

H. 21 CFR 201.25 Bar code; *conforms.*

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

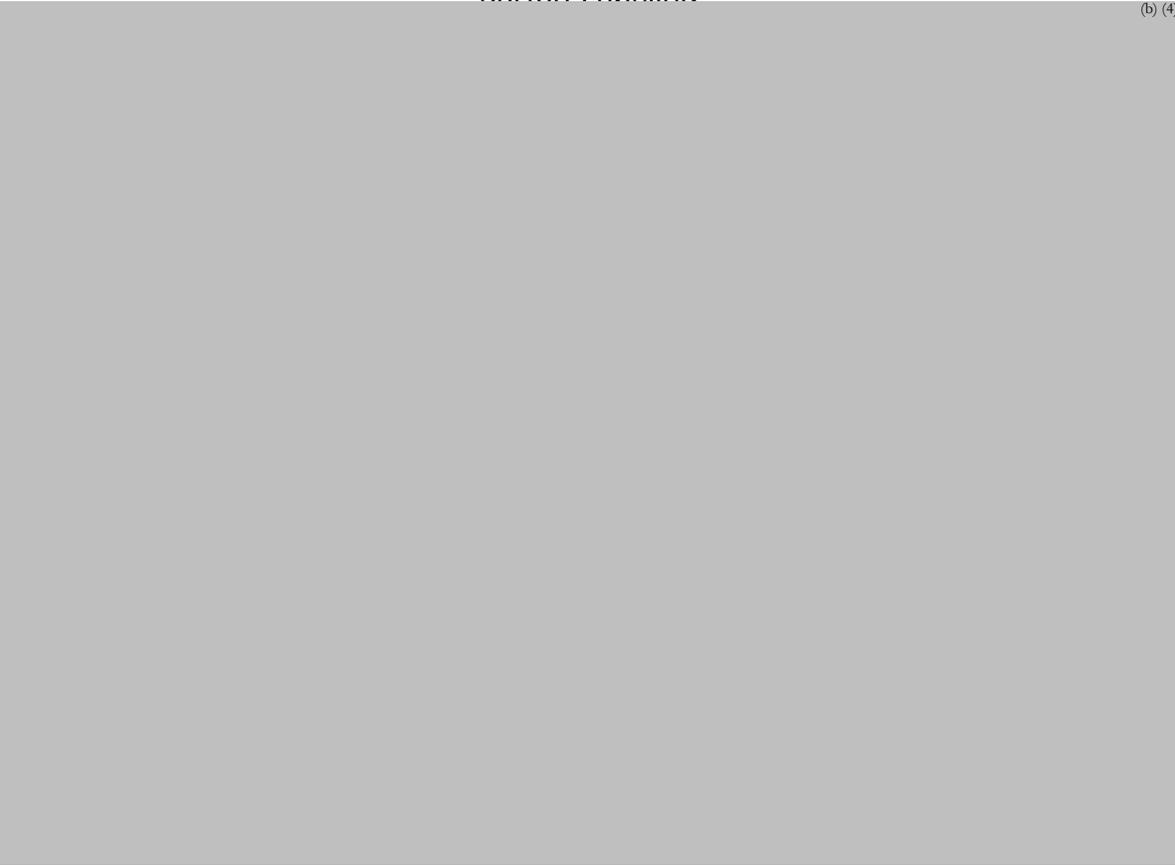
- J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- K. 21 CFR 201.55 Statement of dosage; *conforms.*
- L. 21 CFR 201.100 Prescription drugs for human use. *conforms.*
However, we recommend revising the list of ingredients to display the amount of ingredients per mL.

OBP Request: Revise the list of ingredients to read:
Contents: Each mL contains 16 mg necitumumab, citric acid anhydrous (0.256 mg), glycine (9.984 mg), mannitol (9.109 mg), polysorbate 80 (0.1 mg), sodium chloride (2.338 mg), sodium citrate dihydrate (2.55 mg), and water for injection.
Applicant revised as requested.

Start of Sponsor Material

Carton Labeling

(b) (4)



End of Sponsor Material

Applicant's response in Times New Roman.
OBP decisions in Tahoma italics.

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; *conforms.*
 - 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"; *conforms.*
 - 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. However, OBP recommends improving the storage statements.*

OBP Requests:

Add the units of measure to the temperature range in the storage statement so that it appears as "2°C to 8°C (36°F to 46°F)".

Applicant's Response August 31, 2015: Lilly has revised the PORTRAZZA carton and container labeling to reflect "2° to 8°C (36° to 46°F)," which is consistent with other Lilly products including Cyramza. *Acceptable.*

Combine the storage and protection from light statements.
For example:

Storage: Refrigerate at "2°C to 8°C (36°F to 46°F)" in original carton to protect from light.

Applicant's Response August 31, 2015: Lilly prefers not to combine the storage and protection from light statements for carton and container labeling in order to maintain consistency with other Lilly products such as Cyramza and to reduce clutter, especially on the container label.
Acceptable.

- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*
- 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.*
- 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"; *conforms*.

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*.

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)]. *Exempt. Portrazza (necitumumab) is a monoclonal antibody.*

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

D. 21 CFR 610.64 Name and address of distributor; *not applicable*

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

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

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]; *conforms*.

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]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Requests:

Decrease the prominence of "Rx only" by remove the bolding.

Consider relocating "Rx only" to the top right corner of the label.

Applicant's Response August 31 2015: Lilly has revised the PORTRAZZA carton and container labeling to reflect relocation of "Rx only" to the top right corner. Lilly prefers to maintain the existing bolding of "Rx only," which is consistent with other Lilly products including Cyramza. *Acceptable.*

Add the route of administration "For Intravenous Infusion Only" below the strength statement on the side and top panels. Additionally, consider deleting "Route of Administration: Intravenous Infusion" from the side panel.

Applicant's Response August 31 2015: Lilly believes that adding the route of administration "For Intravenous Infusion Only" below the strength statement on the side and top panels would crowd the presentation of information, especially on the top panel. In addition, Lilly prefers to retain current reference to route of administration on the side panel, which is consistent with other Lilly products such as Cyramza. *Acceptable.*

Consider decreasing the size of the logo to provide more white space on the principal display panel to improve the readability of the critical information.

Applicant's Response August 31 2015: Lilly prefers to retain the size of the logo on the principal display panel, (b) (4) and standard for other Lilly products including Cyramza. (b) (4)
Acceptable.

- 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.*
- O. 21 CFR 201.55 Statement of dosage; *conforms.*

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*.
However, we recommend revising the list of ingredients to display the amount of ingredients per mL.

OBP Request: Revise the list of ingredients to read:

Contents: Each mL contains 16 mg necitumumab, citric acid anhydrous (0.256 mg), glycine (9.984 mg), mannitol (9.109 mg), polysorbate 80 (0.1 mg), sodium chloride (2.338 mg), sodium citrate dihydrate (2.55 mg), and water for injection.
Applicant revised as requested.

CDER Labeling Recommendations

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

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with United States Pharmacopeia General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals. *Applicant confirmed.*
2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). *The Applicant confirmed there is appropriate area for visual inspection.*

B. Vial Container Label

1. Consider decreasing the size of the logo to provide more white space on the principal display panel to improve the readability of the critical information.

Applicant's Response August 31 2015: Lilly prefers to retain the size of the logo on the principal display panel, (b) (4) and standard for other Lilly products including Cyramza. (b) (4)

Acceptable.

2. Add the units of measure to the temperature range in the storage statement so that it appears as "2°C to 8°C (36°F to 46°F)".

Applicant's Response August 31, 2015: Lilly has revised the PORTRAZZA carton and container labeling to reflect "2° to 8°C (36° to 46°F)," which is consistent with other Lilly products including Cyramza. *Acceptable*.

3. Combine the storage and protection from light statements. For example:

Storage: Refrigerate at "2°C to 8°C (36°F to 46°F)" in original carton to protect from light.

Applicant's Response August 31, 2015: Lilly prefers not to combine the storage and protection from light statements for carton and container labeling in order to maintain consistency with other Lilly products such as Cyramza and to reduce clutter, especially on the container label. *Acceptable*.

Conclusions

The container label and carton labeling for Portrazza™ (necitumumab) 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), USP 38/NF 33 [August 1 2015 to November 30 2015]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on August 31, 2015 acceptable (see below).

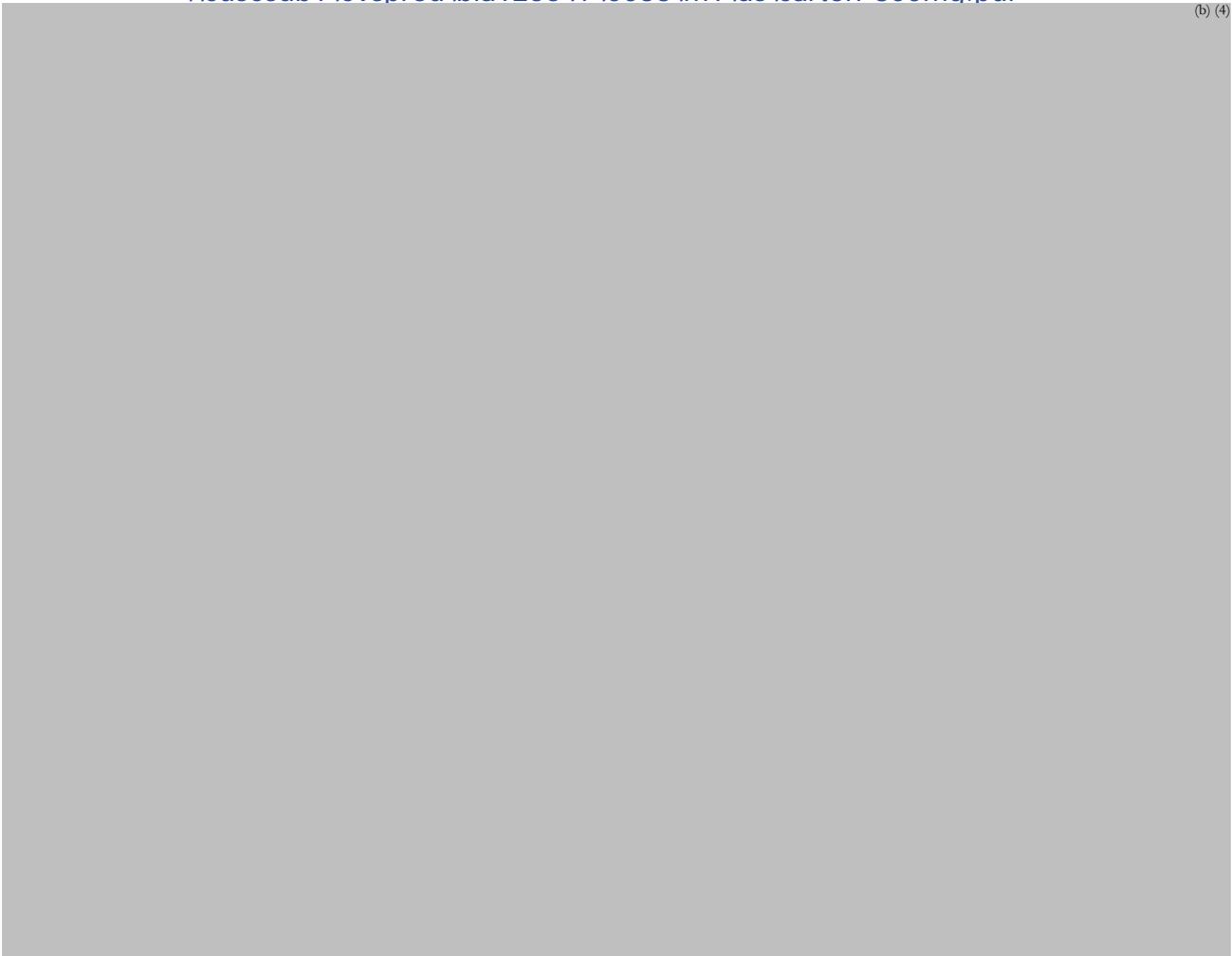
Container Label

[\\cdsesub1\evsprod\bla125547\0033\m1\us\contain-800mg.pdf](#)



Carton Labeling

[\\cdsesub1\evsprod\bla125547\0033\m1\us\carton-800mg.pdf](#)



**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: 09/03/2015

To: Mimi Biable, MS, RAC
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nazia Fatima, Pharm.D, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: Portrazza (necitumumab) Injection
BLA 125547

Office of Prescription Drug Promotion Comments on proposed
labeling (PI)

Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI) for necitumumab as requested in consult from Division of Oncology Products 2 (DOP2) dated 12/10/2014

OPDP's review of the proposed PI is based on the substantially completed draft labeling titled, "proposed.docx" sent via electronic mail on 08/28/2015 to OPDP from DOP2(Mimi Biable). OPDP's comments are provided directly on the marked-up version of the label attached below.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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

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

/s/

NAZIA FATIMA

09/14/2015

OPDP comments reviewed with DOP2 on 09/03/2015.



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

PLLR Labeling Memorandum

Date: September 1, 2015

From: Tamara Johnson, MD, MS
Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne Yao, MD
Division Director
Division of Pediatric and Maternal Health

To: Division of Oncology Products 2

Drug: Portrazza (necitumumab) injection

BLA: 125547

Applicant: Eli Lilly and Company

Drug Class: epidermal growth factor receptor (EGFR) antagonist

Indication(s) For first-line treatment of metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Submission Date: November 25, 2014

Consult Date: July 28, 2015

Materials Reviewed:

- Original BLA submission, annotated and draft labeling
- Erbitux (cetuximab) labeling, last approved April 10, 2015

- Vectibix (panitumumab) labeling, last approved March 11, 2015

INTRODUCTION

On November 25, 2014, the applicant Eli Lilly submitted the original BLA 125547 for Portrazza (necitumumab) for the treatment of metastatic squamous non-small cell lung cancer (NSCLC). The Division of Oncology Products 2 (DOP2) requested the assistance of the Division of Pediatric and Maternal Health (DPMH) to provide labeling recommendations for subsections 8.1 through 8.4, to include bringing the labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format.

BACKGROUND

Disease

Approximately 85% of lung cancer cases are NSCLC with squamous NSCLC cases accounting for 34% of NSCLC cases.¹ NSCLC is often diagnosed in the later stages with the majority (70%) of patients having regional, nodal or metastatic disease. At these stages, surgical resection is not curative and chemotherapy has been shown to increase survival by an additional 2 to 6 months.² The five-year survival for lung cancer is ~17%. Patients with EGFR mutation have better survival when compared to those without the mutation due to the availability of targeted treatment options.

Drug

Necitumumab is a recombinant human monoclonal antibody which acts to inhibit binding of human epidermal growth factor receptor (EGFR). Inhibition of EGFR is thought to prevent malignant progression and angiogenesis, and allow cell apoptosis. Necitumumab is the third monoclonal antibody in the class of EGFR antagonists, behind the previous approvals of Erbitux (cetuximab) and Vectibix (panitumumab) in 2010 and 2013, respectively. Like all antibodies, the necitumumab molecule is large with a molecular weight of 144.8 kDa.

PLLR

On December 4, 2014, the Food and Drug Administration (FDA) published the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR).³ The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with

¹ Gibbons D, Pisters K.M., Johnson F, Eapen G.A. (2011). Chapter 15. Non-Small Cell Lung Cancer. In Kantarjian H.M., Wolff R.A., Koller C.A. (Eds), *The MD Anderson Manual of Medical Oncology, 2e*. Retrieved August 28, 2015 from

<http://accessmedicine.mhmedical.com/content.aspx?bookid=379&Sectionid=39902039>

² Cornett P.A., Dea T.O. (2016). Cancer. In Papadakis M.A., McPhee S.J., Rabow M.W. (Eds), *Current Medical Diagnosis & Treatment 2016*. Retrieved September 01, 2015 from

<http://accessmedicine.mhmedical.com/content.aspx?bookid=1585&Sectionid=98107878>

³ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Pregnancy

There are no human or animal data available on necitumumab use in pregnancy. In animal studies with other monoclonal antibodies in the class, pregnant animals given the drug during the period of organogenesis have demonstrated increased embryoletality and abortions at doses similar to the recommended human dose.⁴ Due to its mechanism of action and the role of EGFR in fetal development, use of necitumumab during pregnancy should be avoided. DPMH recommends use of effective contraception in females of reproductive potential during treatment with necitumumab and for three months after the final dose (6 x 14 days ($t_{1/2}$) = 84 days).

Lactation

The applicant provides no human or animal data on necitumumab use during lactation. LactMed was searched and no data is available on necitumumab use during lactation.⁵ Human IgG is present in human milk. Necitumumab, having a molecular weight (b) (4) is not expected to enter the breastmilk in large amounts. However, with the potential for serious adverse reactions, DPMH does not recommend use during lactation.

Pediatric Labeling

The sponsor proposes the following statement:

8 Use in Specific Populations

8.4 Pediatric Use

The safety and effectiveness of PORTRAZZA have not been established in pediatric patients.

DPMH does not recommend any changes to this statement.

CONCLUSIONS/RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 8.3 in the necitumumab labeling for compliance with the PLLR. DPMH recommendations are below and reflect discussion with DOP2. DPMH refers to the final BLA action for final labeling.

⁴ Recent labelings for Erbitux and Vectibix accessed August 5, 2015, from the Drugs@FDA website, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name.

⁵ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

-----**WARNINGS AND PRECAUTIONS**-----

Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (b) (4) 8.1, 8.3)

-----**USE IN SPECIFIC POPULATIONS**-----

- Lactation: Do not breastfeed. (8.2)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

(b) (4) **Embryo-Fetal Toxicity**

Based on animal data and its mechanism of action, PORTRAZZA (b) (4) cause fetal harm when administered to a pregnant woman. Disruption or depletion of EGFR in animal models results in impairment of embryofetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR signaling has resulted in embryoletality as well as post-natal death Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PORTRAZZA and for three months following the final dose [*see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, PORTRAZZA (b) (4) cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. Disruption or depletion of EGFR in animal models results in impairment of embryofetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR signaling has resulted in embryoletality as well as post-natal death [*see Data*]. No animal reproduction studies have been conducted with necitumumab. (b) (4)

(b) (4). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No animal studies have been (b) (4) conducted to evaluate the effect of necitumumab on reproduction and fetal development; however, based on its mechanism of action, PORTRAZZA (b) (4) cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. (b) (4)

(b) (4) In monkeys, administration of an anti-EGFR antibody during the period of organogenesis resulted in detectable exposure of the antibody in the amniotic fluid and (b) (4)

8.2 Lactation

Risk Summary

There is no information regarding the presence of necitumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from PORTRAZZA, advise a nursing woman not to breastfeed during treatment with PORTRAZZA and for three months following the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, PORTRAZZA (b) (4) cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations* (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with PORTRAZZA and for three months following the final dose.

8.4 Pediatric Use

The safety and effectiveness of PORTRAZZA have not been established in pediatric patients.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus [see *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with PORTRAZZA and for three months following final dose [see *Use in Specific Populations* (8.3)].

Lactation

Advise women not to breastfeed during treatment with PORTRAZZA [*see Use in Specific Populations (8.2)*].

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

/s/

TAMARA N JOHNSON
09/01/2015

LYNNE P YAO
09/02/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 28, 2015

TO: Mimi Biable, Regulatory Health Project Manager
Lee Pai-Scherf, M.D., Medical Reviewer (Efficacy)
Division of Oncology Products 2

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

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125547

APPLICANT: Eli Lilly and Company

DRUG: Portrazza (necitumumab)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION(S): Treatment of locally advanced or metastatic squamous
non-small cell lung cancer (NSCLC)

CONSULTATION REQUEST DATE:	January 22, 2015
INSPECTION SUMMARY GOAL DATE:	August 8, 2015
DIVISION ACTION GOAL DATE:	December 2, 2015
PDUFA DATE:	December 2, 2015

I. BACKGROUND:

Eli Lilly and Company [Lilly] seeks approval to market Portrazza (necitumumab) for the treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). Necitumumab is a recombinant human monoclonal antibody of the immunoglobulin G1 class, which targets the epidermal growth factor receptor (EGFR). EGFR is present in tumor specimens taken from patients with metastatic NSCLC at a very high rate: >85%. Necitumumab demonstrates a high affinity to its target and blocks ligand-induced receptor phosphorylation and downstream signaling. In vitro studies demonstrate that necitumumab inhibits EGFR-dependent tumor cell proliferation, and can exert cytotoxic effect in tumor cells through antibody-dependent cell-mediated cytotoxicity.

The key study supporting this application is Study I4X-IE-JFCC (CP11-0806), also known as SQUIRE. This study is a randomized, multicenter, open-label, phase 3 study of gemcitabine-cisplatin chemotherapy plus necitumumab versus gemcitabine-cisplatin alone in first-line treatment of stage IV squamous NSCLC. The study was multinational, with a projected enrollment of 1080 subjects with Stage-IV squamous NSCLC (AJCC Staging Manual, Seventh Edition). Subjects were randomized on a 1:1 basis to receive first-line necitumumab plus chemotherapy consisting of gemcitabine and cisplatin in study Arm A, or first-line gemcitabine-cisplatin chemotherapy alone in Arm B. A treatment cycle was defined as 3 weeks. In total, 1093 subjects (545 patients in the GC+N Arm, 548 patients in the GC Arm) were enrolled. The study was conducted at 184 centers in 26 countries. The study was conducted under IND #102512.

The primary efficacy endpoint is overall survival (OS); the outcome measure is defined as the time from the date of randomization to the date of death from any cause. Subjects who are alive at the time of study completion or are lost to follow-up will be censored at the time they were last known to be alive. The data cut-off date for analysis was June 17, 2013.

Three clinical sites were chosen for inspection: Site 321 (Dr. Tudor Eliade Ciuleanu, Romania), Site 133 (Dr. Perrine Crequit, France), and Site 324 (Dr. Mircea Dediu, Romania) based on enrollment of large numbers of study subjects, and significant study drug primary efficacy results and general safety reports pertinent to decision making. The study sponsor, Eli Lilly and Company, was also inspected.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Tudor Eliade Ciuleanu 34-36 Republicii Street Cluj-Napoca, 400015 Romania	Protocol: I4X-IE-JFCC (CP11-0806) Site Number: 321 Number of Subjects: 39	April 27,– May 1, 2015	Pending Interim classification: VAI
CI#2: Perrine Crequit 4 Rue de la Chine Paris, 75020 France	Protocol: I4X-IE-JFCC (CP11-0806) Site Number: 133 Number of Subjects: 10	April 20-24, 2015	NAI
CI#3: Mircea Dediu 252 Fundeni Street Bucharest, 22328 Romania	Protocol: I4X-IE-JFCC (CP11-0806) Site Number: 324 Number of Subjects: 27	April 20-24, 2015	Pending Interim classification: NAI
Sponsor: Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285	Protocol: I4X-IE-JFCC (CP11-0806) Number of Sites Audited: 5 (Sites 321, 133, 324, 156, and 702)	May 4-12, 2015	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

1. CI#1: Dr. Tudor Eliade Ciuleanu (Site 321)

- a. What was inspected:** The site screened forty one subjects and thirty nine subjects were enrolled and randomized. At the time of the inspection thirty eight subjects had completed the end-of-study visit. The study records of all subjects were audited for informed consent, thirty nine for primary (OS) and secondary (Progression Free Survival [PFS]) efficacy endpoints, and twelve for eligibility and general protocol compliance. The record audit included comparison of source documentation to eCRFs and data listings submitted to the original BLA #125547. The FDA investigator also assessed test article accountability, and monitoring reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint of OS was verifiable. The secondary endpoint of PFS was also verifiable. There was no evidence of under-reporting of AEs or SAEs. The inspection revealed a number of protocol deviations as well as two incidences where the drug accountability log failed to document the disposition of unused test article for two study subjects. A Form FDA 483 was issued citing 2 inspectional observations for failure to follow the investigational plan and inadequate drug disposition records.

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

Specifically, the following protocol deviations were observed regarding versions 1.0, 2.2, 3.0, and/or 6.0 of Clinical Trial Protocol IMCL CP11-0806:

- a. The protocol, IMCL CP11-0806, Section 3.2, Inclusion Criteria #7, specifies ALT levels at screening may not exceed 2.5x ULN (41 U/L x 2.5= 103 U/L). Subject 3216003 had an ALT value of 121 U/L at screening, on July 30, 2010. Subject 3216003 did not meet inclusion criteria #7, yet the subject was randomized on August 2, 2010 and treated with the investigational product on the same day.

OSI Reviewer Notes: Dr. Ciuleanu provided a written response, dated May 21, 2015, to the Form FDA 483 inspectional observations. Regarding observation 1.a., Dr. Ciuleanu concurs with the observation and indicated that this was an oversight. The subject was subsequently retested at Cycle 2 Day 1 and Cycle 3 Day 1, as per protocol, and the subject's ALT was within the normal range. The deviation was also documented by the monitor at the next monitoring visit after this subject was randomized. The site staff was immediately retrained on study procedures. A request for approving the subject to continue in the study was sent to the study medical monitor on October 7, 2010, and granted on October 8, 2010. Subject 3216003 was randomized to the active treatment arm (gemcitabine-cisplatin chemotherapy plus necitumumab). No other subject enrollment violations were noted. Dr. Ciuleanu promised continuous improvement and corrective actions to mitigate such protocol violations moving forward.

- b. The site did not always report SAEs to the sponsor within 24 hours of becoming aware of the event. The protocol, IMCL CP11-0806, Section 8.9, specifies SAEs to be reported to the sponsor by facsimile within 24 hours of the site's initial awareness of the event.
- i. An SAE, death [REDACTED] ^{(b) (6)}, for Subject 3216019 was reported to the sponsor on May 14, 2013. The site had documented awareness of the event on June 18, 2012.

- ii. An SAE, death [REDACTED]^{(b) (6)}, for subject 3216034 was reported to the sponsor on February 26, 2012. The site had documented awareness of the event on January 26, 2012.

OSI Reviewer Notes: Dr. Ciuleanu provided a written response, dated May 21, 2015, to the Form FDA 483 inspectional observations. Regarding observation 1.b., Dr. Ciuleanu stated that the site initially reported the SAE for Subject 3216019 on June 18, 2012. However, the initial report apparently was not received by the sponsor and the site was unaware. Documentation of the initial SAE report could not be found at the site, therefore, the site generated a new SAE report and provided it to the sponsor on May 14, 2013. With respect to Subject 3216034, Dr. Ciuleanu concurs that the SAE was reported one month late. The corrective action plan includes additional site staff training and more robust procedures for tracking and documenting study events for each study subject. Subjects 6019 and 6034 were both randomized to the active treatment arm (gemcitabine-cisplatin chemotherapy plus necitumumab).

- c. The protocol, IMCL CP11-0806, Section 8.9, requires follow-up information of an SAE to be immediately sent to the sponsor as it becomes available. The sponsor and/or CRA requested follow-up information from the site on an SAE (death) reported [REDACTED]^{(b) (6)} for subject 3216029 more than 4 times beginning May 25, 2011. The site did not provide the requested follow-up information until January 17, 2012.

OSI Reviewer Notes: Dr. Ciuleanu stated in his written response, dated May 21, 2015, that the first three times the sponsor sent emails requesting additional information on the SAE reported on [REDACTED]^{(b) (6)} for Subject 3216029, the sponsor sent them to an incorrect email address for the sub-investigator, Dr. [REDACTED]^{(b) (4)}. On October 28, 2011, the study CRA was contacted by the sponsor for assistance in obtaining the additional information. Dr. Ciuleanu stated that the first request for additional information on the above SAE was received by the site on November 18, 2011, approximately [REDACTED]^{(b) (6)} after the subject died. According to Dr. Ciuleanu, as the subject had died, the medical chart was sent for registration to the hospital archive, on or about [REDACTED]^{(b) (6)}. The medical chart was made available to the site on January 17, 2012.

- d. The Cycle 1/Day 8 chemistry lab report dated September 30, 2011 for Subject 3216038 did not include 15 analytes as required by section 6.5.1 of the protocol, e.g. sodium, potassium, chloride, blood urea nitrogen, glucose, total protein, albumin, phosphorus, etc.
- e. The Cycle 55/Day 1 lab report dated July 28, 2014 for Subject 3216028 did not include coagulation factors, albumin, uric acid, total protein, or lactate dehydrogenase as required by Section 6.5.1 of the protocol.

OSI Reviewer Notes: Dr. Ciuleanu stated in his written response that these protocol violations were discovered during routine monitoring visits at the site in 2011 and 2014, respectively. When discovered they were immediately addressed during the monitoring visit, and in the monitoring follow up letters. Preventative and corrective actions were implemented after the violations were discovered. These protocol violations should not importantly impact overall study outcomes, nor would they have put subjects at significantly increased risk.

- f. Section 13.10 of the protocol states that financial disclosure information must be provided by all subinvestigators prior to the start of the study. This was not always done.
 - i. Subinvestigator (b) (4) started with the study on January 13, 2011, signed a patient record March 1, 2011, yet did not provide financial disclosure information until April 6, 2011.
 - ii. Subinvestigator (b) (4) started with the study July 6, 2010, conducted IVRS patient randomization and visit notifications in July 2010, yet did not provide financial disclosure information until afterwards on July 29, 2010.

OSI Reviewer Notes: Dr. Ciuleanu provided a written response, dated May 21, 2015, to the Form FDA 483 inspectional observations. Dr. Ciuleanu confirmed that these sub-investigators were being trained and as such, were not directly responsible for any medical decisions and never acted without direct supervision by Dr. Ciuleanu or Dr. (b) (4). Explanations and corrective action plans were provided for each inspectional observation. These protocol violations should not importantly impact overall study outcomes, nor would they have put subjects at increased risk.

Observation 2. Investigational drug disposition records are not adequate with respect to quantity and use by subjects.

Specifically, the "Investigational Product IMC-11F8 Accountability - Site Master Log" did not record unused but IVRS-dispensed investigational product, and did not record the destruction of these products. Subjects 3216022 and 3216027 were each dispensed an IMC-11F8 kit that were not used and were not recorded as unused or disposed of in the Site Master Log.

OSI Reviewer Notes: Dr. Ciuleanu concurred with the observation and explained that the site initially misunderstood how to use the "Investigational Product IMC-11F8 Accountability-Site Master Log" tool. Apparently, instead of filling the log with the number of vials actually administered to subjects this tool has been completed to reflect the IVRS dispensed vials of IP. The correct information regarding treatment received by each patient is reflected on the "Subject Investigational Product Accountability Records IMC-11F8". The site

acknowledges the misuse of the “Investigational Product IMC-11F8 Accountability-Site Master-Log”, and they have since corrected this by documenting separately the number of IP vials that were not used, matching the information in “Subject Investigational Product Accountability Records IMC-11F8”. Dr. Ciuleanu provided supporting documentation. With respect to IP destruction, the site routinely performs IP destruction according to the hospital’s Destruction SOP, which was also provided with the written response.

- c. Assessment of data integrity:** Notwithstanding the inspection observations noted, the data for Dr. Ciuleanu’s site, associated with Study I4X-IE-JFCC submitted to the Agency in support of BLA #125547, 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.

2. CI#2: Dr. Perrine Crequit (Site 133)

- a. What was inspected:** The site screened ten subjects and all ten subjects were enrolled. At the time of this inspection seven subjects had completed the study and three had discontinued. The study records of all ten subjects were audited. The following information was reviewed during the inspection: correspondences between the site, sponsor and monitor, contract research organizations (CRO), and the site ethics committee, adverse event reporting, delegation of authority, study schedules, training, statement of investigators, financial disclosures, test article accountability, eCRFs, randomization, protocol deviations, and all ten subject source study records. Subject folders included informed consent forms, and inclusion/exclusion criteria, screening, enrolling, dosing, laboratory results and subject visits/phone calls source documentation. Source documents were compared to the site’s electronic records. Source documents were also compared with the information provided to the FDA for the site.
- b. General observations/commentary:** Generally, the investigator’s execution of the protocol was found to be good. Records and procedures were clear, and generally well organized. There were no observations of data integrity issues. The primary (OS) and secondary (PFS) efficacy endpoint data were verified. There was no evidence of underreporting of adverse events. However, there were a few instances of late reporting of SAEs that were discussed with site staff at the close out meeting. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no major discrepancies. A Form FDA 483 Inspectional Observations was not issued.

c. Assessment of data integrity: The data for Dr. Crequit's site, associated with Study I4X-IE-JFCC submitted to the Agency in support of BLA 125547, appear reliable based on available information.

3. CI#3: Dr. Mircea Dediu (Site 324)

a. What was inspected: The site screened thirty one subjects and twenty seven subjects were enrolled. At the time of this inspection twenty subjects had completed the end-of-study visit, but only seven of those completed the study treatments. All subject study records were audited for informed consent, and twenty seven subject records were reviewed for the primary (OS) and secondary (PFS) efficacy endpoints and general protocol compliance. The record audit included comparison of source documentation to eCRFs and data listings submitted to the original BLA 125547, focusing on protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed test article accountability, and monitoring reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be good. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary (OS) and secondary (PFS) efficacy endpoint data were verified. With one minor exception, grade 1 nausea for one subject that was not listed in the application datalistsings, there was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. Investigational drug accountability records were sufficient to reconcile the quantity received, dispensed, and destroyed/returned. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. Dediu's site, associated with Study I4X-IE-JFCC submitted to the Agency in support of BLA #125547, 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.

4. Sponsor: Eli Lilly and Company

- a. **What was inspected:** The inspection focused on study Sites 133, 321, 324, 156, and 702. The inspection included but was not limited to oversight and control of study conduct, firm organizational structure, assessment of adverse events/serious adverse events reporting, efficacy endpoint data, Principal Investigator site qualification (financial disclosure, IRB, and curriculum vitae), test article accountability, monitoring and sponsor audits, vendor qualification, and vendor selection.
- b. **General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight and control of the study. Monitoring reports for five study sites were reviewed in detail (Sites 133, 321, 324, 156 and 702). Monitoring appeared to be adequate. There was no evidence of the sponsor underreporting AEs. The primary efficacy endpoint data were verified for Sites 133, 32,1 and 324 against data listings submitted to the application. No discrepancies were noted. Compliance with the study protocol, the sponsor's own SOPs, and relevant regulatory requirements appeared to be adequate. No study sites were closed due to non-compliance. A Form FDA 483 was not issued.
- c. **Assessment of data integrity:** The data from this sponsor submitted to the Agency associated with Study I4X-IE-JFCC submitted to the Agency in support of BLA 125547, appear reliable based on available information.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of inspectional findings for Site 321 (Dr. Tudor Eliade Ciuleanu), Site 133 (Dr. Perrine Crequit), Site 324 (Dr. Mircea Dediu) and the study sponsor, Eli Lilly and Company, the Study I4X-IE-JFCC (CP11-0806) data submitted to the Agency in support of BLA 125547 appear reliable based on available information.

With respect to Dr. Ciuleanu's site, the inspection revealed a number of protocol deviations, as well as two incidences where a drug accountability log failed to document the disposition of unused test article for two study subjects. Dr. Ciuleanu provided a written response, dated May 21, 2015, to the Form FDA 483 inspectional observations. The written response provided adequate explanations and detailed corrective actions to prevent reoccurrences moving forward. The observations noted for Dr. Ciuleanu's site should not importantly impact overall study outcome or have placed study subjects at increased risk.

Note: Some of the observations noted above are based on the preliminary communications 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.

{ See appended electronic signature page }

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

CONCURRENCE:

{ See appended electronic signature page }

Susan D. Thompson, M.D.
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Division of Clinical Compliance Evaluation
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/s/

LAUREN C IACONO-CONNORS
07/28/2015

SUSAN D THOMPSON
07/28/2015

KASSA AYALEW
07/29/2015

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: May 20, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: BLA 125547
Product Name and Strength: Portrazza (Necitumumab) Injection,
800 mg/50 mL (16 mg/mL)
Product Type: Single-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Eli Lilly and Company
Submission Date: December 2, 2014 and February 13, 2015
OSE RCM #: 2014-2463
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed Portrazza (Necitumumab) prescribing information, container label, 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.

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

Container label and carton labeling are acceptable from a medication error perspective. However, the Prescribing Information can be improved to provide clarity.

4 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI) can be improved to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR DOP2

Prescribing Information (PI)

1. Delete the statement, [REDACTED] (b) (4) after the recommended dose 800 mg as this is redundant and may confuse readers.
2. As discussed with Clinical Pharmacology and the remainder of the review team, and as communicated to the Applicant during the mid-cycle meeting held on Friday, May 8, 2015; to avoid confusion between the numerals [REDACTED] (b) (4) when spoken, we recommend the infusion time be change [REDACTED] (b) (4) to 60 minutes.

3. In section 2.2 (Premedication), delete the first sentence (b) (4)
(b) (4).

4. Spell out the abbreviation, IRR, the first time it is used in the body of the Full Prescribing Information (section 2.2), such that it reads, “Infusion-related Reaction (IRR)”. We would also recommend the same for the sub-heading, “IRR” in section 2.3 Dose Modifications.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Portrazza that Lilly submitted on February 13, 2015.

Table 2. Relevant Product Information for Portrazza	
Initial Approval Date	N/A
Active Ingredient	Necitumumab
Indication	In combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.
Route of Administration	Intravenous infusion
Dosage Form	Injection for intravenous infusion
Strength	800 mg/50 mL (16 mg/mL)
Dose and Frequency	800 mg via intravenous infusion over (b) (4) minutes on Day 1 and Day 8 of a 3 week cycle.
How Supplied	Single-dose glass vial with (b) (4) stopper and aluminum seal with (b) (4) (b) (4) flip top.
Storage	Store refrigerated at 2°C to 8°C

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,¹ along with postmarket medication error data, we reviewed the following Portrazza labels and labeling.

- Container label (submitted December 2, 2014)
- Carton labeling (submitted December 2, 2014)
- Prescribing Information (submitted February 13, 2015)

G.2 Label and Labeling Images



¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

(b) (4)



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/s/

OTTO L TOWNSEND
05/20/2015

CHI-MING TU
05/20/2015



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 9, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Mimi Biable, RPM
DOP2

Subject: QT-IRT Consult to BLA 125547

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/9/2015 regarding the sponsor's interim QTc data analysis for the ongoing Study I4X-IE-JFCI described in the Summary of Clinical Pharmacology and the proposed labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT's previous review (8/29/2011, 10/22/2012, 2/10/2014, and 5/29/2014)
- Summary of Clinical Pharmacology
- Proposed label

QT-IRT Comments for DOP2

The interim QTc data analysis for the ongoing Study I4X-IE-JFCI is reasonable. The sponsor did not include any QT-related language in their current proposed label. The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.6 Cardiac Electrophysiology

Necitumumab as a recombinant human monoclonal antibody has a low likelihood of direct ion channel interactions and thus a small QT prolongation risk.

BACKGROUND

In Section 2.7.2.2.4 of the Summary of Clinical Pharmacology, the sponsor described their interim QTc data analysis for the ongoing Study I4X-IE-JFCI. We had previously reviewed their preliminary results in our pre-BLA review and considered they are acceptable. The final study report, once completed, will be submitted along with datasets, waveforms, and additional documentation requested by FDA in its October 2011 advice letter.

Thank you for requesting our input into the development of this product under BLA 125547. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderderpqt@fda.hhs.gov

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/s/

JIANG LIU
03/09/2015

NORMAN L STOCKBRIDGE
03/09/2015

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		
NDA # BLA# 125547/0	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: PORTRAZZA Established/Proper Name: Necitumumab Dosage Form: injection Strengths: 800 mg/50 mL		
Applicant: Eli Lilly and Company Agent for Applicant (if applicable):		
Date of Application: December 2, 2014 Date of Receipt: December 2, 2014 Date clock started after UN:		
PDUFA/BsUFA Goal Date: December 2, 2015		Action Goal Date (if different):
Filing Date: January 31, 2015		Date of Filing Meeting: January 23, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): For the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin.		
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	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR
<ul style="list-style-type: none"><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i>	<input type="checkbox"/> QIDP
<ul style="list-style-type: none"><i>The product is a Qualified Infectious Disease Product (QIDP)</i>	<input type="checkbox"/> Tropical Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A Tropical Disease Priority Review Voucher was submitted</i>	<input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<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 checked="" type="checkbox"/> Fast Track Designation	<input type="checkbox"/> PMC response
<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"/> PMR response:
<input checked="" type="checkbox"/> Rolling Review	<input type="checkbox"/> FDAAA [505(o)]
<input type="checkbox"/> Orphan Designation	<input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)
<input type="checkbox"/> Rx-to-OTC switch, Full	<input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
<input type="checkbox"/> Rx-to-OTC switch, Partial	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 102512

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA 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 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</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Standard
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<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"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <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>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<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>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• 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)].		<input type="checkbox"/>	<input type="checkbox"/>		
• 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)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted 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 for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
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)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input 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 type="checkbox"/>	
BLAs only: 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 checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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 checked="" 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?				
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 type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<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.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
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 (3397/3792), 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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
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 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <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> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC meeting is scheduled for February 11, 2015.

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 12/09/2014

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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.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Request for full waiver of pediatric studies included
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
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) <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>				

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/09/2014

8

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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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"/>	No MedGuide, PPI, IFU
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? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" 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) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT consult sent on 1-9-2015.
Meeting Minutes/SPAs	YES	NO	NA	Comment

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		10-5-2008
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		6-23-2014
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 23, 2015

BACKGROUND: This BLA proposes the use of necitumumab for the first-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic squamous non-small cell lung cancer. Fast track designation, under IND 102512, was granted on October 10, 2013. An End-of Phase 2 meeting was held with Lilly on October 5, 2008 and a pre-BLA meeting was held on June 23, 2014 where an agreement on the content of a complete application was reached. On August 13, 2014, Lilly submitted a request for rolling submission and FDA accepted the request and their plan for submitting portions of the proposed application on August 26, 2014. The nonclinical portion of the BLA was received on October 22, 2014, the clinical piece on November 25, 2014 and the last piece, the CMC portion was received on December 2, 2014.

Summary of Discussion: No filing issues were discussed or identified by any of the review divisions during this meeting. There are pending information requests, and additional information requests to be sent; however, they are not potential filing issues.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mimi Biable	Y
	CPMS/TL:	Monica Hughes	Y
Cross-Discipline Team Leader (CDTL)	Gideon Blumenthal		Y
Division Director/Deputy	Patricia Keegan		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Lee Pai-Scherf	Y
	TL:	Gideon Blumenthal	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial</i>)	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Pharmacology	Reviewer:	Safaa Burns	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Lijun Zhang	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Margaret E Brower	Y
	TL:	Whitney Helms	Y
Pharmacometrics	Reviewer:	Hongshan Li	Y
	TL:	Yaning Wang	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:	Audrey Jia	Y
	TL:	Chana Fuchs	N
Product Quality (CMC)	Reviewer:	Audrey Jia	Y
	TL:	Chana Fuchs	N
Biopharmaceutics	Reviewer		
	TL:		
Quality Microbiology <i>(for sterile products)</i>	Reviewer:	Candace Gomez-Broughton (DS)	Y
	Reviewer:	Lakshmi Narasimhan (DP)	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Jibril Abdus-Samad	Y
	TL:		
Facility Review/Inspection	Reviewer:	Candace Gomez-Broughton (DS)	Y
	Reviewer:	Lakshmi Narasimhan (DP)	Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name,	Reviewer:	Otto Townshend	Y

carton/container labels))	TL:	Alice Chi-Ming Tu	N
	Reviewer:	Mona Patel	N
OSE/DRISK (REMS)	TL:	Naomi Redd	Y
	Reviewer:		
OC/OSI/DSC/PMSB (REMS)	TL:		
	Reviewer:		
Bioresearch Monitoring (OSI)	TL:	Susan Thompson	N
	Reviewer:	Lauren Iacono-Connor	N
Controlled Substance Staff (CSS)	TL:		
	Reviewer:		
Other reviewers/disciplines OPDP	TL:		
	Reviewer:	Nazia Fatima	Y
Other attendees	Latonia Ford, OSE RPM Frances Fahnbulleh, , OSE RPM Shaily Arora, , OSE/DPVII reviewer Tracy Salaam, OSE/DPVII team leader		

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? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments 	<input type="checkbox"/> Not Applicable

List comments:	<input checked="" type="checkbox"/> No comments
CLINICAL Comments:	<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
<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? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <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> 	<input checked="" type="checkbox"/> YES Date if known: The week of July 6 th , 2015 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<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? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
New Molecular Entity (NDAs only)	
<ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u>	
<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
Comments:	

<p><u>Quality Microbiology</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: No longer needed to submit an establishment evaluation request form as this information is readily available in panorama.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></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><u>CMC Labeling Review</u></p> <p>Comments: None</p>	<input type="checkbox"/> Review issues for 74-day letter
<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? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	N/A
<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? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): April 24, 2015.</p>	
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 checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input 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, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone 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"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

MISSIRATCH BIABLE
01/29/2015

MELANIE B PIERCE
01/29/2015

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 125547/0

Application Type: New BLA

Name of Drug/Dosage Form: PORTRAZZA (necitumumab) Injection, for intravenous use

Applicant: Eli Lilly and Co (Lilly)

Receipt Date: December 2, 2014

Goal Date: December 2, 2015

1. Regulatory History and Applicant's Main Proposals

This BLA proposes the use of necitumumab for the first-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic squamous non-small cell lung cancer. Fast track designation, under IND 102512, was granted on October 10, 2013. An End-of Phase 2 meeting was held with Lilly on October 5, 2008 and a pre-BLA meeting was held on June 23, 2014 where an agreement on the content of a complete application was reached. On August 13, 2014, Lilly submitted a request for rolling submission and FDA accepted the request and their plan for submitting portions of the proposed application on August 26, 2014. The nonclinical portion of the BLA was received on October 22, 2014, the clinical piece on November 25, 2014 and the last piece, the CMC portion was received on December 2, 2014.

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).

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 19, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

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.

Highlights

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

HIGHLIGHTS GENERAL FORMAT

- 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: No comments.
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment: No comments.
- 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: No comments.
- 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 comments.
- 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 no white space between the HL Heading and HL Limitation Statement. There is also no white space between the product title and initial U.S. Approval.
- YES** 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 is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
Comment: No comments.
- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• 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: No comments.

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: No comments.

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: No comments.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment: No comments.

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: No comments.

Boxed Warning (BW) in Highlights

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

Comment: N/A

- 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

Selected Requirements of Prescribing Information

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: *N/A*

- 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: *N/A.*

- 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: *N/A*

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: *N/A*

- 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: *N/A*

- 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: *N/A*

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: *No comments.*

Dosage Forms and Strengths in Highlights

- YES** 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: *No comments.*

Selected Requirements of Prescribing Information

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: *contraindication is listed in HL and the FPI*

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: *No comments*

Patient Counseling Information Statement in Highlights

- YES** 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: *No comments*

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: *No comments*

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:** No comments*
- 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:** No comments*
- 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:** N/A*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
***Comment:** No comments*
- 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:** No comments*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
***Comment:** No comments*
- 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:** No comments*

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: *No comments*

- 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: *No comments*

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: *N/A*

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: *No comments*

BOXED WARNING Section in the FPI

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

Comment: *N/A*

- 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: *N/A*

CONTRAINDICATIONS Section in the FPI

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

Comment: (b) (4)

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: *No comments*

- 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: *N/A*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 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*

- 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: *N/A*

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)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

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

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

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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.

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

/s/

MISSIRATCH BIABLE
01/29/2015

MELANIE B PIERCE
01/29/2015