CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761231Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 8, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761231
Product Name and Strength:	Alymsys (bevacizumab-maly)[1] injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Applicant/Sponsor Name:	Amneal Pharmaceuticals (Amneal)
OSE RCM #:	2021-758-3
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 5, 2022 for Alymsys. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Alymsys (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memo.[2]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[1] The proposed nonproprietary name (bevacizumab-maly) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Alymsys (BLA 761231). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JAN 27. OSE RCM No.: 2021-23.

[2] Thomas, S. Label and Labeling Review for Alymsys (BLA 761231). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APRIL 1. RCM No.: 2021-758-2.

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/s/

SARAH E THOMAS
04/08/2022 01:07:42 PM

JANINE A STEWART
04/08/2022 02:52:43 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 1, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761231
Product Name and Strength:	Alymsys (bevacizumab-maly)[1] injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Applicant/Sponsor Name:	Amneal Pharmaceuticals (Amneal)
OSE RCM #:	2021-758-2
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 28, 2022 for Alymsys. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Alymsys (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

After review of the container labels and carton labeling that the Applicant revised since our last memorandum[2], we note that the Applicant reformatted the labels and labeling, made edits to the color scheme for strength differentiation, removed the "(b) (4)." statement as requested by the Agency, replaced the trademark symbol ("™") with the registered mark symbol ("®") since Alymsys is registered with the US PTO, and added a graphic to the presentation of their proposed proprietary name. The new presentation of the proposed proprietary name was implemented due to a desire to create uniformity of labeling style across

[1] The proposed nonproprietary name (bevacizumab-maly) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Alymsys (BLA 761231). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JAN 27. OSE RCM No.: 2021-23.

[2] Thomas, S. Label and Labeling Review for Alymsys (BLA 761231). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 9. RCM No.: 2021-758-1.

all of Amneal's biosimilar products. We find their proposed edits acceptable from a medication safety perspective but provide one additional recommendation related to the presentation of the proper name and dosage form below in Section 3.

3 RECOMMENDATIONS FOR AMNEAL

We recommend the following be implemented prior to approval of this BLA:

A. We recommend revising the presentation of the proper name and dosage form on the carton labeling in accordance with 21 CFR 201.10(g)(2)[3], as follows:

Alymsys
(bevacizumab-maly)
Injection

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

[3] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

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SARAH E THOMAS
04/01/2022 09:55:37 PM

JANINE A STEWART
04/04/2022 01:09:03 AM

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

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

Memorandum

Date: March 24, 2022

To: Gina Davis, MT, Senior Regulatory Health Project Manager, Division of Oncology 3 (DO3)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ALYMSYS™ (bevacizumab-maly) injection, for intravenous use

BLA: 761231

In response to DO3's consult request dated May 20, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original BLA submission for ALYMSYS™ (bevacizumab-maly) injection, for intravenous use (Alymsys).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling downloaded from DO3's SharePoint on March 18, 2022, and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 1, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
03/24/2022 07:50:43 AM

Clinical Inspection Summary

Date	2/14/2022
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Margaret Thompson MD, Clinical Reviewer Sandra Casek MD, Clinical Team Leader 'Lola Fashoyin-Aje, Deputy Division Director Gina Davis, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761231
Applicant	Amneal Pharmaceuticals LLC
Drug	Bevacizumab (a biosimilar to Avastin)
NME (Yes/No)	No
Therapeutic Classification	Vascular Endothelial Growth Factor (VEGF) Inhibitor
Proposed Indication	Metastatic colorectal carcinoma; non-small cell lung cancer; recurrent glioblastoma; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer.
Consultation Request Date	9/2/2021
Summary Goal Date	3/10/2022
Action Goal Date	4/13/2022
PDUFA Date	4/13/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study MB02-C-02-17 (NCT 03296163) were submitted to the Agency in support of a New Biologics Application (BLA 761231) for a biosimilar to bevacizumab (also known as MB02) for the treatment of adults with metastatic colorectal carcinoma (mCRC), non-squamous, non-small cell lung cancer (nsNSCLC), glioblastoma, metastatic renal cell carcinoma (mRCC), cervical cancer.

Two clinical investigators, Drs. Levenko (Site 2807) and Bondarenko (Site 2801) were selected for clinical inspections. The inspections were not done because of travel restrictions due to COVID-19 pandemic and increased political unrest in Ukraine.

The study sponsor, MAbxience Research SL, and the clinical research (b) (4) were inspected.

Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of the NDA.

II. BACKGROUND

The applicant, Amneal Pharmaceuticals LLC., seeks approval of a biosimilar to bevacizumab for the proposed indication. In support of the BLA, the Applicant submitted clinical data from Study MB02-C-02-17, a phase 3, multi-center, double blind, randomized, parallel group study comparing the proposed bevacizumab biosimilar plus chemotherapy with Avastin plus chemotherapy given as first line in subjects with Stage IIIB/IV non-squamous non-small cell lung cancer (nsNSCLC).

The primary objective of Study MB02-C-02-17 is to compare the objective response rate (ORR) of MB02 and EU-Avastin given with chemotherapy in subjects with advanced nsNSCLC.

The primary endpoint is objective response rate (ORR), either complete response (CR) or partial response (PR), at week 18 (ORR18), evaluated by independent radiological review committee (IRC) as per the Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1) guidelines.

The key secondary endpoints are progression-free survival (PFS) defined as radiological progression per RECIST version 1.1 or death and overall survival (OS) defined as the time from randomization to death, at week 18 and week 52. PFS is evaluated by investigators.

Key inclusion criteria include adult subjects with:

- Newly diagnosed or recurrent Stage IIIB/IV nsNSCLC (not amenable to curative surgery) and have not received systemic therapy for advanced disease,
- For subjects with recurrent disease, at least 6 months were to have elapsed from previous adjuvant treatment before randomization,
- For Stage IV disease, if pleural or pericardial the effusion was the only lesion that confirmed Stage IV of the disease, the malignant effusion was to be confirmed by cytological examination,
- At least one unidimensional measurable target lesion according to RECIST v1.1 assessed by the investigator,
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1,
- Previous radiation therapy if completed > 4 weeks before randomization,
- Palliative radiotherapy to bone lesions if completed >2 weeks prior to randomization.

Key exclusion criteria – subjects could not have:

- Previous treatment with monoclonal antibodies or small molecule inhibitors against vascular endothelial growth factor (VEGF) or VEGF receptors, including Avastin,
- Previous chemotherapy, immunotherapy, targeted therapy, or biological therapy for their lung cancer,

- Known malignant central nervous system disease.

Eligible subjects were to be stratified for gender, smoking status, disease diagnosis (newly diagnosed vs. recurrent) and disease stage (IIIB/IV). Subjects were to be randomized 1:1 to receive either (Arm A) MB02: 15 mg/ kg over 30-90 minutes IV, on Day 1 of every 3-week cycle plus paclitaxel and carboplatin, or (Arm B) Avastin: 15 mg/kg IV on Day 1 of every 3-week cycle plus paclitaxel and carboplatin. Subjects were to be started on paclitaxel 200 mg/m^2 IV over 3 hours, followed by carboplatin AUC_6 IV over 15 to 60 minutes followed by MB02 or Avastin. Treatment was to continue every 3 weeks for 6 cycles. After 6 cycles of combination treatment, subjects were to be able to receive maintenance monotherapy (MB02 or Avastin) every 3 weeks until progressive disease, unacceptable toxicity, death, or Week 52, whichever occurred first. After Week 52, all subjects (including those randomized to Avastin) were to be offered the opportunity to receive biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, initiation of any new treatment, Week 52 (End-of- Study Visit), or death.

Baseline assessments were to be performed up to 28 days before the start of study treatment. Subjects were to undergo tumor assessments for the primary endpoint using CT and/or MRI of the chest, upper abdomen, and any other involved regions at baseline and every 6 weeks at weeks 6, 12, and 18 regardless of treatment cycles completed, then every 9 weeks (3 cycles) until study competition. Subjects who discontinue the study drug without disease progression were to continue tumor assessments every 9 weeks until disease progression, death or until Week 52(End-of-Study Visit), whichever occurs first. Subjects who withdraw because of progressive disease (PD) and/or initiated new antitumor therapy, or those who progress during the follow-up period, were to be followed up for survival at intervals of 12 weeks until death or Week 52 (End-of-Study Visit), whichever occurred first. No further tumor assessment was required. End-of-Study Visit was to take place within 3 weeks of the last treatment cycle, or before the subsequent antitumor therapy (if this is the reason for withdrawal), or at Week 52.

This multicenter study included 102 sites in 16 countries (Brazil, Bulgaria, Chile, Georgia, Greece, Hungary, India, Lebanon, Malaysia, Mexico, Philippines, Russia, Serbia, Thailand, Turkey, and Ukraine) who screened subjects for enrollment into the study. For the study, 627 subjects were randomized 1:1 to two treatment arms MB02 (315 subjects) or Avastin (312 subjects.) Of those randomized, 621 subjects were treated with the study drug. The data cutoff for the current submission is March 31, 2020.

III. RESULTS

1. **mAbxience Research SL (Sponsor)**
C/ Manuel Pombo Angulo, 28, 3rd Floor
Madrid, Spain 28050

Inspection dates: December 13-15, 2021.

MAbxience was inspected as a surveillance inspection for Study MB02-C-02-17. This is the first FDA inspection for the firm.

MAbxience had oversight over the final approval or rejection of sites chosen by the CRO, Quality Assurance, and Pharmacovigilance review. Pharmacovigilance responsibilities included review and approval of serious adverse event (SAE) cases and regulatory unblinding for the reporting of suspected unexpected SAEs, the creation and update of the investigator's brochure (IB) and for distributing it to the sites and ethics committees, and the forwarding of SAEs that occur in other trials studying MB02 to the CRO, (b) (4) Site monitoring was overseen by the CRO, however, issues were escalated to a medical monitor at mAbxience, as needed.

Records reviewed included organizational charts, master service agreements (MSAs), audit plans, transfer of regulatory obligation (TORO) agreements, meeting minutes and emails between the CRO and sponsor, pharmacovigilance (PV) plans, unblinding information (unintentional and SUSAR reporting), Data Safety Monitoring Board minutes, Independent Review Charter and communications, standard operating procedures (SOPs) for vendor selection, investigator brochure creation, and updating and medical oversight

MAbxience appeared to follow their SOPs, conducted audits of their vendors during the study and observed the site audits completed by (b) (4) personnel. They offered proper support to the CRO for trial related activities and were available for appropriate escalation of issues. During the study, two suspected, unexpected serious adverse reactions (SUSARs) for subjects (b) (6) were created that required unblinding. The reports were created and submitted in accordance with the regulations.

There were no regulatory violations regarding mAbxience's responsibilities for the trial.

2. (b) (4)

Inspection dates: December (b) (4)

(b) (4) was inspected as a surveillance inspection for Study MB02-C-02-17. (b) (4) .

This location was last inspected (b) (4) with a regulatory finding of no action indicated. This inspection summary was generated from a preliminary report from the inspector. An inspection summary addendum will be generated in the event there are any changes to the inspection results upon receipt and review of the EIR. (b) (4) is the clinical research organization (CRO) contracted to perform study monitoring and selection of investigators and all 3rd party vendors, data management, statistical analysis, clinical supplies, and oversight for the adjudication committee for the primary endpoint.

There was one instance of blinded personnel receiving unblinded information in an email from the IRT vendor (b) (4). Specifically, blinded personnel at (b) (4) received information about the treatment assignment for Subject (b) (6) via email. The unblinding was limited to one study subject, and is adequately reported in the submitted data as a protocol violation. The CRO had a communication plan in place to prevent unblinding, but the vendor did not follow the communication plan. A randomization sheet generated by the IXRS system was emailed to the site and CRO study team with the study arm (medication name) instead of dosing being provided. The vendor incident report stated that the MB02 or AVASTIN Dosage field wasn't clearly defined in the IRT subject visit notification. The vendor created a CAPA and issue was corrected prior to the enrollment of any other subjects and review of the protocol deviations listing did not demonstrate further instances of unintentional blinding.

Reviewer's Comments: The unblinding occurred due to vendor error: They did not always mark e-mails as "UN-BLINDED" or password protect attachments to prevent unblinding. The vendor stated the MB02 or AVASTIN Dosage field wasn't clearly defined in the IRT subject visit notification. The vendor's CAPA was acceptable and no further instances of unintentional unblinding occurred.

There was no evidence of inadequate monitoring or site selection and oversight. There were no regulatory violations regarding (b) (4) responsibilities for the trial.

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

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

cc:

Review Division /Division Director/'Lola Fashoyin-Aje, MD
Review Division /Project Manager/ Gina Davis
Review Division/Cross Discipline Team Lead/Sandra Casek, MD
Review Division/Clinical Reviewer/ Margaret Thompson, MD
OSI/Office Director/Dave Burrow
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

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KAREN B BLEICH
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KASSA AYALEW
02/17/2022 05:45:37 AM

M E M O R A N D U M

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

DATE: February 11, 2022

TO: Steven Lemery, M.D.
Associate Director
Division of Oncology III (DO-III)
Office of Oncologic Diseases (OOD)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Senior Staff Fellow
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI/OSIS

SUBJECT: Routine inspection of PAREXEL International GmbH, Berlin, Germany; and remote record review (RRR) of (b) (4)

1. Summary

1.1 Inspection (Clinical)

Per the request of OND/OOD/DO-III, OSIS arranged an inspection of clinical portion of **Study MB02-A-05-18** [**BLA 761231,** Alymsys® (MB02, a proposed biosimilar to bevacizumab/Avastin®)] conducted at PAREXEL International GmbH, Berlin, Germany. No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the clinical data from the audited study are reliable.

1.2 Remote Record Review (Analytical)

OSIS conducted a remote record review (RRR) of analytical portion of **Studies MB02-A-05-18 and MB02-C-02-17** [**BLA 761231,** Alymsys® (MB02, a proposed biosimilar to bevacizumab/Avastin®)]

conducted at (b) (4) An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

I did not observe any objectionable conditions during the RRR that impact reliability of study data.

Recommendation

Based on my review of the inspectional findings and the study records during the RRR, I conclude the clinical and analytical data from **Studies MB02-A-05-18** and **MB02-C-02-17** are reliable.

2. Inspected and Reviewed Studies

BLA 761231

Study #1: **MB02-A-05-18**

Study Title: *"A Randomized, Double-Blind, Three-Arm, Single Dose, Parallel Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licensed Avastin® and EU-approved Avastin® in Healthy Male Volunteers"*

Dates of Clinical Conduct: September 2019 - March 2020

Dates of Analytical Conduct: (b) (4) (PK)
(b) (4) (Immunogenicity)

Clinical Site: **PAREXEL International GmbH**
Klinikum Westend, Haus 31
Spandauer Damm 130
Berlin, Germany

Study #2: **MB02-C-02-17**

Study Title: *"A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination with Carboplatin and Paclitaxel for the Treatment of Subjects with Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)"*

Dates of Clinical Conduct: February 2018 - February 2020

Dates of Analytical Conduct: (b) (4) (Immunogenicity)*

***PK sample analysis was not performed.

Study #3: **MB02-A-04-18 (surveillance purpose)**

Study Title: *"A Randomized, Double Blind, Two-Arm, Single Dose, Parallel Phase I Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (a proposed bevacizumab biosimilar drug) and EU approved Avastin® in Japanese Healthy Male Volunteers"*

Dates of Clinical Conduct: August - December 2019

Dates of Analytical Conduct: (b) (4) (PK)
(b) (4) (Immunogenicity)

Analytical Site: (b) (4)

3. Inspectional Findings

ORA Investigator Craig A. Garmendia (OBIMO) inspected PAREXEL International GmbH, Berlin, Germany from November 8 - 12, 2021.

The previous FDA BIMO onsite inspection was conducted by ORA in (b) (4) covering two studies submitted to a 505(b)(2) (b) (4) for comparison between Test and Reference products with different formulations. The final classification was Voluntary Action Indicated (VAI). Form FDA 483 was issued because the reserve samples of the Investigational Products (IPs) were not selected and retained by the clinical site due to no availability of an onsite pharmacy. Instead, the reserve samples were selected and retained by a third-party pharmacy prior to shipping the IPs to the clinical site. During the current inspection, Investigator Garmendia verified that PAREXEL has implemented corrective and preventive actions by sending delegated PAREXEL personnel to the pharmacy to select the reserve samples.

A remote regulatory assessment (RRA) of PAREXEL was conducted by ORA in September 2020 when an onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic. No objectionable conditions were observed at the RRA close-out.

The current inspection included a review of **Study MB02-A-05-18** records and procedures related to the authority and study administration, study protocols, Institutional Ethics Committee (IEC) submissions and approvals, subject selection criteria and informed consents, investigational medication controls, source data evaluation, adverse event reports, clinical source data, investigational drug accountability, randomization and blinding, reserve samples, monitoring, concomitant therapies, and sponsor audit activities.

At the conclusion of the inspection, Investigator Garmendia did not have significant objectionable findings and did not issue Form FDA 483 to the clinical site. He verbally discussed one item with the site's management. The discussion item and my evaluations are presented below.

(b) (4)

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ARINDAM DASGUPTA
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: January 12, 2022 **Date consulted:** May 26, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

To: Division of Oncology 3

Drug: Alymsys (bevacizumab) for injection

Drug Class vascular endothelial growth factor (VEGF) inhibitors

BLA: 761231

Applicant: Amneal Pharmaceuticals, LLC

Subject: Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Proposed Indications:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-

based chemotherapy for second-line treatment in patients who have progressed on a first line Alymsys-containing regimen.

- **Proposed Limitations of Use**: Alymsys is not indicated for adjuvant treatment of colon cancer.
  - Unresectable, locally advanced, recurrent, or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment.
  - Recurrent glioblastoma in adults.
  - Metastatic renal cell carcinoma in combination with interferon alfa.
  - Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.

Materials Reviewed:

- DPMH consult request, dated May 26, 2021, DARRTS Reference ID: 4801639.
- Applicant's submission of Marketing Application for BLA 761231, Alymsys, a biosimilar to Avastin, of April 13, 2021
- Applicant's Response to Agency's Information Request (IR) of September 14, 2021 named "A Summary of Literature for Bevacizumab Use in Pregnant and Lactating Women and its Effects on Male and Female Fertility" of October 2021
- Avastin Safety Review by Carol Kasten, M.D., in DARRTS, dated April 17, 2017, Reference ID: 4081239
- Original or First Drug Safety Report (DSR1) No. 1-059-564, "Fetal abnormalities with Avastin use," dated August 25, 2014
- First Addendum or Second DSR (DSR2) No. 1-065-816, "Fetal malformations with intravitreally administered bevacizumab or ranibizumab," dated June 12, 2015
- Second Addendum or Third DSR (DSR3) No. 1-067-719, "Embryo-fetal development and pregnancy outcomes with intravitreal administration of bevacizumab or ranibizumab," dated Nov 9, 2015

Consult Question: The Division of Oncology 3 received a Marketing Application for BLA 761231 for Alymsys, a biosimilar to Avastin, BLA 125085, and approved on February 26, 2004. The Division requests DPMH-MHT assistance in the Pregnancy and Lactation subsections of the labeling as per PLLR and if DPMH identifies any issues that may impact the review/action of the marketing application.

INTRODUCTION AND BACKGROUND

On April 13, 2021, Amneal Pharmaceuticals, LLC, the applicant , submitted a Marketing Application for BLA 761231, Alymsys, a biosimilar to Avastin.
On May 26, 2021, the Division Oncology 3 consulted DPMH to provide input to the Pregnancy and Lactation subsections of the labeling as per PLLR.

Regulatory History

Avastin, BLA 125085, was approved on February 26, 2004. Alymsys is a biosimilar to Avastin and seeks approval under the 351(k) pathway.

State of Current Labeling

The last approved Avastin labeling is dated December 9, 2020. The labeling is in Physician Labeling Rule (PLR) and PLLR format.

HIGHLIGHTS OF PRESCRIBING INFORMATION
----WARNINGS AND PRECAUTIONS----

- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception.
- Ovarian Failure: Advise females of the potential risk.

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

- Lactation: Advise not to breastfeed.

FULL PRESCRIBING INFORMATION
5 WARNINGS AND PRECAUTIONS
5.10 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, Avastin may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.11 Ovarian Failure

The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or an FSH level < 30 mIU/mL during the post-treatment period. Long-term effects of Avastin on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)],* Avastin may cause fetal harm in pregnant women. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug-associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *(see Data)*. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryofetal development, and postnatal development. 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% to 4% and 15% to 20%, respectively.

Data

Animal Data

Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6−18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

Risk Summary

No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females Avastin may 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 Avastin and for 6 months after the last dose.

Infertility

Females

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared to patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients *[see Warnings and Precautions (5.11), Adverse Reactions (6.1)]*.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Characteristics[1]

Drug Class	Vascular endothelial growth factor (VEGF) inhibitor. A recombinant humanized monoclonal IgG1 antibody
Molecular Weight	149 KDaltons
Terminal Half-Life	20 days (11 days-50 days)
Bioavailability	Bevacizumab is administered intravenously
Serious Adverse Reactions	Gallbladder perforation, pancytopenia, thromboembolic events, heart failure and ovarian failure, osteonecrosis of the jaw, arterial aneurysms and dissections

[1] Existing labeling for Avastin last approved on December 9, 2020.

REVIEW
PREGNANCY

Review of Nonclinical Data[1]
The applicant did not perform any nonclinical studies except to compare BEVZ92 (Alymsys) to Avastin. In the proposed labeling for Alymsys, the applicant proposes the same language and information as in Avastin.

Review of Clinical Data
Applicant Review of Literature
There have been no studies evaluating the effects of bevacizumab in pregnant women. In clinical trials pregnant women were excluded. Published single patient case reports, with off label use of the drug with intravitreal drug injection, did not show any adverse reactions for the pregnant patient or the fetus. These are single patient case reports and all authors conclude that "there is insufficient information to suggest that such use is safe, as well as there is no definitive evidence to suggest that it causes harm."[2,3,4]
A literature search was performed in Embase with terms "bevacizumab" AND "congenital disorder" OR "pregnancy" OR "pregnant*" OR 'pregnanc*"or "pregnancy complication" OR "pregnancy disorder" OR "abortion" OR "fetus" OR "embryo" OR "prenatal" OR "perinatal" OR "newborn" OR "teratogenicity" OR "congenital malformation" OR "pregnancy outcome" and all publications addressing safety of monoclonal antibodies (mAbs) during pregnancy were reviewed.
As per applicant, very few data on the use of bevacizumab in pregnant women exists. From the identified publications, the applicant reviewed only literature published in the years 2020 and 2021 because they consider these publications to be "most relevant for the discussion of its potential labelling update because the updated labelling of the Reference Product in December 2020 is deemed to have reflected the relevant safety information at least until the end of year 2019". Therefore, no publications were identified. Some older publications include:

1. Pagniez D.C. 2019[5] reports on one patient who was treated for breast carcinoma with partial mastectomy, chemotherapy associated with Bevacizumab, and radiotherapy. Three years later, bilateral ovariectomy was about to be performed, when an unexpected pregnancy was found. The patient elected to continue with this pregnancy. Severe intra uterine growth retardation occurred, and cesarean section was performed at 29 weeks of amenorrhea, because of preeclampsia with the HELLP syndrome. Four months later after delivery, blood pressure and renal function were normal, and there was no proteinuria. The author concluded that "antiangiogenic drugs can alter the transcription profile of acetylation genes and this observation supports the hypothesis that bevacizumab may have long-lasting endothelial effects through epigenetic pathways."

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[2] Sullivan L., Kelly S.P., Glenn A., Williams C.P.R., McKibbin M. Intravitreal bevacizumab injection in unrecognised early pregnancy. Eye (Basingstoke) (2014) 28:4 (492-494).
[3] Introini U., Casalino G., Cardani A., Scotti F., Finardi A., Candiani M., Bandello F. Intravitreal bevacizumab for a subfoveal myopic choroidal neovascularization in the first trimester of pregnancy. Journal of Ocular Pharmacology and Therapeutics (2012) 28:5 (553-555).
[4] Tarantola R.M., Folk J.C., Boldt H.C., Mahajan V.B. Intravitreal bevacizumab during pregnancy. Retina (2010) 30:9 (1405-1411).
[5] Pagniez D.C. Severe placental insufficiency 3 years after treatment with bevacizumab: An epigenetic effect? Journal of the American Society of Nephrology (2019) 30 (807).

2. Duriseti P. *et. al*.[6]. A 27-year-old female with hypertension, chronic kidney disease, uncontrolled type 1 diabetes mellitus complicated by proliferative diabetic retinopathy treated with intravitreal bevacizumab. Her pregnancy was complicated by severe preeclampsia and acute kidney injury. The authors consider

   > Pre-eclampsia has been associated with kidney injury causing thrombotic microangiopathy and collapsing glomerulopathy secondary to endothelial injury following inhibition of vascular endothelial growth factor (VEGF) by the soluble fms-like tyrosine kinase 1 (sflt 1) produced by placenta. Intravitreal bevacizumab, an inhibitor of vascular endothelial growth factor (VEGF), which is used in the management of proliferative diabetic retinopathy has similarly been associated with acute kidney injury and proteinuria/ nephrotic syndrome with a wide spectrum of histological changes, including collapsing or proliferative glomerulonephritis, interstitial nephritis, and thrombotic microangiopathy.

3. Wu Z *et. al*.[7] A case of bevacizumab administered to treat choroidal neovascularisation in a woman later discovered to be pregnant. Anti-vascular endothelial growth factor (VEGF) therapy did not result in any detectable short-term adverse event in this mother and baby

DPMH Review

In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for bevacizumab and use in pregnancy. No additional publications were identified.

Micromedex/TERIS databases did not reveal any additional information. Briggs GG and Freeman RK in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, did not identify any new safety data of concern. No specific adverse reactions were identified. The available data failed to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Review of Pharmacovigilance Database (PV)

The applicant did not perform a cumulative search in their pharmacovigilance database to retrieve any cases reported with the use of Alymsys (bevacizumab) in pregnant and lactating women and effects on male and female fertility from the time of product development. The applicant states

> No cases of pregnancies or infants exposed to drug were reported in any of the Clinical trials conducted during clinical trials of MB02 (bevacizumab) during the development of the biosimilar. Therefore, a review and summary of any reported cases of drug exposure in pregnancy during clinical trials for MB02 is not warranted.

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[6] Duriseti P., Cabrales J., Almeqdadi M., Shnawa A.:A rare case of nephrotic syndrome precipitated by pre-eclampsia and bevacizumab in a patient with underlying diabetic nephropathy. Journal of the American Society of Nephrology (2019) 30 (1214).

[7] Wu Z., Huang J., Sadda S. Inadvertent use of bevacizumab to treat choroidal neovascularisation during pregnancy: A case report. Annals of the Academy of Medicine Singapore (2010) 39:2 (143-145).

Summary
There is insufficient clinical information to evaluate safe use of bevacizumab during pregnancy. Because of the mode of action as antivascular agent, there is potential risk for bevacizumab to affect placental vascularization and as such to affect pregnancy with possible early miscarriage or preterm delivery.

LACTATION
Review of Nonclinical Data
No data are available on the presence of bevacizumab in animal milk

Applicant Review of Clinical Data
The applicant did not provide any PV data relevant to lactational exposure of bevacizumab.

Review of Literature
The applicant did not identify any publications on lactation and use of bevacizumab. A literature search was performed in Embase with terms "bevacizumab" AND "lactation" OR "breastfeeding" OR "breast milk". No publications were identified.

DPMH Review
DPMH conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases, Briggs GG and Freeman RK in Drugs in Pregnancy and Lactation and Thomas Hale in Medications and Mothers' Milk for bevacizumab and use in lactation.
No adverse reactions have been reported in the breastfed infants. Because bevacizumab is a monoclonal IgG antibody, it is expected to be present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Hale reports two breastfeeding mothers who during active treatment with the drug did not have any detectable levels of bevacizumab. He states that "there are no pediatric concerns reported with breastfeeding." Reduced growth in epiphyseal plates has been reported in monkeys. "Infants should be monitored for vomiting, diarrhea, fever and frequent infections. Use alternative drugs during breastfeeding".

Summary
Bevacizumab is expected to be present in human milk as it is an IgG antibody. Based on published literature, no adverse reactions have been reported in the breastfed infant. However, because of the potential for serious adverse reactions in breastfed infants from bevacizumab exposure, lactating women should not breastfeed during treatment with Alymsys and for 6 months after the last dose.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Review of Nonclinical Data
As per proposed and the Avastin labeling:

> Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the

> 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

The applicant also identified one publication by Ince S, *et. al.*[8]that investigated the bevacizumab-induced ovarian damage and reproductive dysfunction in female albino Wistar rats. The results of this study revealed that bevacizumab administration increased malondialdehyde levels and significantly decreased in total glutathione in the ovarian tissue of animals. Severe (Grade 3) vacuolization was observed in the primary and secondary follicles of the ovaries in animals treated with bevacizumab, whereas moderate (Grade 2) degeneration was observed in the primordial follicles. Bevacizumab significantly decreased the number of breeding animals compared to the control.

Review of Clinical Data
Applicant Review of Clinical Data
Review of Literature
The applicant identified one publication by Zhukova *et. al.*[9] A case report of two adolescent girls who were post-pubertal with established menstrual cycles and normal baseline hormone values prior to initiating therapy with bevacizumab as a single agent and in combination with vinblastine for NF2- associated vestibular schwannomas and brainstem glioma, respectively. Adverse outcomes of amenorrhea with levels of FSH/LH/estradiol suggestive of premature ovarian failure occurred shortly after starting the therapy. One patient remained asymptomatic, whereas the other developed profound post-menopausal symptoms interfering with quality of life which necessitated starting of hormone-replacement therapy. The authors concluded that :

> Appropriate pre-treatment fertility investigation and consultation should be offered to all post-pubertal females starting on bevacizumab and warrants a further research into the long-term effects of gonadal toxicity in both females and males with drugs inhibiting angiogenesis.

DPMH Review
DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases, and Briggs GG and Freeman RK in Drugs in Pregnancy and Lactation. No additional publications with any safety signals regarding female and male fertility were identified.

Summary
Review of the available literature support that bevacizumab may increase the risk of ovarian failure and thus impair female fertility. In addition, because of the potential risk

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[8] Ince S, Ozer M, Goktug Kadioğlu B, Kuzucu M, Karahan Yilmaz S, Özkaraca M, Gezer A, Suleyman H. The effect of adenosine triphosphate on bevacizumab-induced ovarian damage and reproductive dysfunction in rats. Gen Physiol Biophys. 2021;40(1):71-78.
[9] Zhukova N., Chan K., Walshe K., Downie P.A., Wood P. Bevacizumab-associated secondary amenorrhea and premature ovarian failure in adolescent female patients with low-grade CNS disease. Neuro-Oncology: 2020; 22:SUPPL 3 (iii374).

to the fetus based on animal studies and the mode of action of bevacizumab, the use of contraception is warranted in females of reproductive potential during treatment and for six months after the last dose of bevacizumab.

DISCUSSION/CONCLUSIONS

Review of the literature are insufficient to determine drug associated risks of adverse pregnancy and infant outcomes. Some published single patient case reports show normal deliveries without any adverse pregnancy outcomes. All authors are quick to say that there is insufficient information to suggest that use of bevacizumab during pregnancy is safe, as well as there is no definitive evidence to suggest that it causes harm. Animal studies and mode of action of bevacizumab suggest possible fetal harm. Because of the potential risk with use of the drug during pregnancy, women should use contraception during treatment and for 6 months after. Bevacizumab may increase the risk of ovarian failure and thus impair fertility. Therefore, prior to initiation of treatment, women should be counseled accordingly.

There is no information of use of bevacizumab during lactation. Because of the potential for serious adverse reactions in breastfed infants from bevacizumab, it is recommended that women not breastfeed during treatment with the drug and for 6 months after the last dose.

Bevacizumab is indicated for treatment of metastatic colorectal cancer that mostly occurs in individuals older than 40-50 years of age[10]. For this reason, and because the labeling recommends females of reproductive use effective contraception and advises lactating women not to breastfeed, it will not be feasible to conduct postmarketing pregnancy or lactation safety studies in these patients. It will be futile to find patients for evaluation. Therefore, no postmarketing requirement (PMR) studies on safe drug use during pregnancy or lactation are recommended. Safety concerns and advice for mitigation are described in the labeling recommendations below. If any new safety issues arise related to drug use during pregnancy and/or lactation, the need for postmarketing pregnancy or lactation safety studies should be re-assessed.

[10] Uptodate. Age and early onset colorectal cancer

LABELING RECOMMENDATIONS
DPMH has the following recommendations for bevacizumab labeling. Bevacizumab labeling has been edited to comply with the current practices for PLLR. DPMH revised labeling subsections 8.1, 8.2, and 8.3 (see below).
DPMH refers to the final BLA action for final labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----WARNINGS AND PRECAUTIONS----

•Embryo-Fetal Toxicity: May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)
•Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)

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

•Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION: CONTENTS
5 WARNINGS AND PRECAUTIONS
5.10 Embryo-Fetal Toxicity
Based on its mechanism of action and findings from animal studies, bevacizumab products may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Alymsys and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.11 Ovarian Failure
The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving bevacizumab products with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing bevacizumab products, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving bevacizumab products. Long-term effects of bevacizumab products on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Alymsys *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on findings from animal studies and their mechanism of action *[see Clinical Pharmacology (12.1)]*, bevacizumab products may cause fetal harm in pregnant women. The small number of published postmarketing reports describe cases of fetal malformations with use of bevacizumab products in pregnancy; however, these reports are insufficient to determine drug-associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain

and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *(see Data)*. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data
Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6 to 18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

Risk Summary

No data are available regarding the presence of bevacizumab products in human milk, the effects on the breast fed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. Published data from other monoclonal antibodies generally indicate low passage of monoclonal antibodies into human milk and limited systemic exposure in the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from bevacizumab products, advise women not to breastfeed during treatment with Alymsys and for 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females
Bevacizumab products may 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 Alymsys and for 6 months after the last dose.

Infertility

Females
Bevacizumab products increase the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first dose of Alymsys. Long-term effects of bevacizumab products on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without bevacizumab, the incidence of ovarian failure was higher in patients who received bevacizumab with chemotherapy (34%) compared to patients who received chemotherapy alone (2%). After discontinuing bevacizumab with chemotherapy, recovery of ovarian function occurred in 22% of these patients *[see Warnings and Precautions (5.11), Adverse Reactions (6.1)]*.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity: Advise female patients that bevacizumab products may cause fetal harm and to inform their health care provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Alymsys and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Bevacizumab products may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise women not to breastfeed during treatment with Alymsys and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
01/13/2022 10:48:38 AM

TAMARA N JOHNSON
01/13/2022 11:40:03 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Ndidi Nwokorie, MD, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic & Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Oncology 3 (DO3)
Office of Oncologic Diseases (OOD)

Subject: Labeling Review and Identification of Pediatric Exclusivities and Patents Precluding Review or Action

Drug: MB02 (biosimilar to US-licensed Avastin)

Proprietary Name: ALYMSYS (biosimilar to bevacizumab)

Application Number: BLA 761231

Applicant: Amneal Pharmaceuticals, LLC

Proposed Indications: Treatment of:

1. **Metastatic colorectal cancer** (mCRC)
    a. in combination with intravenous fluorouracil- based chemotherapy for first- or second-line treatment.
    b. in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for the second-line treatment of patients with mCRC who have progressed on a first-line bevacizumab product-containing regimen
2. **First-Line Non-Squamous Non–Small Cell Lung Cancer**
    a. in combination with carboplatin and paclitaxe for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).
3. **Recurrent glioblastoma (GBM)** in adults.
4. **Metastatic renal cell carcinoma** (mRCC)
    a. in combination with interferon alfa.
5. **Persistent, recurrent, or metastatic cervical cancer**
    a. in combination with paclitaxel and cisplatin or paclitaxel and topotecan for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.
6. **Epithelial ovarian, fallopian tube, or primary peritoneal cancer**:
    a. in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Proposed Dosage Form & Strength: Injection: 100 mg/4 mL and 400 mg/16 mL solution in single-dose vials

Route of Administration: Intravenous Infusion

Consult Request:
DO3 consulted DPMH to identify any pediatric issues that may impact the review of or action on this marketing application submitted by Amneal in which the biosimilar Applicant is seeking all currently approved indications for Avastin not covered under exclusivity. DO3 also requested DPMH assist with pediatric use information in the biosimilar labeling, specifically subsection 8.4, Pediatric Use.

Materials Reviewed:
Documents tracked under BLA 761231, MB02 (bevacizumab),

- eCTD#0001_April 13, 2021
    - Cover Letter
    - Agreed Initial Pediatric Study Plan
- Approval Letter for Glioblastoma indication May 5, 2009 accessed from Drugs@FDA on September 16, 2021

Documents tracked under BLA 125085, Avastin (bevacizumab)

- Cover Letter, eCTD#355_April 20, 2009
- eCTD#0376_September 30, 2009
    - Cover Letter
    - Postmarketing Commitment Report on Glioblastoma.

Accessed from Drugs@FDA

- Approved MVASI USPI_Drugs@FDA.8-17-21
- Approved Zirabev USPI_Drugs@FDA.8-17-21
- Approved Avastin USPI_Drugs@FDA.8-17-21

Agreed Initial Pediatric Study Plan for Zirabev_BLA761099.eCTD#0001.January 26, 2018
Pediatric Study Plan for MVASI_BLA 761028.eCTD#0001.November 4, 2016

I. Regulatory Background:

Amneal Pharmaceuticals, LLC (Applicant) submitted a Biologic Licensing Application (BLA) on April 12, 2021 for MB02 through the 351k pathway as a proposed biosimilar to US-licensed Avastin (bevacizumab) (here-in-after Avastin). Avastin is licensed in the United States (US) by Genentech USA, Inc. and was first approved in the US on February 26, 2004 in combination with intravenous 5-fluorouracil–based chemotherapy as a first-line treatment of patients with metastatic

carcinoma of the colon or rectum. Subsequently, Avastin has been approved for the following indications in adults:[1]

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first line Avastin-containing regimen
- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment
- Recurrent glioblastoma
- Metastatic renal cell carcinoma in combination with interferon alfa
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
    - in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection
    - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens
    - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease
- Hepatocellular Carcinoma (HCC)
    - in combination with Tecentriq (atezolizumab) for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy

Avastin has no outstanding pediatric post-marketing requirements or commitments for any of these approved adult indications. Genentech, Inc., the BLA holder for Avastin, received either a full waiver of the requirement to provide a pediatric assessment under the Pediatric Research Equity Act (PREA) because necessary pediatric studies would be impossible or highly impracticable due to extremely low incidences of these diseases in pediatric patients; or was exempt from PREA requirements because Avastin possessed orphan drug designation for one or more of the indications approved in adults.[2]

There are no unexpired exclusivities impacting pediatric use information in labeling for this biosimilar application. Genentech had submitted a report entitled 'Preliminary Experience with Bevacizumab Used in the Treatment of Pediatric Glioblastoma' to fulfill a post-marketing commitment (PMC) on September 30, 2009.[3,4] This report described the lack of antitumor activity among pediatric patients treated with bevacizumab. The report also described the observation that there is no improvement in event-free survival in these patients. Subsequently, this information was included in labeling in subsection 8.4, Pediatric Use, but this information is not protected by

[1] Approved Avastin USPI from Drugs@FDA; accessed 8/17/21
[2] Approval Letters for Avastin as accessed from Drugs at FDA on 8/17/2021
[3] Cover Letter, eCTD#355_April 20, 2009
[4] Cover Letter, eCTD#0376_September 30, 2009

exclusivity. The orphan drug exclusivity FDA granted Avastin for the treatment of glioblastoma in adult patients expired in 2016.

Avastin has unexpired orphan drug exclusivities that are due to expire on December 6, 2023 for the following adult indications:

- Therapeutic treatment of patients with ovarian cancer
    - Protected Indication: Either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian cancer.
- Treatment of primary peritoneal carcinoma
    - Protected Indication: Either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent primary peritoneal cancer.
- Treatment of fallopian tube carcinoma
    - Protected Indication: Either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent fallopian tube cancer.

Avastin, in addition, has unexpired orphan drug exclusivity that will expire on May 29, 2027 for its use in combination with Tecentriq (atezolizumab) for the following adult indication:

- Treatment of hepatocellular carcinoma (HCC)
    - Protected Indication: AVASTIN for the treatment of patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy.

II. Pediatric Study Plan

Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA. A pediatric assessment is required unless waived, deferred, or inapplicable. Subsequently, FDA published the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2),* on December 12, 2018 which provides recommendations on fulfilling PREA requirements for biosimilars. The draft guidance states in the answer to Q.I.16, "If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and PREA requirements were waived for, or inapplicable to, the reference product for those

pediatric age groups, a biosimilar applicant should note this information in its initial pediatric study plan (iPSP), if any, but does not need to request a waiver of PREA requirements for those age groups."

Amneal Pharmaceuticals, LLC submitted an Agreed iPSP with this NDA submission. In the Agreed iPSP, the Division agreed with mAbxience Research S.L.'s (the original IND Sponsor, IND 135128) plan to request a full waiver of the safety and effectiveness of MB02[5] for each of the indications approved for US-licensed Avastin for the reasons noted in Section I of this review. Accordingly, Amneal Pharmaceuticals, LLC is not required to provide a pediatric assessment for these indications under PREA.

III. DPMH Review of Pediatric Use Labeling:

DPMH Recommended Labeling

This DPMH labeling review of MB02 focuses primarily on subsection 8.4. Avastin labeling includes the findings of Genentech's PMC evaluation of bevacizumab use in pediatric patients. Currently, there are no unexpired exclusivities for Avastin that render this information protected and so should be included in MB02 labeling. Avastin labeling also includes juvenile animal toxicity data that shows the development of physeal dysplasia following exposure of bevacizumab in juvenile cynomolgus monkeys[6]. DPMH recommends retaining this labeling language. DPMH proposed the following labeling recommendation. Underlined text represents our proposed additions and strikethroughs represent our proposed deletions to the Applicant's proposed labeling.

Note, the Applicant's proposed tradename for MB02 is Alymsys.

Applicant's Proposed Labeling

8 Use in Specific Populations

8.4 Pediatric Use

The safety and effectiveness of bevacizumab products, including ALYMSYS, ~~in pediatric patients~~ have not been established in pediatric patients.

In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received bevacizumab. Bevacizumab products are not approved for use in patients under the age of 18 years.

[5] Agreed Initial Pediatric Study Plan, eCTD#0001, April 13, 2021
[6] Approved Avastin USPI from Drugs@FDA on 8-17-21

Antitumor activity was not observed among eight pediatric patients with relapsed GBM who received bevacizumab and irinotecan. Addition of bevacizumab to standard of care did not result in improved event-free survival in pediatric patients enrolled in two randomized clinical studies, one in high grade glioma (n= 121) and one in metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma (n= 154).

Based on the population pharmacokinetics analysis of data from 152 pediatric and young adult patients with cancer (7 months to 21 years of age), bevacizumab clearance normalized by body weight in pediatrics was comparable to that in adults.

Juvenile Animal Toxicity Data
Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

IV. Conclusion:

DPMH reviewed the Applicant's draft labeling and participated in the team meetings held during October 2021 through January 2022. The final labeling and approval letter will reflect DPMH's input. The final labeling will be agreed upon with the Applicant.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NDIDI N NWOKORIE
01/31/2022 12:04:03 PM

MONA K KHURANA
01/31/2022 01:24:31 PM

JOHN J ALEXANDER
01/31/2022 03:14:53 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 9, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761231
Product Name and Strength:	Alymsys (bevacizumab-xxxx)[a] injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Applicant/Sponsor Name:	Amneal Pharmaceuticals (Amneal)
OSE RCM #:	2021-758-1
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 4, 2021 for Alymsys. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Alymsys (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

After review of the revised container labels and carton labeling, we note that the Applicant implemented most of our recommendations. In response to our comment about the presence of multiple barcodes on the container labels, Amneal responded that the extra barcode outside of the linear barcode on the container labels "is a pharmacode / laeuts…,because of space, this is expressed as a small QR/datamatrix. Its purpose is to link a code with a specific product/material during packaging line, and to avoid potential misbranding." We find their

[a] The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder, bevacizumab-xxxx, is used throughout this review to refer to the nonproprietary name for this product.

[b] Thomas, S. Label and Labeling Review for Alymsys (BLA 761231). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEPT 20. RCM No.: 2021-758.

rationale for the additional barcode reasonable, and we note the two barcodes on the container labels appear to have appropriate space and location to be correctly read.

We have no additional recommendations at this time.

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

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/s/

SARAH E THOMAS
11/09/2021 04:53:58 PM

ASHLEIGH V LOWERY
11/16/2021 01:01:58 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	September 20, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761231
Product Name, Dosage Form, and Strength:	Alymsys (bevacizumab-xxxx)[a] injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amneal Pharmaceuticals (Amneal)
FDA Received Date:	April 13, 2021 and June 17, 2021
OSE RCM #:	2021-758
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

[a] The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder, bevacizumab-xxxx, is used throughout this review to refer to the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for Alymsys (bevacizumab-xxxx) injection, the Division of Oncology 3 (DO3) requested in their May 20, 2021 consult that we review the proposed Alymsys prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors. Of note, Alymsys is a proposed biosimilar to US-licensed Avastin (bevacizumab) (BLA 125085).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that the proposed indications and associated dosing regimens for Alymsys are the same as US-licensed Avastin's indications and dosing regimens except for the epithelial ovarian, fallopian tube, and primary peritoneal cancers and hepatocellular carcinoma indications, as these indications are protected by orphan exclusivity and are therefore not included in the Alymsys labeling. In addition, the proposed product characteristics of Alymsys (bevacizumab-xxxx) injection (e.g., dosage form, route of administration, strengths, packaging configuration) and preparation and administration instructions align with those of US-licensed Avastin. Upon review of the proposed container labels, carton labeling, and PI, we note areas of the labels and labeling that could be improved to promote the safe use of this product. Thus, we provide related recommendations for the labels and labeling in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels, carton labeling, and PI may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Dosage and Administration Section, Highlights

   a. We recommend adding the route of administration ("Administer as an intravenous infusion after dilution.") back to the Highlights, Dosage and Administration section of the PI.

   b. We recommend adding the following statement at the end of the Highlights, Dosage and Administration section to alert the end-user that there is additional preparation and administration instructions and dosage modifications for adverse reactions provided in the Dosage and Administration section of the full PI: "See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions."

2. How Supplied/Storage and Handling Section

   a. We recommend adding the mg/mL concentration (e.g., 25 mg/mL) after the 100 mg/4 mL and 400 mg/16 mL strengths[b] in section 16.

   b. We recommend revising the packaging configuration description to include that the vial is packaged within a carton, from "…solution for intravenous infusion supplied as single-dose vials in the following strengths:" to "…solution for intravenous infusion supplied in a single-dose vial packaged within cartons in the following strengths and packaging configurations:".

4.2 RECOMMENDATIONS FOR AMNEAL PHARMACEUTICALS (AMNEAL)

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. We recommend enclosing the "25 mg/mL" quantity per milliliter strength expression in parentheses,[c] in accordance with USP General Chapters <7> Labeling as follows:

"100 mg/ 4 mL (25 mg/mL)"	and	"400 mg/16 mL (25 mg/mL)"

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

2. Revise the route of administration statement that reads "For Intravenous Use" to read "For Intravenous Infusion After Dilution." We recommend this to minimize the risk of administering the drug as an intravenous push.

3. We note the format of the expiration date on the container labels is "MM YYYY", and the expiration date format is not specified on the carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the carton labeling and consider revising the format on the container labels to align with the Drug Supply Chain Security Act. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a slash be used to separate the portions of the expiration date.[d]

4. We recommend revising the storage information provided on the container labels and carton labeling to the following, in order to match the storage information provided in Section 16 of the PI: "**Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.**" We also recommend bolding the storage information to increase the prominence of this important information and to minimize the risk of the storage information being overlooked on the labels and labeling.

A. Container Labels

1. We note the net quantity statements "4 mL Single-Dose Vial" and "16 mL Single-Dose Vial" are prominently displayed on the principal display panel (PDP) in red font. Consider revising the font color to black to avoid the net quantity statements appearing more prominent than the statements of strength.[e]

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[d] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

[e] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

2. Add the dosage form "injection" to the PDP below the proper name[f], as follows:

"Alymsys

(bevacizumab-XXXX)

Injection"

**Please note the example above demonstrates our recommendations only (not to size, spacing, color, etc.).

3. If space allows on the 100 mg/4 mL vial container label, add the "Discard unused portion." statement to the PDP underneath the package type term statement "4 mL Single-Dose Vial", as follows:

"4 mL Single-Dose Vial

Discard unused portion."

We recommend this to minimize the risk of the entire contents of the vial, including any overfill, being given as a single dose.[g]

4. If space permits on the 400 mg/16 mL vial container label, relocate the "Discard unused portion." statement to the PDP underneath the package type term statement "16 mL Single-Dose Vial", as follows:

"16 mL Single-Dose Vial

Discard unused portion."

We recommend this to minimize the risk of the entire contents of the vial, including any overfill, being given as a single dose.[h]

5. We note the following barcode on the container labels near the linear barcode:

Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[g] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/downloads/Drugs/Guidances/UCM468228.pdf.

[h] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/downloads/Drugs/Guidances/UCM468228.pdf.

confusing to the healthcare providers.[i] Clarify the purpose of this barcode. Also, consider relocating this barcode away from the linear barcode containing the NDC number and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the labels.

6. We note the usual dose statement that appears on the side panel: "DOSAGE AND ADMINISTRATION: DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. See package insert for full prescribing information and instructions for preparation and administration."

    a. Consider removing the statement, [redacted (b) (4)]". Please see the recommendation to revise the route of administration statement to "For Intravenous Infusion After Dilution." We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative action.[j] Also, we recommend this to minimize the use of error prone abbreviations (e.g., IV).[k]

    b. Revise the usual dose statement "DOSAGE AND ADMINISTRATION:… See package insert for full prescribing information and instructions for preparation and administration." to "Recommended Dosage: See prescribing information. **Must be diluted in 0.9% Sodium Chloride Injection, USP before Intravenous Infusion**." to allow for more white space on the container labels and improve readability. Consider bolding the statement "Must be diluted in 0.9% Sodium Chloride Injection, USP before Intravenous Infusion." as shown to highlight its importance.

B. Carton Labeling

1. Revise the presentation of the proprietary name, proper name, and dosage form on the 100 mg/4 mL vial and 400 mg/16 mL vial carton labeling for the cartons containing 10 vials to the following[l]:

"Alymsys

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[i] Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-3.

[j] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

[k] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 JUNE 10]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

[l] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

(bevacizumab-XXXX)

Injection"

2. We recommend removing the statements "4 mL Single-Dose Vials." and "16 mL Single-Dose Vials." on the 100 mg/4 mL vial and 400 mg/16 mL vial carton labeling for the cartons containing 10 vials, respectively, since the statements are redundant with the net quantity statements "10 x 4 mL Single-Dose Vials" and "10 x 16 mL Single-Dose Vials". In addition, consider relocating the net quantity statements "10 x 4 mL Single-Dose Vials" and "10 x 16 mL Single-Dose Vials" to above the "Discard Unused Portion." statement on the carton labeling. This will allow for more white space on the carton labeling and improve readability.

3. To improve readability of more important information on the PDP of the carton labeling, consider relocating the statement "No Preservatives." to the side panel on all carton labeling.

4. We note the usual dose statement that appears on the side panel of all carton labeling: "DOSAGE AND ADMINISTRATION: DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. Must be further diluted prior to IV administration. See package insert for full prescribing information and instructions for preparation and administration."

    a. Consider removing the statement, "… (b) (4) ". Please see the recommendation to revise the route of administration statement to "For Intravenous Infusion After Dilution." We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative action.[m] Also, we recommend this to minimize the use of error prone abbreviations (e.g., IV).[n]

    b. Revise the rest of the usual dose statement "DOSAGE AND ADMINISTRATION:… Must be further diluted prior to IV administration. See package insert for full prescribing information and instructions for preparation and administration." to "Recommended Dosage: See prescribing information. **Must be diluted in 0.9% Sodium Chloride Injection, USP before Intravenous Infusion**." to allow for more white space on the carton labeling and improve readability. Consider bolding

[m] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

[n] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 JUNE 10]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

the statement "Must be diluted in 0.9% Sodium Chloride Injection, USP before Intravenous Infusion." as shown to highlight its importance.

5. We recommend stating the strength as total mg/total mL[o] in the following statements on the side panel of the carton labeling, as follows:

   - 100 mg/4 mL vial carton labeling for carton containing 1 vial: "CONTENTS: Each carton contains one preservative-free 100 mg/4 mL (25 mg/mL) single-dose vial…",
   - 100 mg/4 mL vial carton labeling for carton containing 10 vials: "CONTENTS: Each carton contains ten preservative-free 100 mg/4 mL (25 mg/mL) single-dose vials…",
   - 400 mg/16 mL vial carton labeling for carton containing 1 vial: "CONTENTS: Each carton contains one preservative-free 400 mg/16 mL (25 mg/mL) single-dose vial…"
   - 400 mg/16 mL vial carton labeling for carton containing 10 vials: "CONTENTS: Each carton contains ten preservative-free 400 mg/16 mL (25 mg/mL) single-dose vials…"

   **Please note the underline is intended to highlight the location of the recommended edits and not for implementation.

6. We note a placeholder for the product identifier (2D data matrix barcode, GTIN, Lot, Exp. & Sr. No.) on the 100 mg/4 mL vial and 400 mg/16 mL vial carton labeling for the cartons containing 10 vials. We note a product identifier is not present on the 100 mg/4 mL carton labeling for the carton containing one 100 mg/4 mL vial. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.
   The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier.
   The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following:

   NDC: [insert NDC]
   SERIAL: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]

[o] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Alymsys received on June 17, 2021 from Amneal Pharmaceuticals (Amneal), and US-licensed Avastin.

Table 2. Relevant Product Information for Alymsys and US-Licensed Avastin

Product Name	**Alymsys**	**Avastin**[p]
Initial Approval Date	N/A	February 26, 2004
Nonproprietary Name	bevacizumab-xxxx	bevacizumab
Indications	• Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. • Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Alymsys-containing regimen. Limitations of Use: Alymsys is not indicated for adjuvant treatment of colon cancer. • Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. • Recurrent glioblastoma in adults.	• Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. • Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer. • Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. • Recurrent glioblastoma in adults.

[p] Avastin [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 JUNE 3. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125085s337lbl.pdf.

	• Metastatic renal cell carcinoma in combination with interferon alfa. • Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.	• Metastatic renal cell carcinoma in combination with interferon alfa. • Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. •Epithelial ovarian, fallopian tube, or primary peritoneal cancer: o in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection o in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens o in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease • Hepatocellular Carcinoma (HCC): o in combination with atezolizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy
Route of Administration	intravenous	intravenous
Dosage Form	injection	injection

Strength	100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)	100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Dose and Frequency	Withhold for at least 28 days prior to elective surgery. Do not administer Alymsys for 28 days following major surgery and until adequate wound healing. -Metastatic colorectal cancer: • 5 mg/kg every 2 weeks with bolus-IFL • 10 mg/kg every 2 weeks with FOLFOX4 • 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Alymsys containing regimen -First-line non−squamous non−small cell lung cancer: • 15 mg/kg every 3 weeks with carboplatin and paclitaxel -Recurrent glioblastoma: • 10 mg/kg every 2 weeks -Metastatic renal cell carcinoma: • 10 mg/kg every 2 weeks with interferon alfa -Persistent, recurrent, or metastatic cervical cancer: • 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan	Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for 28 days following major surgery and until adequate wound healing. -Metastatic colorectal cancer: • 5 mg/kg every 2 weeks with bolus-IFL • 10 mg/kg every 2 weeks with FOLFOX4 • 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Avastin containing regimen -First-line non−squamous non−small cell lung cancer: • 15 mg/kg every 3 weeks with carboplatin and paclitaxel -Recurrent glioblastoma: • 10 mg/kg every 2 weeks -Metastatic renal cell carcinoma: • 10 mg/kg every 2 weeks with interferon alfa -Persistent, recurrent, or metastatic cervical cancer: • 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan -Stage III or IV epithelial ovarian, fallopian tube or primary

		peritoneal cancer following initial surgical resection: • 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles -Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: • 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week • 15 mg/kg every 3 weeks with topotecan given every 3 weeks -Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer: • 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent • 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent -Hepatocellular Carcinoma: • 15 mg/kg after administration of 1,200 mg of atezolizumab every 3 weeks Administer as an intravenous infusion.
How Supplied	-Alymsys (bevacizumab-xxxx) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as	-Avastin (bevacizumab) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:

	single-dose vials in the following strengths: • 100 mg/4 mL: carton of one vial (NDC 70121-1754-1); carton of 10 vials (NDC 70121-1754-7). • 400 mg/16 mL: carton of one vial (NDC 70121-1755-1); carton of 10 vials (NDC 70121-1755-7).	• 100 mg/4 mL: carton of one vial (NDC 50242-060-01); carton of 10 vials (NDC 50242-060-10). • 400 mg/16 mL: carton of one vial (NDC 50242-061-01); carton of 10 vials (NDC 50242-061-10).
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.
Container Closure	-4 mL solution in a single-use 8 mL (b) (4) clear glass vial containing 100 mg of bevacizumab-xxxx and a 16 mL solution in a single-use 20 mL (b) (4) clear glass vial containing 400 mg of bevacizumab-xxxx -Each vial is closed with a (b) (4) stopper and an aluminium seal with a (b) (4) flip-off cap (yellow cap for the 100 mg vial and (b) (4) cap for the 400 mg vial)	-Single-dose vials

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 4, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Alymsys, BLA# 761231, and bevacizumab. Our search identified 13 previous reviews[q,r,s,t,u,v,w,x,y,z,aa,bb,cc], and we considered our previous recommendations to see if they are applicable for this current review.

[q] Mathew, D. Label and Labeling Review for Avastin (bevacizumab) Injection (BLA 125085/S-305). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Oct 2. RCM No.: 2014-1800.

[r] Gao, T. Labeling Review for Avastin (bevacizumab) Injection (BLA 125085/S-323). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Mar 8. RCM No.: 2017-2107.

[s] Stewart, J. Label and Labeling Review for Mvasi (bevacizumab-xxxx) Injection (BLA 761028). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Aug 22. RCM No.:2016-2212.

[t] Little, C. Label and Labeling Review for Mvasi (bevacizumab-awwb) Injection (BLA 761028/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 10. RCM No.:2018-2095.

[u] Little, C. Label and Labeling Review Memo for Mvasi (bevacizumab-awwb) Injection (BLA 761028/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 28. RCM No.: 2018-2095-1.

[v] Little, C. Label and Labeling Review for bevacizumab-xxxx Injection (BLA 761099). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 4. RCM No.:2018-258.

[w] Little, C. Label and Labeling Review Memo for Zirabev (bevacizumab-xxxx) Injection (BLA 761099). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 31. RCM No.: 2018-258-1

[x] Little, C. Label and Labeling Review Memo for Zirabev (bevacizumab-bvzr) Injection (BLA 761099). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 April 25. RCM No.: 2018-258-2

[y] Thomas, S. Label and Labeling Review for Zirabev (bevacizumab-bvzr) Injection (BLA 761099/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Oct 6. RCM No.: 2020-1433

[z] Stewart, J. Label and Labeling Review for Bevluma (bevacizumab-xxxx) Injection (BLA 761153). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Sept 19. RCM No.:2019-1953.

[aa] Stewart, J. Label and Labeling Review for Abevmy (bevacizumab-nwdg) Injection (BLA 761175). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Sept 16. RCM No.:2019-2680.

[bb]. Thomas, S. Label and Labeling Review for Tecentriq (atezolizumab), BLA 761034/S-25, and Avastin (bevacizumab), BLA 125085/S-332. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MARCH 18. RCM No.: 2020-2.

[cc] Gao, T. Label and Labeling Review for "BAT1706" Pobevcy (bevacizumab-xxxx), BLA 761198. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 20. RCM No.: 2020-2547.

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,[dd] along with postmarket medication error data, we reviewed the following Alymsys labels and labeling submitted by Amneal Pharmaceuticals (Amneal).

- Container labels received on April 13, 2021
- Carton labeling received on April 13, 2021 and June 17, 2021
- Prescribing Information (Image not shown) received on June 17, 2021, available from \\CDSESUB1\evsprod\bla761231\0012\m1\us\1-14-1-3-draft-package-insert-word.docx.

G.2 Labels and Labeling Images

Container Labels

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

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

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/s/

SARAH E THOMAS
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ASHLEIGH V LOWERY
09/20/2021 05:24:34 PM