

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761060Orig1s000

761060Orig2s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

SECTION A: Administrative Information

BLA #	761060
PMR/PMC Set #	3266
Product Name:	Mylotarg (gemtuzumab ozogamicin)
Applicant Name:	Wyeth
ODE/Division:	OHOP DHP

SECTION B: PMR/PMC Information

1. PMR #1 Description

Further characterize the safety and pharmacokinetics of the 3 mg/m² day 1, 4, and 7 dose-schedule of Mylotarg as a single agent for treatment of patients with relapsed or refractory CD33-positive acute myelogenous leukemia. Submit a study report and datasets, including an analysis of hemorrhage, complete blood counts, PT, aPTT, and fibrinogen, hepatotoxicity, hepatic veno-occlusive disease (VOD), and the impact of hematopoietic stem cell transplantation pre- or post-Mylotarg on the incidence of VOD. Enroll at least 50 patients.

2. Schedule Milestones^{2, 3}

Draft Protocol Submission:	03/2018
Final Protocol Submission:	06/2018
Trial Completion:	01/2021
Final Trial Report Submission:	09/2021

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The integrated analyses of safety and efficacy indicated that the fractionated dosing regimen of Mylotarg monotherapy of 3 mg/m² days 1, 4, and 7 was safer than and at least as effective as the unfractionated regimen of 9 mg/m² for two doses, 14 days apart. However, the only safety and efficacy data that we have for the fractionated regimen comes from the literature, with the largest trial consisting of 57 patients, and safety data collection was not complete. Furthermore, we do not have pharmacokinetic (PK) data for this dose and schedule. The goal of the PMR study is to prospectively characterize the safety and exposure-toxicity of Mylotarg at the dose of 3 mg/m² days 1, 4, and 7 in patients with relapsed or refractory AML.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements*
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC.

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

3. **For FDAAA PMRs and 506B PMCs only**

The study or trial can be conducted post-approval because:

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason:

4. **For FDAAA PMRs only.**

a. The purpose of the study/clinical trial is to:

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

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient because the safety issue involves:

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☒ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient, is a study sufficient?

- ☒ **Yes, a study is sufficient**
- ☐ **No, a study is not sufficient**
 - ☐ Need to minimize bias and/or confounding via randomization
 - ☐ Need for placebo control
 - ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
 - ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
 - ☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☒ Other: A prospective study of fractionated dosing

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

- 1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- ☐ Yes
- ☒ No

- 2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

- 3. Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)**

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because:

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. The following ethical considerations were made with regard to:

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

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

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹⁰ PMRs and PMCs only

SECTION B: PMR/PMC Information

1. PMR #2 Description

Conduct a study to determine the effect of Mylotarg on the QT interval.

2. Schedule Milestones^{11, 12}

Draft Protocol Submission:	03/2018
Final Protocol Submission:	06/2018
Study Completion:	01/2021
Final Study Report Submission:	09/2021

¹⁰ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

¹¹ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

¹² Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study¹³ or clinical trial¹⁴ in the text box below.

The sponsor collected no information on ECG intervals for the patients treated with Mylotarg, and there is no thorough QT study for this product. In an analysis of QT data for Besponsa (inotuzumab ozogamicin), another antibody linked to calicheamicin, the proposed labeling includes a warning for QT prolongation.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements*
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC.

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because:

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason:

¹³ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

¹⁴ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only.**

a. The purpose of the study/clinical trial is to:

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

b. FAERS¹⁵ and Sentinel's postmarket ARIA¹⁶ system are not sufficient because the safety issue involves:

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☒ Other: ECG collection and determination of QT is needed.

¹⁵ FDA Adverse Event Reporting System (FAERS)

¹⁶ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☒ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient, is a study sufficient?

- ☒ **Yes, a study is sufficient**
- ☐ **No, a study is not sufficient**
 - ☐ Need to minimize bias and/or confounding via randomization
 - ☐ Need for placebo control
 - ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
 - ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
 - ☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☒ Other: QT study

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- ☐ Yes
- ☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)**

SECTION E: PMR/PMC Development Coordinator Statements¹⁷

1. The PMR/PMC is clear, feasible, and appropriate¹⁸ because:

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. The following ethical considerations were made with regard to:

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

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

¹⁷ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

¹⁸ See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹⁹ PMRs and PMCs only

SECTION B: PMR/PMC Information

1. PMR #5 Description

Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to gemtuzumab ozogamicin with the validated assay developed under PMR 3266-3 and 3266-4.

2. Schedule Milestones^{20, 21}

Draft Protocol Submission:	03/2018
Final Protocol Submission:	06/2018
Final Study Report Submission:	09/2021

¹⁹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

²⁰ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

²¹ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study²² or clinical trial²³ in the text box below.

The Applicant provided no data on whether patients treated with Mylotarg develop ADA. Patients may be treated with Mylotarg in multiple cycles, but there are no data to determine whether patients may develop neutralizing antibodies that will inhibit efficacy in later cycles.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements*
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC.

²² A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

²³ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

3. **For FDAAA PMRs and 506B PMCs only**

The study or trial can be conducted post-approval because:

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason:

4. **For FDAAA PMRs only.**

a. The purpose of the study/clinical trial is to:

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

b. FAERS²⁴ and Sentinel's postmarket ARIA²⁵ system are not sufficient because the safety issue involves:

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☒ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other:

²⁴ FDA Adverse Event Reporting System (FAERS)

²⁵ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient, is a study sufficient?

- ☒ **Yes, a study is sufficient**
- ☐ **No, a study is not sufficient**
 - ☐ Need to minimize bias and/or confounding via randomization
 - ☐ Need for placebo control
 - ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
 - ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
 - ☐ Other

f. ☒ Because a study is not sufficient, a clinical trial is required

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☒ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

- 1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- ☐ Yes
- ☒ No

- 2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

- ☐ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

- 3. Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)**

SECTION E: PMR/PMC Development Coordinator Statements²⁶

1. The PMR/PMC is clear, feasible, and appropriate²⁷ because:

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. The following ethical considerations were made with regard to:

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

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

²⁶ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

²⁷ See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable²⁸ PMRs and PMCs only

SECTION B: PMR/PMC Information

1. PMR #6 Description

Provide data to confirm the safety of gemtuzumab ozogamicin in pediatric patients. Submit an abbreviated study report, including data sets, for Study AAML0531, a randomized trial of approximately 1000 pediatric patients with acute myeloid leukemia evaluating Mylotarg in approximately 500 pediatric patients.

2. Schedule Milestones^{29, 30}

Draft Data Analysis Plan Submission:	10/2017
Final Data Analysis Plan Submission:	12/2017
Final Abbreviated Study Report Submission:	05/2018

²⁸ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

²⁹ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³⁰ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study³¹ or clinical trial³² in the text box below.

The approved indication for use of Mylotarg for the treatment of relapsed or refractory AML will include the pediatric population on the basis of a single-arm trial in 29 children in addition to an extensive adult experience. There is published data suggesting that some children may have a higher risk of complications from Mylotarg, including hepatic veno-occlusive disease, but there is not sufficiently detailed information in the BLA to address that question. Study AAML0531 is a randomized trial evaluating gemtuzumab ozogamicin in 1022 pediatric patients with AML.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements*
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC.

³¹ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

³² A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

3. **For FDAAA PMRs and 506B PMCs only**

The study or trial can be conducted post-approval because:

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason:

4. **For FDAAA PMRs only.**

a. The purpose of the study/clinical trial is to:

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

b. FAERS³³ and Sentinel's postmarket ARIA³⁴ system are not sufficient because the safety issue involves:

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other:

³³ FDA Adverse Event Reporting System (FAERS)

³⁴ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☒ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient, is a study sufficient?

- ☐ Yes, a study is sufficient
- ☒ No, a study is not sufficient
 - ☒ Need to minimize bias and/or confounding via randomization
 - ☐ Need for placebo control
 - ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
 - ☒ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
 - ☐ Other

f. ☒ Because a study is not sufficient, a clinical trial is required

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☒ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**
 - ☐ Yes
 - ☒ No
2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**
 - ☒ *For non-PREA pediatric studies/trials only:* Pediatric population
 - ☐ Geriatric population
 - ☐ Lactating/nursing mothers
 - ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
 - ☐ Orphan or rare disease population
 - ☐ Pregnant women
 - ☐ Racial/ethnic population
 - ☐ Not applicable
3. **Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)**

SECTION E: PMR/PMC Development Coordinator Statements³⁵

1. The PMR/PMC is clear, feasible, and appropriate³⁶ because:

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. The following ethical considerations were made with regard to:

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

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

³⁵ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

³⁶ See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable³⁷ PMRs and PMCs only

SECTION B: PMR/PMC Information

1. PMR #3 Description

Submit a validation report for a validated, sensitive, and accurate assay(s) for the detection of binding antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of binding antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay(s) should be able to detect and confirm binding antibodies directed against both gemtuzumab and the calicheamicin/linker moiety.

2. Schedule Milestones^{38, 39}

Final Validation Plan Submission:	09/2017
Final Report Submission:	10/2017

³⁷ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

³⁸ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³⁹ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴⁰ or clinical trial⁴¹ in the text box below.

Immunogenicity was not assessed in the clinical studies used to support the BLA. Given that the overall safety profile observed in the clinical studies was considered as part of the initial determination regarding approvability, the presence of anti-drug antibodies can be considered post-approval in the context of evaluating safety for a subset of patients. The presence of binding antibodies can lead to changes in PK and can include the presence of neutralizing antibodies, both of which can result in a loss of efficacy, meaning that patients who develop such antibodies would be subject to all the safety risks of the product with no chance of benefit from the product. The study required under this PMR will provide assurance that anti- gemtuzumab ozogamicin binding antibodies can be detected in patient samples characterized by the level of gemtuzumab ozogamicin expected to be present at the time of sample collection. Validation of a sensitive, accurate assay for the detection and confirmation of anti-drug antibodies to gemtuzumab ozogamicin. This PMR is linked to PMR 5 regarding a post-marketing clinical study.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements*
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC.

⁴⁰ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁴¹ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

3. **For FDAAA PMRs and 506B PMCs only**

The study or trial can be conducted post-approval because:

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason:

4. **For FDAAA PMRs only.**

a. The purpose of the study/clinical trial is to:

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

b. FAERS⁴² and Sentinel's postmarket ARIA⁴³ system are not sufficient because the safety issue involves:

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☒ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other:

⁴² FDA Adverse Event Reporting System (FAERS)

⁴³ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient, is a study sufficient?

- ☒ **Yes, a study is sufficient**
- ☐ **No, a study is not sufficient**
 - ☐ Need to minimize bias and/or confounding via randomization
 - ☐ Need for placebo control
 - ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
 - ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
 - ☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☒ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- ☐ Yes
- ☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)**

SECTION E: PMR/PMC Development Coordinator Statements⁴⁴

1. The PMR/PMC is clear, feasible, and appropriate⁴⁵ because:

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. The following ethical considerations were made with regard to:

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

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

⁴⁴ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁴⁵ See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable⁴⁶ PMRs and PMCs only

SECTION B: PMR/PMC Information

1. PMR #4 Description

Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of neutralizing antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling.

2. Schedule Milestones^{47, 48}

Draft Validation Plan Submission:	04/2018
Final Validation Plan Submission:	06/2018
Final Report Submission:	12/2018

⁴⁶ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

⁴⁷ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

⁴⁸ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴⁹ or clinical trial⁵⁰ in the text box below.

Validation of an assay capable of detecting neutralizing antibodies against gemtuzumab ozogamicin was not included in the submission. Given that the overall safety profile observed in the clinical studies was considered as part of the initial determination regarding approvability, the presence of neutralizing antibodies can be considered post-approval in the context of evaluating safety for a subset of patients. Validation of an assay capable of detecting neutralizing antibodies against gemtuzumab ozogamicin was not included in the submission. The presence of neutralizing antibodies would lead to a loss of efficacy, meaning that any patient who develops neutralizing antibodies would be subject to all the safety risks of the product with no chance of benefit from the product. These patients could still benefit from a different product, so there is additional risk from lack of treatment. The study required under this PMR will provide assurance that neutralizing antibodies directed against gemtuzumab ozogamicin can be detected in patient samples. Validation of a sensitive, accurate assay for the detection of neutralizing antibodies to gemtuzumab ozogamicin. This validation study would be performed if PMR X leads to the identification of binding antibodies to gemtuzumab ozogamicin.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements*
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC.

⁴⁹ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵⁰ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

3. **For FDAAA PMRs and 506B PMCs only**

The study or trial can be conducted post-approval because:

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason:

4. **For FDAAA PMRs only.**

a. The purpose of the study/clinical trial is to:

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

b. FAERS⁵¹ and Sentinel's postmarket ARIA⁵² system are not sufficient because the safety issue involves:

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☒ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other:

⁵¹ FDA Adverse Event Reporting System (FAERS)

⁵² Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient, is a study sufficient?

- ☒ **Yes, a study is sufficient**
- ☐ **No, a study is not sufficient**
 - ☐ Need to minimize bias and/or confounding via randomization
 - ☐ Need for placebo control
 - ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
 - ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
 - ☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☒ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

- 1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- ☐ Yes
- ☒ No

- 2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

- 3. Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)**

SECTION E: PMR/PMC Development Coordinator Statements⁵³

1. The PMR/PMC is clear, feasible, and appropriate⁵⁴ because:

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. The following ethical considerations were made with regard to:

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

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

⁵³ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁵⁴ See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable⁵⁵ PMRs and PMCs only

SECTION B: PMR/PMC Information

1. PMC #7 Description

Determine the effect of a broad range of concentrations of Mylotarg on the potential to inhibit platelet function by conducting in vitro studies on platelets and megakaryocytes. Assessment methods should include evaluation of effects on platelet aggregation, including GPIIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

2. Schedule Milestones^{56, 57}

Draft Protocol Submission:	02/2018
Final Protocol Submission:	03/2018
Study Completion:	03/2019
Final Report Submission:	06/2019

⁵⁵ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

⁵⁶ *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

⁵⁷ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁵⁸ or clinical trial⁵⁹ in the text box below.

In the clinical trials of Mylotarg, there was a high rate of hemorrhages, and the bleeding events occurred even when patients did not have severe thrombocytopenia. Whether Mylotarg has a direct toxic effect on platelets or progenitors is unknown.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements*
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC.

⁵⁸ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵⁹ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

3. **For FDAAA PMRs and 506B PMCs only**

The study or trial can be conducted post-approval because:

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason:

4. **For FDAAA PMRs only.**

a. The purpose of the study/clinical trial is to:

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

b. FAERS⁶⁰ and Sentinel's postmarket ARIA⁶¹ system are not sufficient because the safety issue involves:

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other: ECG collection and determination of QT is needed.

⁶⁰ FDA Adverse Event Reporting System (FAERS)

⁶¹ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient, is a study sufficient?

- ☐ Yes, a study is sufficient
- ☐ No, a study is not sufficient
 - ☐ Need to minimize bias and/or confounding via randomization
 - ☐ Need for placebo control
 - ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
 - ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
 - ☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☒ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- ☐ Yes
- ☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

- ☐ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)**

SECTION E: PMR/PMC Development Coordinator Statements⁶²

1. The PMR/PMC is clear, feasible, and appropriate⁶³ because:

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. The following ethical considerations were made with regard to:

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

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

⁶² This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁶³ See POLICY section of CDER MAPP 6010.9.

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/s/

BARRY W MILLER
08/31/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 21, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761060
Product Name and Strength:	Mylotarg (gemtuzumab ozogamicin) For Injection 4.5 mg per vial
Applicant/Sponsor Name:	Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Submission Date:	July 17, 2017 and August 1, 2017
OSE RCM #:	2017-87-1
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Mylotarg (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a We note that since our previous review, after discussions with the Office of Pharmaceutical Quality Pfizer revised the strength of the product to 4.5 mg/vial to reflect the accurate amount contained in the vial and the amount that can be extracted after reconstitution.

2 CONCLUSION

The revised container labels and carton labeling for Mylotarg are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Garrison N. Label and Labeling Review for Mylotarg (BLA 761060). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Jun 29. RCM No.: 2017-87.

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/s/

NICOLE B GARRISON
08/21/2017

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08/21/2017

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

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

Memorandum

Date: 8/16/17

To: Kristopher Kolibab, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Nisha Patel, Acting Team Leader
OPDP

Subject: Comments on draft labeling (Package Insert, Carton/Container Labeling) for MYLOTARG™ (gemtuzumab ozogamicin) for injection, for intravenous use
BLA 761060

In response to your labeling consult request dated December 20, 2016, we have reviewed the draft Package Insert (PI) and carton/container labeling for MYLOTARG™ (gemtuzumab ozogamicin) for injection, for intravenous use (Mylotarg). This review is based upon the version of the draft PI emailed to OPDP on August 7, 2017, and the draft carton/container labeling emailed to OPDP on August 14, 2017.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
HIGHLIGHTS OF PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION	(b) (4) 	OPDP notes that section 2.1 states to, "Premedicate adults with acetaminophen 650 mg orally and diphenhydramine 50 mg orally or intravenously 1 hour prior to MYLOTARG dosing and ^(b) ₍₄₎ mg methylprednisolone or an equivalent dose of an alternative corticosteroid within 30 minutes prior to infusion of MYLOTARG" (emphasis added).

		In order to be consistent with section 2.1, OPDP recommends revising the Highlights section to communicate that the corticosteroid should be administered within 30 minutes prior to infusion of Mylotarg.
HIGHLIGHTS OF PRESCRIBING INFORMATION: WARNINGS AND PRECAUTIONS	<u>"Infusion related reactions"</u>	OPDP recommends revising the heading for this Warning and Precaution to be consistent with the heading in 5.2, "Infusion-Related Reactions (Including Anaphylaxis)" (emphasis added). Omission of the information regarding anaphylaxis from the heading in the Highlights section may minimize the risks associated with Mylotarg.
HIGHLIGHTS OF PRESCRIBING INFORMATION: WARNINGS AND PRECAUTIONS	"Infusion related reactions: Premedicate with a corticosteroid, acetaminophen (b) (4) and (b) (4) and monitor patients during and for at least 1 hour after the end of the infusion. Interrupt the infusion, administer steroids or antihistamines, or permanently discontinue treatment as necessary" (emphasis added).	OPDP notes that section 2.1 states to, "Premedicate adults with acetaminophen 650 mg orally and diphenhydramine 50 mg orally or intravenously 1 hour prior to MYLOTARG dosing and (b) (4) methylprednisolone or an equivalent dose of an alternative corticosteroid within 30 minutes prior to infusion of MYLOTARG" (emphasis added). Should the premedication instructions for Infusion related reactions in the Highlights section be revised to include "antihistamine" or "diphenhydramine" as well? E.g., "Premedicate with a corticosteroid, acetaminophen (b) (4) and diphenhydramine." Additionally, OPDP notes that section 5.2 states to, "Monitor patients until signs and symptoms completely resolve," while this section of the Highlights includes the recommendation, "monitor patients during and for at least 1 hour after the end of the infusion." Is the recommendation to "monitor . . . for at least 1 hour after the end of the infusion," an accurate timeframe? If so, should section 5.2 be revised to be consistent with this recommendation?
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	"The most common adverse reactions (b) (4) were (b) (4), nausea, infection, (b) (4), vomiting, hemorrhage, (b) (4) headache, (b) (4)"	(b) (4) Should a listing of the most common adverse reactions in Combination Therapy be included in this section?

	(b) (4) (emphasis added)	
FULL PRESCRIBING INFORMATION: Boxed Warning	“Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use of MYLOTARG”	OPDP notes that the Boxed Warning in the Highlights section of the label states, “Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use of MYLOTARG” (emphasis added). OPDP recommends revising the Boxed Warning in the Full Prescribing information to be consistent with the Boxed Warning in the Highlights section (i.e., to include that fatal VOD has been reported.)
2.1 Premedication and Special Considerations	“(b) (4) with the same dose of methylprednisolone or an equivalent corticosteroid for any sign of an infusion reaction, such as fever, chills, hypotension, or dyspnea during the infusion or within 4 hours afterwards” (emphasis added).	OPDP notes that in the Warnings and Precautions portion of the Highlights section, the information for Infusion related reactions includes the recommendation, “Interrupt infusion, administer steroids or antihistamines, or permanently discontinue treatment as necessary” (emphasis added). Would it be appropriate to revise the recommendations for retreatment in section 2.1 to include diphenhydramine or antihistamines? E.g., (b) (4) with the same dose of methylprednisolone (or an equivalent corticosteroid) [and/or] diphenhydramine for any sign of an infusion reaction”
5.1 Hepatotoxicity, Including Veno-occlusive Liver Disease (b) (4) (VOD)	(b) (4)	OPDP notes the review division’s comment to the sponsor to revise this section (b) (4). However, as we are not able to review the revisions, we offer the following comments on the current version of the SCPI. OPDP recommends revising this statement (b) (4) (b) (4) (b) (4)
5.1 Hepatotoxicity, Including Veno-	(b) (4)	Similar to our above comment, OPDP notes the RD’s comment to the sponsor to revise this section;

**occlusive Liver
Disease**

(b) (4)

(b) (4)

(b) (4) **(VOD)**

(b) (4)

however, we are unable to review the revised version at this time.

OPDP is concerned that the language

(b) (4)

(b) (4)

6.1 Monotherapy for Relapsed or Refractory AML		OPDP notes that section 6.1 <u>Combination Therapy in Newly-Diagnosed AML</u> includes the information, “Discontinuation due to any adverse reaction occurred in 31% of patients in the MYLOTARG arm versus 7% in the DA arm. The most frequent (≥1%) adverse reactions for patients treated with MYLOTARG that led to permanent discontinuation were thrombocytopenia, VOD, and septic shock.” If available, OPDP recommends revising this section to include discontinuation information for monotherapy (similar to the information included for combination therapy).

Carton/Container Label

OPDP acknowledges and concurs with the Division of Medication Error Prevention and Analysis’s August 10, 2017, review and has no additional comments on the carton/container labeling at this time.

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

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

/s/

RACHAEL E CONKLIN
08/16/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 29, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761060
Product Name and Strength:	Mylotarg (gemtuzumab ozogamicin) For Injection 5 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Submission Date:	November 2, 2016 and April 4, 2017
OSE RCM #:	2017-87
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) for Mylotarg (gemtuzumab ozogamicin) for Injection, 5 mg (BLA 761060), for areas of vulnerability that could lead to medication errors. The Division of Hematology Products (DHP) requested this review as a part of their evaluation to the 351(a) BLA submission for Mylotarg (gemtuzumab ozogamicin) for Injection.

1.1 REGULATORY HISTORY

Mylotarg (gemtuzumab ozogamicin) for Injection was originally approved under NDA 021174 on May 17, 2000 under an accelerated approval for the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. On May 21, 2010, FDA requested that Wyeth voluntarily withdraw Mylotarg from the market after results of a required post-approval clinical trial failed to verify clinical benefit to patients and raised concerns about the drug's safety. Pfizer is requesting full approval of the BLA following completion of several studies.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS 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

Pfizer submitted a 351(a) application to obtain marketing approval of Mylotarg for Injection. Mylotarg's proposed indication is for use in combination with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia as well as for the treatment of acute myeloid leukemia in patients who have a first relapse that are 60 years of age or older and who are not considered candidates for other

cytotoxic chemotherapy. The proposed product will be supplied as a lyophilized powder in a 5 mg single dose vial for intravenous infusion. We performed a risk assessment of the proposed container labels, carton labeling, and PI for Mylotarg (gemtuzumab ozogamicin) for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors.

We searched ISMP newsletters to identify whether additional medication errors had previously occurred with Mylotarg. Our search of ISMP newsletters identified one article, which is relevant to this review (See Appendix D). The newsletter article described a medication error related to confusion of the net quantity and total product volume on the labeling of Mylotarg. After our review of the reported error in the ISMP newsletter, we reviewed the proposed labels and labeling of the product and determined there have been revisions to the labeling, which clarify the total product strength. However, we have recommended for the Sponsor to include the net quantity statement on the labeling.

We searched FAERS database and identified five medication error cases (see Appendix E for a detailed description of the cases) relevant to this review as follows:

- Wrong technique during drug usage process (n =3)
- Product label confusion (n = 1)
- Potential for medication error (n=1)

In the cases of wrong technique of Mylotarg, reported doses were administered without the use of an in-line filter. Root causes or contributing factors were not reported. Our review of the proposed PI determined the administration information was clear, however it was not prominent. Thus, we recommend bolding statements regarding the use of an in-line filter during the administration of Mylotarg.

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we recommend to replace symbols with their intended meaning and to include additional statements on precautions of light sensitivity under the Dosage and Administration section of the PI. (b) (4)

For the Applicant, we recommend changes to the carton and container labels to improve readability and prominence of important information. Specifically, we recommend increasing prominence of the route of administration, storage requirements, and inclusion of the net quantity statement on the labeling.

Finally, we note that FDA recently issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant

post-approval to implement a proper name consistent with the principles outlined in the guidance].

4 CONCLUSION & RECOMMENDATIONS

We reviewed the proposed carton labeling, container label, and Prescribing Information (PI) and identified areas of the PI where information should be revised in order to help ensure the safe use of the product. We provide recommendations below in Section 4.1 and Section 4.2 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comments

FDA issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the decision of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.

B. Highlights of Prescribing Information

1. Include the statement, "See full prescribing information for instructions on reconstitution of lyophilized powder, preparation, and administration of reconstituted drug (2.4).

C. Full Prescribing Information

1. Section 2, Dosage and Administration

- a. To prevent misinterpretation of the symbols such as, "<" and ">", spell out the words. For example, change < to read, "less than."^a

2. Section 2.4, Instructions for Reconstitution, Dilution, and Administration

- a. Revise the statement, (b) (4)

[REDACTED] to "Mylotarg is light sensitive, protect the reconstituted and diluted solution from light.

^a ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2017 Mar 29]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

- b. Revise the statement, (b) (4) to “Add reconstituted solution to an infusion container with 0.9% Sodium Chloride for Injection, USP, to make a total volume of 50 mL or 100 mL, depending on the dose.”
- c. We recommend bolding the statement; “ (b) (4) .” We recommend this revision as we identified post-marketing medication errors stating that patients were receiving Mylotarg without an in-line filter. This revision will increase prominence if this important information and may mitigate the risk of this error occurring again.

4.2 RECOMMENDATIONS FOR WYETH PHARMACEUTICALS, INC.

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

A. Carton labeling

1. Remove the statement “ (b) (4) .” 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 misinterpret the warning as an affirmative action. Additionally, increase the prominence of the route of administration on the principal display panel (PDP).
2. Include the statement “Reconstitution and dilution required ” on the Principal Display Panel (PDP). We recommend this to minimize the risk of administering the product as an intravenous bolus.
3. Include the net quantity statement (i.e. one vial) on the PDP in accordance with 21 CFR 201.51.
4. Relocate the security logo on the principal display panel to the side panel as it takes readers’ attention away from important information such the route of administration.
5. The NDC number on the carton labeling and container label is usually the same when the quantity within the carton is equal to the quantity of the container. We note that the carton labeling has NDC (b) (4) and the container label NDC (b) (4) . Consider revising to have the same NDC number on the carton and container or provide your rationale for having different NDC numbers.
6. Clarify the significance of the number located next to the lot number and expiration date (b) (4) . If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due its close proximity to the lot number and expiration date.

B. Container labels

1. See A5 and revise the container labels accordingly.
2. Clarify the significance of the number located next to the lot number and expiration date [REDACTED] (b) (4). If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due its close proximity to the lot number and expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mylotarg that Pfizer submitted on November 2, 2016 and April 4, 2017.

Table 2. Relevant Product Information for Mylotarg	
Initial Approval Date	N/A
Active Ingredient	Gemtuzumab ozogamicin
Indication	- In combination with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia (AML) - For the treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy
Route of Administration	Intravenous
Dosage Form	For injection
Strength	5 mg
Dose and Frequency	<u>Combination therapy in previously untreated AML</u> <i>Induction:</i> The recommended dose of Mylotarg is 3 mg/m²/dose (up to a maximum of 5 mg per dose) infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR 60 mg/m²/day infused over 30 minutes on Days 1-3 and AraC 200 mg/m²/day by continuous infusion on Days 1-7. Mylotarg should not be administered during second induction therapy. <i>Consolidation:</i> 3 mg/m²/dose infused over 2 hours up to a maximum dose of 5 mg/dose on Day 1) are recommended. <u>Monotherapy in AML in first relapse</u> - The recommended dose of Mylotarg is 9 mg/m², infused over a 2-hour period - The recommended treatment course with Mylotarg is a total of 2 doses with 14 days between the doses. Recovery from hematologic toxicities is not a

	requirement for administration of the second dose.
How Supplied	(b) (4)
Storage	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 5, 2017, we searched the L:drive and AIMS using the terms, Mylotarg to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous proprietary name reviews^{b, c}.

^b Rutledge, M. Proprietary Name Review for Mylotarg (IND 046635). Silver Spring (MD):FDA, CDER, OSE, DMEPA (US); 2015 May 11. RCM No.: 2014-45070.

^c Rahimi, L. Proprietary Name Review for Mylotarg (BLA 761060). Silver Spring (MD):FDA, CDER, OSE, DMEPA (US); 2017 Jan 11. RCM No.: 2016-11204176.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 30, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing Joint Commission Long-Term Care PA Patient Safety Canada Safety
Search Strategy and Terms	Match Exact Word or Phrase: Mylotarg

D.2 Results

Our search described one^d relevant newsletter. The article reported a physician ordered Mylotarg 17 mg for a patient. The product was not on the hospital formulary and had to be ordered. When the medication came in, it was entered into the hospital computer system using the invoice information, which listed the product as “Mylotarg 5 mg- 20 mL vial.” When the chemotherapy order was entered into the pharmacy’s computer, the total volume for 17 mg was listed as 68 mL. However, the pharmacist read the package insert that stated that the 5 mg of lyophilized powder in the vial should be reconstituted with 5 mL for a concentration of 1 mg/mL. Thus, a 17 mg dose would be 17 mL, not 68 mL. The invoice and the wholesaler’s catalog was again consulted and both showed it as a 20 mL. The package insert was also consulted again which read, “Single 5 mg package: each 20 mL vial contains 5 mg of Mylotarg.” Yet, on the vial label, it correctly states 5 mg should be mixed as a 1 mg/mL concentration. It was concluded the 20 mL vial apparently refers to the size of the container, not the volume after it is reconstituted.

To analyze the product strength and reconstitution steps, we evaluated the proposed container label, carton labeling, and PI for Mylotarg. The proposed container label and carton labeling state each vial contains 5 mg of Mylotarg. The product should be reconstituted with 5 mL of Sterile Water for Injection, USP. Additionally, the Dosing and Administration Section of the

^d Institute for Safe Medication Practices. Safety briefs. ISMP Med Saf Alert. 2002; 7(15):1.

proposed PI state similar instructions. However, we recommend including the net quantity statement on the PDP of container label and carton labeling.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On February 21, 2017, we searched FAERS using the criteria in the table below and identified nine cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.^e

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	2000May17 to 2010May21
Product Name:	Mylotarg
Product Active Ingredient (PAI):	Gemtuzumab Ozogamicin
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified nine cases, of which 5 cases described errors relevant for this review.

Wrong technique during drug usage process (n = 3)

Three cases (FAERS case No. 3498438, 7326942, 5734935) described the administration of Mylotarg without the use of a filter.

- In one case, a patient received Mylotarg without a filter. In addition, Mylotarg was not prepared under light precautions and was left at room temperature for 16 hours before administration. The patient experienced fever, chills, and rigors post-infusion, which resolved after receiving hydrocortisone intravenously and sodium bicarbonate containing intravenous solutions. The fever chills and rigors were not felt to be hypersensitivity or infusion related reaction. All chemotherapy was discontinued after this event.
- In the second case, a patient received Mylotarg without a filter experienced slight renal impairment, rigors, and nausea. The rigors resolved after two doses of Demerol. The reporter of this incident could not say if the renal impairment, rigors, and nausea were a result of the medication error or the patient's deteriorating condition.
- The third patient described a patient that received one-half of the infusion of Mylotarg without a filter and the other half of the dose was infused with a filter. The patient

^e The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

experienced chills, fever, headache, nausea, and vomiting. The patient was subsequently hospitalized and observed as an inpatient for 2 days. A second dose of Mylotarg was administered and the patient had the same reaction. It was determined that the resulting adverse effects were to be expected according to the US product labeling for Mylotarg.

A review of Section 2 Dosage and Administration of the Prescribing Information for Mylotarg indicates, “(b) (4)”. However, we recommend bolding these statements to bring prominence to this important information.

Product label confusion (n =1)

FAERS case No. 3839561 is the same case previously discussed in Appendix D.

We evaluated the proposed container label, carton labeling, and PI for Mylotarg and recommend including the net quantity statement on the PDP of container label and carton labeling to mitigate confusion of the total product strength and net quantity.

Potential for medication error (n=1)

FAERS case No. 3561065 described a report in which stated that Mylotarg was very light sensitive. The manufacturer recommends that doses be prepared with the lights off under the laminar flow hood. The reporter was concerned that this could increase the potential for mix-ups with other products.

A review of Section 2 Dosage and Administration of the Prescribing Information for Mylotarg indicates, (b) (4)

After further discussion with CMC, we recommend including the following statement at the end of the paragraph, “All preparation should take place in a biologic safety cabinet with the fluorescent light off,” to ensure the stability of the product.

We excluded 4 cases because they described errors involving: accidental exposure (n =1), potential confusion with the nonproprietary name for Mylotarg (Gemtuzumab) and the proprietary name, Gemzar (n =1), and medication errors not related to Mylotarg (n =2).

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case Number	Manufacturer Control Number	Version Number
3498438	HQ6932706JUN2000	1
7326942	US-WYE-H14108810	1
3839561	N/A	1

5734935	HQWYE781621JAN05	1
3561065	N/A	1

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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,^f along with postmarket medication error data, we reviewed the following Mylotarg labels and labeling submitted by Pfizer on November 2, 2016 and April 4, 2017.

1. Container label
2. Carton labeling
3. Prescribing Information

G.2 Label and Labeling Images

Container label with security feature



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

Carton labeling

(b) (4)



Prescribing Information

[Application 761060 - Sequence 0001 - 1.14.1 Draft Labeling -](#)

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/s/

NICOLE B GARRISON
06/29/2017

HINA S MEHTA
07/05/2017

CLINICAL INSPECTION SUMMARY

Date	June 23, 2017
From	Min Lu, M.D., M.P.H., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Susan D. Thompson, M.D., Team Leader for Kassa Ayalew, M.D., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Emily Jen, M.D., Ph.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader Kris Kolibab, Ph.D., Senior Regulatory Project Manager Division of Hematology Products (DHP)
BLA	BLA 761060
Applicant	Pfizer Inc.
Drug	MYLOTARG® (gemtuzumab ozogamicin for injection)
NME	Yes
Therapeutic Classification	Antibody-drug conjugate (ADC)
Proposed Indication	Treatment of previously untreated, de novo acute myeloid leukemia
Consultation Request Date	November 21, 2016
Summary Goal Date	July 14, 2017
Action Goal Date	September 2, 2017
PDUFA Date	September 2, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical sites (Drs. Dombret, Bordessoule, Malfuson, and Vekhoff) and the sponsor (Pfizer and Versailles Hospital Center) sites were selected for inspection for Study ALFA-0701, a Phase 3, multicenter, open-label, randomized, parallel-group study to evaluate the efficacy and safety of fractionated doses of gemtuzumab ozogamicin in addition to daunorubicin + cytarabine for induction and consolidation therapy versus daunorubicin + cytarabine alone in previously untreated patients aged 50 to 70 years with acute myeloid leukemia (AML).

The final classification for inspections of three clinical sites (Drs. Dombret, Bordessoule, and Malfuson), Pfizer, (sponsor for Part 2, retrospective data analysis used for study report), and Versailles Hospital Center, Dr. Castaigne (sponsor/investigator for actual study) is No Action

Indicated (NAI). The preliminary classification for inspection of one clinical site (Dr. Vekhoff) is Voluntary Action Indicated (VAI) for failure to retain investigational records for a period of two years following approval of a drug's marketing application. Overall, the study data derived from these clinical sites are considered acceptable in support of the requested indication.

2. BACKGROUND

Mylotarg (gemtuzumab ozogamicin, GO) is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (MAb) that is covalently linked to the cytotoxic agent N-acetyl (NAc) gamma calicheamicin. The antibody portion binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukemic blast cells and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells. Binding of the anti-CD33 antibody portion of GO to the CD33 antigen results in the formation of a complex, which is then internalized. Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell. The released calicheamicin derivative binds to DNA in the minor groove resulting in DNA double-strand breaks and cell death.

Mylotarg was approved by FDA on May 17, 2000 (NDA 21-174, Wyeth Pharmaceuticals Inc., now a subsidiary of Pfizer Inc.) under accelerated approval regulations for the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who were 60 years of age or older and who were not considered candidates for other cytotoxic chemotherapy. On May 21, 2010, FDA requested that Wyeth voluntarily withdraw Mylotarg from the market, after results of a required postapproval randomized confirmative clinical trial failed to verify clinical benefit to patients and raised new concerns about the drug's safety, specifically increased risk of veno-occlusive disease. In a letter dated October 25, 2010, Wyeth requested that FDA withdraw approval of Mylotarg. Following the decision to withdraw the U.S. NDA in 2010, Mylotarg registrations have been withdrawn in all countries with the exception of Japan.

Repeated administration of lower dose of Mylotarg given as a fractionated dosing regimen was further evaluated in two pilot Phase 2 studies and in a Phase 3 study (Protocol WS936568, Study ALFA-0701) in combination with the standard chemotherapy in patients with untreated de novo AML. Study ALFA-0701 was sponsored and conducted by Versailles Hospital Centre (CHV) at 26 sites in France. This study was not under U.S. IND. After the initial study was completed the sponsor conducted an independent, retrospective, blinded determination of efficacy endpoints to calculate event-free survival. Additionally, a predefined list of adverse events was collected in order to expand the initial CHV safety database. Monitoring activities for the retrospective data collection were managed by CHV. The sponsor intends to use the Phase 3 study to support the proposed indication for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia.

Protocol WS936568/Study ALFA-0701

Protocol Title: Multicenter, Randomized, Phase 3 Study of Fractionated Doses of the Monoclonal Antibody [drug conjugate] Gemtuzumab Ozogamicin (Mylotarg) in Addition to Daunorubicin + Cytarabine for Induction and Consolidation Therapy in Patients With Acute Myeloid Leukemia (AML) Aged 50 to 70 Years

Study ALFA-0701 was a Phase 3, multicenter, open-label, randomized, parallel-group study to evaluate the efficacy and safety of fractionated doses of gemtuzumab ozogamicin in addition to daunorubicin + cytarabine for induction and consolidation therapy versus daunorubicin + cytarabine alone in previously untreated patients with AML aged 50 to 70 years.

The primary objective of the study was to compare the efficacy of gemtuzumab ozogamicin in addition to daunorubicin + cytarabine versus daunorubicin + cytarabine alone in patients with de novo AML aged 50 to 70 years, as measured by event-free survival (EFS). The secondary objectives included comparison of the following endpoints between the two arms: complete remission (CR) and complete remission with incomplete platelet recovery (CRp) rates, duration of remission as measured by relapse-free survival (RFS), overall survival (OS), and safety profiles.

The primary efficacy endpoint was event-free survival (EFS), defined as the time from date of randomization to date of induction failure, relapse, or death due to any cause, whichever came first.

The study inclusion criteria included patients with previously untreated, morphologically documented AML, aged 50 to 70 years inclusive, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 3, and cardiac function within normal limits. Expression of CD33 on leukemic blast cells was not required for study entry. Among the exclusion criteria were AML secondary to previous chemotherapy and/or radiotherapy for another neoplastic disease, central nervous system (CNS) involvement, uncontrolled infection, other active malignant disease, creatinine $\geq 2.5 \times$ upper limit of normal (ULN); alanine aminotransferase (ALT) or AST $\geq 2.5 \times$ ULN; total bilirubin $\geq 2 \times$ ULN, and prior anti-leukemia treatment, with the exception of hydroxyurea in case of hyperleukocytic leukemia.

The study enrolled 271 subjects in 26 sites in France and was not under U.S. IND. The study was initiated on January 8, 2008. The data cutoff dates were April 30, 2013 for overall survival analysis and November 1, 2013 for retrospective data collection.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
Herve Dombret, M.D. AP-HP Hopital Saint Louis, 1 avenue Claude Vellefaux, 75010 Paris Cedex 10, France	Site #3 Protocol WS936568 Subjects=32	January 9-13, 2017	NAI
Dominique Bordessoule CHU de Limoges – Hôpital Dupuytren 2 avenue Martin Luther King 87042 Limoges Cedex, France	Site #5 Protocol WS936568 Subjects=21	January 23-26, 2017	NAI
Jean Valère Malfuson, M.D., Ph.D. H.I.A. Percy 101 avenue Henri Barbusse 92140 Clamart, France	Site #8 Protocol WS936568 Subjects=11	January 23-25, 2017	NAI
Anne Vekhoff, M.D. AP-HP – Hôpital Saint-Antoine 184 rue du Faubourg Saint- Antoine 75571 Paris Cedex 12, France	Site #19 Protocol WS936568 Subjects=17	January 16-19, 2017	Pending: Preliminary Classification VAI
Sponsor	Protocol #	Inspection Date	Classification
Sponsor - Pfizer Inc. Shiferaw Kibriye, Head of Inspection Management 445 Eastern Point Road Groton, CT 06340, USA	Protocol WS936568	January 10-12, 2017	NAI
Sponsor/Investigator Versailles Hospital Centre (CHV), Dr. Sylvie Castaigne, Centre Hospitalier de Versailles (CHV), Hôpital André Mignot, 177 rue de Versailles 78150 LE Chesnay, France	Protocol WS936568	February 13-17, 2017	NAI

Key to Compliance Classifications

No Action Indicated (NAI) = No deviation from regulations.

Voluntary Action Indicated (VAI) = Deviation(s) from regulations.

Official Action Indicated (OAI) = Significant deviations from regulations. Data unreliable.

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

pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1. Herve Dombret, M.D. (Site #3, Paris, France)

The site screened 33 subjects and enrolled 32 subjects for Study Protocol WS936568. An audit of 32 enrolled subjects' records was conducted. Among the 32 enrolled subjects, 13 subjects completed the treatment, 18 subjects discontinued from the treatment, and one subject didn't receive study treatment. The reasons for discontinuations from the study treatment in the 18 subjects were resistant disease/relapse (10), adverse events (6), and starting new treatment (2). The discontinuations and reasons for discontinuations reported in the BLA data listing were source verified.

The inspection evaluated the following documents: informed consent forms, monitoring logs, delegation logs, enrollment logs, Ethics Committee correspondence and approvals, sponsor correspondence, adverse events, electronic case report forms (e-CRF's), drug accountability records and source documentation. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary and secondary efficacy endpoints were verifiable at the study site. No under-reporting of adverse events or serious adverse events were noted. All source data were generally verifiable at the site. It was noted that one subject (b) (6) received idarubicin instead of daunorubicin on Day 1 of consolidation. The event was reported and documented in the records and a corrective action was listed.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

2. Dominique Bordessoule, M.D. (Site #5, Limoges, France)

The site screened and enrolled 21 subjects for Study Protocol WS936568. All 21 subjects completed the treatment. An audit of all 21 enrolled subjects' records was conducted for efficacy endpoints and serious adverse events. Seven of 21 subject records were reviewed for eligibility and 5 out of 21 were source data verified against the listings for study treatment dosing with Mylotarg, daunorubicin, and cytarabine.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site for all subjects. No under-reporting of serious adverse events were noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

However, the following observations were noted during the inspection and discussed verbally with the principal investigator:

- Inaccurate and incorrect recording:
 - Inaccurate dates for reported adverse events in three subjects (b) (6)
 - An isolated adverse event (constipation) was not reported in one subject (b) (6)

OSI Reviewer Comment:

The problem with illogical dates (stop dates earlier in time than start days) noted during the clinical site inspection was addressed during the sponsor/investigator (CHV) inspection. See explanation below outlining observations/clarifications at CHV inspection.

3. Jean Valère Malfuson, M.D. (Site #8, Clamart, France)

The site screened 12 and enrolled 11 subjects for Study Protocol WS936568. An audit of 11 enrolled subjects' records was conducted. Among the 11 enrolled subjects, 9 subjects completed the treatment and 2 subjects discontinued from the study (due to resistant disease). The discontinuations and reasons for discontinuations reported in the BLA data listing were source verified.

The inspection evaluated the following documents: informed consent forms, monitoring logs, delegation logs, enrollment logs, Ethics Committee correspondence and approvals, sponsor correspondence, adverse events, electronic case report forms (e-CRF's), drug accountability records and source documentation. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary and secondary efficacy endpoints were verifiable at the study site. No underreporting of serious adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

4. Anne Vekhoff, M.D. (Site #19, Paris, France)

The site screened 18 subjects and enrolled 17 subjects for Study Protocol WS936568. An audit of 17 enrolled subjects' records was conducted. Among the 17 enrolled subjects, 8 subjects completed the treatment and 9 subjects discontinued from the study. The reasons for

discontinuations from the study treatment in the 8 subjects were adverse events (5), not eligible (1), starting new treatment (1), and persistent complete remission (1). The discontinuations and reasons for discontinuations reported in the BLA data listing were source verified.

The inspection evaluated the following documents: informed consent forms, monitoring logs, delegation logs, enrollment logs, Ethics Committee correspondence and approvals, sponsor correspondence, adverse events, electronic case report forms (e-CRF's), drug accountability records and source documentation. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary and secondary efficacy endpoints were verifiable at the study site. No under-reporting of adverse events or serious adverse events were noted. All source data except for specific documents listed below were generally verifiable at the site.

An FDA 483, Inspectional Observations, was issued to the site for failure to retain investigational records for a period of two years following the approval of a drug's marketing application, specifically:

- Source documents were missing for two subjects (Subject (b) (6) in the gemtuzumab ozogamicin group and Subject (b) (6) in the control group). Only the signed Informed Consent and computer printed hospitalization reports were present.
- The signed Informed Consent was missing for one subject (b) (6).
- Myelograms were missing for one subject (b) (6) in the control group).

OSI Reviewer Comment:

The above observations were shared with DHP.

Based on information in the inspection report, the hospital site where the study was initially conducted closed in June 2010 and patients (along with records) transferred to a different hospital facility. The current hospital has modernized their medical record storage between 2010 and 2016. These factors may have contributed to problems locating limited number of subject original source documents.

In general, except for the missing records identified above, this clinical site appeared to be in compliance with Good Clinical Practices.

Sponsor Sites

1. Pfizer Inc. (Groton, CT)

Inspectional coverage included review of the following areas: overall organization and personnel of the clinical research activities and monitoring of the study, quality assurance (QA), safety and adverse drug event (ADR) reporting, data collection, handling and record retention, and electronic records and electronic signatures. The standard operation procedures (SOPs), work

orders and the process performed for data collection and transfer were reviewed to evaluate the integrity of the data.

Study WS936568 was initiated as a Sponsor/Investigator trial by Dr. Sylvie Castaigne at the Centre Hospitalier de Versailles (CHV). Wyeth Pharmaceuticals Inc. agreed to provide drug to the Sponsor/ Investigator for use in this study. The agreement required CHV to provide Wyeth with information obtained from the study prior to any planned public presentation of results. In 2009, Pfizer, Inc. acquired Wyeth Pharmaceuticals Inc. as a wholly owned subsidiary. CHV submitted an abstract to the American Society of Hematology for a meeting to be held in late 2011. CHV provided a copy of the abstract containing only cumulative data (no raw data) to Pfizer in October 2011. The study reportedly showed positive results and CHV published the study results in the April 2012 issue of Lancet. Pfizer, Inc. subsequently entered into a data acquisition agreement with CHV in 2013 granting Pfizer, Inc. exclusive rights to the study data for potential regulatory submissions for marketing authorization. (b) (4)

Pfizer was not involved in sponsor related activities during the original study. An overview of sponsor responsibilities for the original and retrospective studies was provided during the inspection.

(b) (4) was the contract research organization (CRO) contracted to be responsible for data collection and analysis of the retrospective study by the Independent Review Committee (IRC). The IRC Charters and work orders of the CRO (start-up and full study) were collected and reviewed. The CRO oversight plans were also collected and reviewed during the inspection. No evidence was observed for any transfer of raw data prior to July 2013 except for April 2013 when CHV sent data for 20 subjects via compact disc to (b) (4) as a test to assess the structure of the data. The (b) (4) statistician reported that they had no access to or knowledge of any pharmacovigilance data prior to writing the SAP. The SAP was dated 22 March 2013.

Per the Agreement for the Supply of a Product for a Clinical Trial between Wyeth and CHV, CHV “will provide WYETH, on a quarterly basis, with a progress report of the TRIAL” and “the SPONSOR will send WYETH the TRIAL report and any information, data and documents that WYETH could reasonably request concerning the TRIAL”. However, Wyeth reported that they had progress telephone meetings with the CHV lead team regarding the safety but CHV did not provide data from the study and no subject specific information was discussed during the meetings and no record was kept of the meetings. Pfizer asserted that they did not see any effectiveness outcome data until it was to be officially published and the only pharmacovigilance task was to see that adverse events were being sent to the pharmacovigilance group.

The above observation was shared with DHP. In general, the sponsor site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

2. Versailles Hospital Centre (CHV), Dr.Sylvie Castaigne (Principal Investigator)

Inspectional coverage included review of the following areas: organization and personnel, selection and monitoring of clinical investigators (CI) and clinical monitors, monitoring

procedures and activities, safety and adverse drug event (ADR) reporting, protocol deviations (PD), quality assurance (QA), third party contracts, and test article integrity and accountability. Data reporting from the four clinical sites linked to this sponsor inspection were reviewed.

Study WS936568 was originally initiated as an academic research study, not under U.S. IND at Centre Hoptitalier de Versailles (CHV). Study drug was supplied by Wyeth Pharmaceuticals (now a subsidiary of Pfizer, Inc.) as part of a “biomedical research product provision agreement” which was signed on August 24, 2007 by Wyeth Pharmaceuticals and the study sponsor/investigator at CHV, Dr. Castaigne. The agreement indicated that the sponsor (CHV) would be responsible for conducting the study per ICH GCP guidelines as well as other applicable regulations and the Declaration of Helsinki. The agreement also stated that the CHV would report SAE’s involving the use of the study test article to Wyeth. The agreement indicated that Wyeth would be responsible for the quality of the test article and shipment of the test article to the clinical sites. In 2009 Pfizer, Inc. acquired Wyeth Pharmaceuticals. On March 19, 2013 Pfizer and CHV signed a data acquisition agreement stating that Pfizer was acquiring from CHV exclusive rights to the study data.

The sponsor (CHV) maintained adequate oversight of the clinical trial. No under-reporting of adverse events or serious adverse events was noted. CVH contracted with (b) (4) to have the clinical sites monitored, perform additional data entry and resolve queries for retrospective data collection. The discrepancy in SAE start and end dates were reviewed for Site 5 for observations noted during the clinical site inspection. The sponsor indicated that the data listings start and end dates for adverse events were imputed based on the document “Oracle Argus Safety User’s Guide” and “Analysis Data Reviewer’s Guide” if dates were missing. The sponsor provided explanations for the SAE dates entered for Subject (b) (6) during the inspection for Site 5.

The problem with illogical dates (stop dates earlier in time than start days) noted during the clinical site inspection were addressed during the sponsor (CHV) inspection. Safety data obtained during actual conduct of the study was entered into a CIOMS pharmacovigilance database. Imputations for partially missing start and stop dates were made in accordance with instructions for the Oracle Argus based system, the year would have needed to be specified and missing days of month default to “15” and missing months default to “JUN”. If no date information for start and stop date was present, the date for final reporting defaulted to the study “Analysis Data Reviewer’s Guide” for the study; start date was imputed as date of first dose of study medication and stop date as date of last dose +27.

A Form FDA 483 (Inspectional Observations) was not issued. However, the following observations were noted during and discussed verbally at the conclusion of the inspection, specifically:

- Several gaps in monitoring occurred during the Phase I portion of the study.
- At the time of Phase II monitoring the informed consent documentation could not be found for two subjects (Site 19 Subject (b) (6) and Site 14 Subject (b) (6)). These protocol deviations were reported and two subject’s data were excluded from analysis in the clinical study report by the sponsor.

- The principal investigator at Site 27 did not sign the study protocol prior to subject screening at the site (the first subject was screened on [REDACTED] (b) (6) and PI signed on April 15, 2010).

In general, the sponsor site appeared to be in compliance with Good Clinical Practices.

{See appended electronic signature page}

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/s/

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06/23/2017

JANICE K POHLMAN
06/24/2017

SUSAN D THOMPSON
06/24/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Memo

Date: May 17, 2017

Reviewer(s): Connie Cheng, PharmD, BCOP
Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Team Leader(s): Afrouz Nayernama, PharmD
DPV II

Deputy Division Director: Ida-Lina Diak, PharmD, MS
DPV II

Product Name(s): Mylotarg[®] (gemtuzumab ozogamicin)

Subject: Summary of post-marketing adverse events

Application Type/Number: BLA 761060

Applicant/Sponsor: Pfizer Inc.

OSE RCM #: 2017-663

1 INTRODUCTION

This memorandum provides a high-level summary of the post-marketing reports for gemtuzumab ozogamicin from the FDA Adverse Event Report System (FAERS) and the Empirica Signal software (datamining). The Division of Hematology Products (DHP) requested the Division of Pharmacovigilance II (DPV II) to provide a high-level summary of post-marketing data associated with the use of gemtuzumab ozogamicin for the review of a new Biologics License Application (BLA) 761060. It is noteworthy that an FDA advisory committee is scheduled for July 11, 2017, and the major questions for discussion of gemtuzumab ozogamicin include whether the fractionated dose is safer than a single high dose and whether event-free survival (EFS) is a surrogate of overall survival (OS) for the efficacy analysis.

On November 2, 2016, the sponsor of gemtuzumab ozogamicin, Pfizer Inc., submitted BLA 761060 for review by the FDA.¹ The proposed indications for labeling include:

- Combination therapy with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo AML.
- Treatment of patients with AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

2 REGULATORY HISTORY

The FDA granted accelerated approval to Mylotarg® (NDA 21174, gemtuzumab ozogamicin) on May 17, 2000 for the treatment of patients with CD33 positive AML in first relapse and aged 60 and older who were not considered candidates for cytotoxic chemotherapy.² However, a post-approval clinical trial did not confirm the clinical benefit of gemtuzumab ozogamicin. Additionally, safety concerns were raised due to the increased number of deaths observed in patients who received gemtuzumab ozogamicin in combination with standard chemotherapy compared to those receiving standard chemotherapy alone.³ Therefore, on June 21, 2010, Pfizer Inc. voluntarily discontinued the commercial marketing of the drug in the U.S. Subsequently, the NDA was withdrawn for gemtuzumab ozogamicin on October 15, 2010.⁴

In light of the voluntary withdrawal of gemtuzumab ozogamicin from the U.S. market, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) conducted a risk-benefit assessment for gemtuzumab ozogamicin as "monotherapy for relapsed or refractory CD33 positive AML patients for whom other re-induction therapies are not indicated," which is the approved indication in Japan.⁵ The PMDA concluded that the efficacy and safety profile of gemtuzumab ozogamicin remains unchanged from the time of approval; therefore, the drug continues to be marketed in Japan.⁵

3 METHODS AND MATERIALS

DPV II searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	May 8, 2017
Time Period of Search	May 17, 2000 [†] – May 07, 2017
Search Type	FBIS – Profile
Product Terms	Product active ingredient: gemtuzumab ozogamicin
* See Appendix A for a description of the FAERS database.	
[†] Date of Initial U.S. Approval	

DPV II searched Empirica Signal with the strategy described in Table 2. OSE uses Empirica Signal software to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. If a drug-event combination has a score (EB05) of ≥ 2 , this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

Table 2. Data Mining Search Strategy*	
Data Refresh Date	April 6, 2017
Product Terms	Generic name: Gemtuzumab
Empirica Signal Run Name	Generic, Suspect Drugs Only
* See Appendix A for a description of the Empirica Signal software.	

4 RESULTS

The FAERS search performed on May 8, 2017 yielded 2774 reports.

4.1 FAERS SEARCH RESULTS

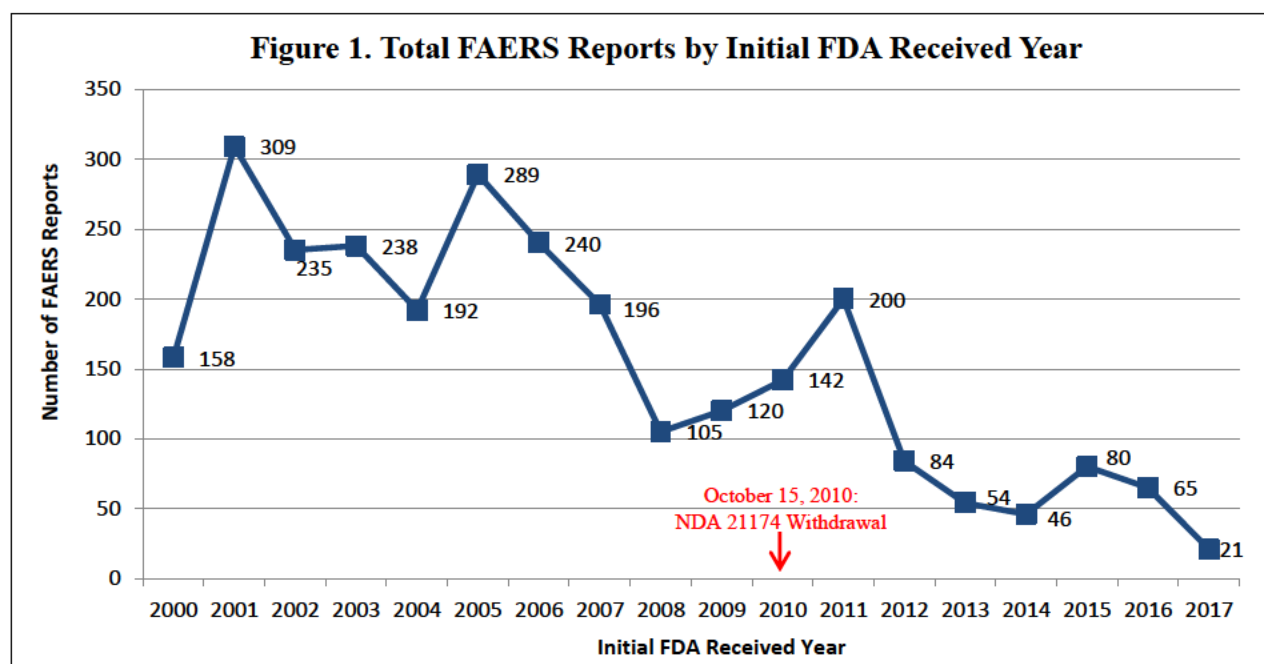
Table 3 provides descriptive characteristics of FAERS reports for gemtuzumab ozogamicin.

Table 3. Descriptive Characteristics of FAERS Reports for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 7, 2017 (N=2774)*		
Sex	Male	1409
	Female	1110
	Unknown	255
Age	< 1 year	9
	1 – <3 years	20
	3 – <7 years	30
	7 – <17 years	96
	17 – <65 years	1340
	≥ 65 years	970
	Not reported	309

Table 3. Descriptive Characteristics of FAERS Reports for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 7, 2017 (N=2774)*					
Country	United States	1541			
	Foreign	1230			
	Not reported	3			
Report type	Expedited	2313			
	Direct	281			
	Periodic	180			
Serious outcomes†		<u>Total</u>	<u>U.S.</u>	<u>Foreign</u>	<u>Not reported</u>
	Death	1156	548	607	1
	Life-threatening	567	226	341	0
	Hospitalization	1384	849	535	0
	Disability	50	24	26	0
	Other serious	1104	564	538	2
* May include duplicates. † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A report may have one or more outcome.					

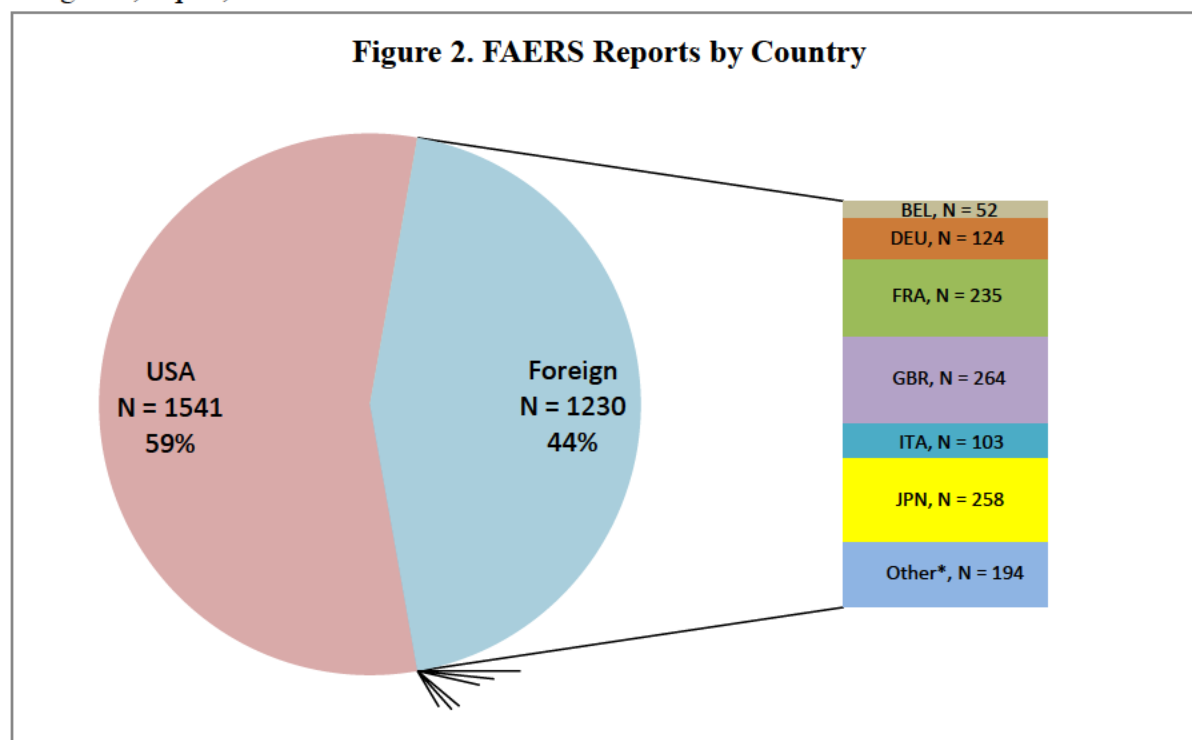
4.2 FAERS REPORTS BY YEAR

Figure 1 shows the number of FAERS reports by initial FDA received year for gemtuzumab ozogamicin, from May 17, 2000 to May 7, 2017. It is noteworthy that the number of FAERS reports decreases over time, especially after the withdrawal of NDA 201170 in 2010.



4.3 FAERS REPORTS BY COUNTRY

Figure 2 shows the number of FAERS reports by country for gemtuzumab ozogamicin, from May 17, 2000 to May 07, 2017. Of note, the majority of foreign reports are from the United Kingdom, Japan, and France.



Abbreviations: BEL = Belgium; DEU = Germany; FRA = France; GBR = United Kingdom; ITA = Italy; JPN = Japan

*Other countries include: Australia (12), Austria (11), Brazil (1), Canada (20), Czech Republic (2), Denmark (26), Finland (1), Greece (3), Hong Kong (1), Hungary (1), , Iceland (1), India (3), Ireland (2), Israel (7), Malaysia (2), Netherland (47), New Zealand (1), Poland (2), Portugal (4), Singapore (1), Slovakia (1), South Africa (5), South Korea (1), Spain (17), Sweden (6), Switzerland (10), Taiwan (4), Turkey (1), Venezuela (1)

4.4 MOST FREQUENTLY REPORTED MEDDRA PREFERRED TERMS (PTs) WITH $N \geq 50$ FAERS REPORTS

Table 4. Most Frequently Reported MedDRA PTs with $N \geq 50$ for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 7, 2017, Sorted by Decreasing Number of FAERS Reports per PT			
Row	MedDRA PT	Number of FAERS Reports[*]	Labeled[†] (Yes/No), Location or Other Category[‡]
1	Pyrexia	400	(b) (4)
2	Febrile neutropenia	343	
3	Sepsis	280	
4	Chills	253	
5	Platelet count decreased	240	
6	Thrombocytopenia	227	
7	Neutropenia	220	
8	Hypotension	215	
9	Venoocclusive liver disease	215	
10	White blood cell count decreased	203	
11	Aspartate aminotransferase increased	201	
12	Pneumonia	197	
13	Blood bilirubin increased	182	
14	Alanine aminotransferase increased	171	
15	Acute myeloid leukaemia	167	
16	Disease progression	163	
17	Ascites	150	
18	Multiple organ dysfunction syndrome	148	
19	Haemoglobin decreased	147	
20	Dyspnoea	145	
21	Pancytopenia	138	
22	Renal failure	134	
23	Infusion related reaction	128	
24	Blood alkaline phosphatase increased	119	

Table 4. Most Frequently Reported MedDRA PTs with $N \geq 50$ for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 7, 2017, Sorted by Decreasing Number of FAER

			(b) (4)
25	Weight increased	118	
26	Nausea	114	
27	Vomiting	112	
28	Pleural effusion	111	
29	Respiratory failure	106	
30	Anaemia	104	
31	Neutrophil count decreased	97	
32	Acute kidney injury	95	
33	Blood lactate dehydrogenase increased	95	
34	Condition aggravated	95	
35	Liver disorder	81	
36	Diarrhoea	80	
37	Disseminated intravascular coagulation	80	
38	Hypoxia	80	
39	Hepatic failure	79	
40	Septic shock	78	
41	Neoplasm malignant	77	
42	Haematocrit decreased	75	
43	Bone marrow failure	72	
44	Hepatomegaly	71	
45	Pulmonary oedema	70	
46	Acute respiratory distress syndrome	69	
47	Infection	69	
48	Tachycardia	69	
49	Gastrointestinal haemorrhage	67	
50	Hypokalaemia	64	
51	Liver function test abnormal	64	
52	Abdominal pain	62	
53	Respiratory distress	62	
54	Blood creatinine increased	60	
55	Abdominal distension	59	

Table 4. Most Frequently Reported MedDRA PTs with N ≥ 50 for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 7, 2017, Sorted by Decreasing Number of FAERS Reports per PT			
56	Cerebral haemorrhage	58	(b) (4)
57	Lung infiltration	56	
58	Confusional state	55	
59	Blood culture positive	54	
60	Epistaxis	53	
61	Bronchopulmonary aspergillosis	52	
62	Fatigue	51	
* A report may contain more than one preferred term † Sponsor-proposed label for BLA 761060 ⁶ ‡ Definitions: BW = Boxed Warning, W/P = Warnings/Precautions, AR = Adverse Reactions, SP= Use in Specific Populations, PCI = Patient Counseling Information, DR = Disease-related, IR = Indication-related, U = Uninformative			

A majority of the reported PTs are either labeled events or expected based on the underlying condition. DPV II identified several adverse events (b) (4) and they are described in Section 5 of this review.

4.5 MEDDRA PTs FROM FAERS REPORTS WITH FATAL OUTCOMES WITH N ≥ 25

Table 5. MedDRA PTs from FAERS Reports with Fatal Outcomes with N ≥ 25 for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 07, 2017, Sorted by Decreasing Number of FAERS Reports per PT			
Row	MedDRA PT	Number of FAERS Reports [*]	Labeled [†] (Yes/No), Location or Other Category [‡]
1	Sepsis	196	(b) (4)
2	Pneumonia	148	
3	Acute myeloid leukaemia	136	
4	Disease progression	135	
5	Pyrexia	134	
6	Venoocclusive liver disease	134	
7	Multiple organ dysfunction syndrome	132	
8	Febrile neutropenia	128	
9	Platelet count decreased	120	
10	Thrombocytopenia	111	
11	Neutropenia	101	
12	White blood cell count decreased	95	
13	Renal failure	92	
14	Respiratory failure	90	

Table 5. MedDRA PTs from FAERS Reports with Fatal Outcomes with N $\geq$ 25 for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 07, 2017, Sorted by Decreasing Number of FAERS Reports per PT

	Aspartate aminotransferase increased	85	(b) (4)
15			
16	Blood bilirubin increased	84	
17	Hypotension	84	
18	Ascites	75	
19	Pancytopenia	70	
20	Hepatic failure	65	
21	Alanine aminotransferase increased	64	
22	Haemoglobin decreased	63	
23	Pleural effusion	63	
24	Anaemia	61	
25	Dyspnoea	60	
26	Chills	59	
27	Neoplasm malignant	59	
28	Condition aggravated	58	
29	Septic shock	57	
30	Disseminated intravascular coagulation	56	
31	Neutrophil count decreased	55	
32	Blood lactate dehydrogenase increased	54	
33	Acute kidney injury	51	
34	Blood alkaline phosphatase increased	50	
35	Liver disorder	50	
36	Acute respiratory distress syndrome	49	
37	Cerebral haemorrhage	46	
38	Weight increased	46	
39	Gastrointestinal haemorrhage	45	
40	Infection	43	
41	Hypoxia	42	
42	Respiratory distress	41	
43	Cardiac arrest	38	
44	Hepatomegaly	38	

Table 5. MedDRA PTs from FAERS Reports with Fatal Outcomes with N $\geq$ 25 for Gemtuzumab Ozogamicin, Received by FDA from May 17, 2000 to May 07, 2017, Sorted by Decreasing Number of FAERS Reports per PT

45	Bone marrow failure	37	(b) (4)
46	Diarrhoea	37	
47	Blood creatinine increased	36	
48	Pulmonary oedema	35	
49	Pulmonary haemorrhage	34	
50	Vomiting	34	
51	Abdominal distension	33	
52	Cardiac failure	33	
53	Confusional state	33	
54	Haematocrit decreased	33	
55	Nausea	33	
56	Blood urea increased	32	
57	Infusion related reaction	31	
58	Liver function test abnormal	30	
59	Abdominal pain	29	
60	Budd-Chiari syndrome	29	
61	Lung infiltration	29	
62	Neutropenic sepsis	29	
63	Renal impairment	29	
64	Bronchopulmonary aspergillosis	28	
65	Drug ineffective	28	
66	Hypokalaemia	28	
67	Coagulopathy	27	
68	Coma	27	
69	Dialysis	27	
70	General physical health deterioration	27	
71	Hepatic function abnormal	27	
72	Epistaxis	25	

* A report may contain more than one MedDRA PT.

† Sponsor-proposed label for BLA 761060⁶

‡ Definitions: BW = Boxed Warning, W/P = Warnings/Precautions, AR = Adverse Reactions, SP= Use in Specific Populations, PCI = Patient Counseling Information, DR = Disease-related, IR = Indication-related, U = Uninformative

A majority of the reported PTs with fatal outcomes were similar to the most frequently reported PTs with $N \geq 50$ for gemtuzumab ozogamicin (Table 4). The unlabeled adverse events are described in Section 5 of this review.

4.6 DATA MINING RESULTS

A datamining search of drug-event combinations with an EB05 greater than zero (0) was performed. Table 6 provides a list of unlabeled events of interest, organized by System Organ Class (SOC), reported with gemtuzumab. The majority of these events were not listed in Tables 4 and 5 due to the PT count, $N < 25$.

Table 6. Data Mining Results for Unlabeled Events of Interest with Gemtuzumab by MedDRA Preferred Terms, Sorted by Descending EB05 Scores					
Row	PT	N	EB05	EBGM	EB95
Blood and lymphatic system disorders					
1	Thrombotic microangiopathy	3	0.57	1.491	3.336
Cardiac disorders					
2	Left ventricular dysfunction	7	2.469	4.824	9.26
3	Cardiac failure	35	1.549	2.058	2.69
4	Atrial fibrillation	41	1.422	1.848	2.37
5	Cardiotoxicity	4	1.155	2.68	5.508
6	Cardiac failure congestive	33	0.983	1.317	1.736
7	Cardiomyopathy	8	0.821	1.494	2.545
8	Cardiomegaly	10	0.723	1.236	2.001
9	Torsade de pointes	5	0.7	1.488	2.859
10	Cardiac failure acute	3	0.666	1.742	3.898
11	Myocardial ischaemia	6	0.484	0.965	1.765
12	Left ventricular failure	3	0.475	1.243	2.781
13	Myocardial infarction	28	0.317	0.435	0.587
14	Acute myocardial infarction	5	0.239	0.509	0.978
Gastrointestinal disorders					
15	Neutropenic colitis	8	24.405	46.437	81.91
16	Abdominal distension	52	2.448	3.089	3.855
17	Pancreatitis	16	0.796	1.214	1.791
18	Acute pancreatitis	4	0.325	0.753	1.543
Hepatobiliary disorders					
19	Budd-Chiari syndrome	45	109.37	140.803	178.986
Immune system disorders					
20	Graft versus host disease	33	7.575	11.126	16.005
21	Acute graft versus host disease	2	0.483	1.532	3.917
22	Acute graft versus host in liver	1	0.27	1.239	4.021
23	Acute graft versus host in skin	1	0.22	1.006	3.258
Infections and infestations					
24	Pneumocystis jirovecii pneumonia	11	1.95	3.249	5.157

Table 6. Data Mining Results for Unlabeled Events of Interest with Gemtuzumab by MedDRA Preferred Terms, Sorted by Descending EB05 Scores					
25	Pulmonary mycosis	3	1.032	2.727	6.204
26	Stenotrophomonas infection	3	1.016	2.679	6.076
Investigations					
27	Blood urea increased	40	2.693	3.512	4.517
28	Ejection fraction decreased	15	2.278	3.525	5.263
29	Blood creatinine increased	57	2.068	2.582	3.192
30	Ejection fraction abnormal	6	1.729	3.456	6.363
31	Electrocardiogram QT prolonged	8	0.596	1.085	1.848
Renal and urinary disorders					
32	Cystitis haemorrhagic	13	4.914	9.695	20.196
33	Renal failure	119	3.161	3.683	4.271
34	Acute kidney injury	88	2.195	2.623	3.114
35	Renal impairment	39	1.856	2.428	3.132
36	Oliguria	11	1.603	2.671	4.238
37	Renal tubular necrosis	6	0.765	1.525	2.79
38	Acute prerenal failure	3	0.741	1.939	4.341
39	Anuria	6	0.736	1.468	2.687
Respiratory, thoracic and mediastinal disorders					
40	Pulmonary veno-occlusive disease	5	3.033	17.181	62.216
41	Interstitial lung disease	23	1.668	2.371	3.289
Surgical and medical procedures					
42	Dialysis	34	3.051	4.072	5.345
43	Haemodialysis	20	1.523	2.222	3.152
Vascular disorders					
44	Capillary leak syndrome	9	3.49	7.069	18.261

5 REVIEWER'S COMMENTS

- It is important to note that these results are overall counts of FAERS reports and may include duplicate reports submitted for the same events in the same patient. Duplicate reports may include additional information from one or more sources (e.g., manufacturer, physician, pharmacist, patient, etc.). A detailed case review was not performed for these reports, and therefore, a drug-event causal association cannot be assessed based on these reports (See **Appendix A** for FAERS Limitations).
- Empirica Signal was used to identify patterns in disproportional reporting associated with gemtuzumab and PTs (b) (4). The output was restricted to drug-event combinations with a reported EB05 > 0.
- DPV II identified the following list of unlabeled events from the FAERS and datamining high-level analyses as potential safety signals that may warrant further investigation due to the serious outcomes, the nature of the event, number of reports and/or EB05 score.

Therefore, DHP may consider issuing an information request (IR) to the sponsor for an overview and analysis of the following unlabeled events from all sources, including post-marketing data and clinical trials:

Blood: thrombotic microangiopathy

Cardiac: cardiac failure, atrial fibrillation, myocardial infarction, torsade de pointes

Gastrointestinal: neutropenic colitis, pancreatitis

Hepatobiliary: Budd-Chiari syndrome^a

Immune: graft versus host disease

Infections: Pneumocystis jirovecii pneumonia, pulmonary mycosis, Stenotrophomonas infection

Renal: cystitis haemorrhagic, renal failure, acute kidney injury

Respiratory: pulmonary veno-occlusive disease, interstitial lung disease

Vascular: capillary leak syndrome

(b) (4)

6 REFERENCES

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2. Mylotarg (Gemtuzumab ozogamicin) FDA approval letter. May 17, 2000. Accessed on May 5, 2017 at: https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2000/21174ltr.pdf
3. Nelson, R. Gemtuzumab Voluntarily Withdrawn From US Market. June 21, 2010. Accessed on May 5, 2017 at: <http://www.medscape.com/viewarticle/723957>
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5. Pharmaceuticals and Medical Devices Safety Information: Safety Measures for Gemtuzumab Ozogamicin. February 2011. Accessed on May 4, 2017 at: <http://www.pmda.go.jp/files/000153067.pdf#page=5>
6. Pfizer Inc, Gemtuzumab BLA 761060. Draft Labeling Text. April 7, 2017. Accessed on May 4, 2017 at: <\\cdsesub1\evsprod\bla761060\0029\m1\us\lab-0868-0-2-pkg-insert-clean.pdf>

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

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

/s/

CONNIE N CHENG
05/17/2017

AFROUZ R NAYERNAMA
05/17/2017

IDA-LINA DIAK
05/17/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 761060	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Mylotarg Established/Proper Name: gemtuzumab ozogamicin Dosage Form: intravenous Strengths: 5 mg/vial		
Applicant: Pfizer Agent for Applicant (if applicable):		
Date of Application: November 2, 2016 Date of Receipt: November 2, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: September 2, 2017		Action Goal Date (if different):
Filing Date: January 1, 2017		Date of Filing Meeting: December 20, 2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Mylotarg is indicated for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia (AML) and treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i>		

http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499	
Type of BLA	☒ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
The application will be a priority review if: • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 046635				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	☒	☐		
If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.				
Are the established/proper and applicant names correct in electronic archive?	☒	☐		
If no, ask the document room staff to make the corrections. Also,				

ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.					
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐		
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>): ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ N/A ☐ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment

Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes , answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	☐	☐		
If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	☐	☐		
If yes , please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	☐	☒		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?	☐	☒	☐	
If yes , consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy				
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☐	☐	
If yes , # years requested:				

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	☐	☐	☐	
If yes, contact the Orange Book Staff (CDER-Orange Book Staff).				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☒	☐	☐	Marlene has been notified.
If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager				
Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	☒	☐		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☒	☐	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☒	☐	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	☒	☐		Orphan designation and therefore PREA does not apply.

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☐	☐	☒	Orphan designation and therefore PREA does not apply.
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☐	☐	☒	Orphan designation and therefore PREA does not apply.
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
BPCA:				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☒	☐	☐	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

alHealthStaff/ucm027829.htm

3

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

<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☒	☐	☐	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

4

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

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	OSI consult sent on 11/21/2016
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/22/2016 Pre-BLA 8/30/2016 Pre-BLA (WRO) 9/28/2016 CMC Pre-BLA (WRO)	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s):	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 20, 2016

BACKGROUND: Pfizer submitted a biologics license application on November 2, 2016 under section 351(a) of the Public Health Service Act to market Mylotarg, a CD33-directed antibody-drug conjugate. Pfizer is seeking to market Mylotarg for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia and treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kris Kolibab	Y
	CPMS/TL:	Amy Baird/Theresa Carioti	N/Y
Cross-Discipline Team Leader (CDTL)	Donna Przepiorka		Y
Division Director/Deputy	Ann Farrell		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Emily Jen and Kelly Norsworthy	Y/Y
	TL:	Donna Przepiorka	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams/Bahru Habtemariam	N/Y
• Genomics	Reviewer:		

• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Chia-Wen Ko	Y
	TL:	Lei Nie	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pedro Del Valle	Y
	TL:	Chris Sheth	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Marjorie Shapiro/Sarah Kennett	N/Y
	RBPM:	Kelly Ballard	N
• Drug Substance	Reviewer:	Antonina Aydanian	Y
• Drug Product	Reviewer:	Antonina Aydanian	Y
• Process	Reviewer:		
• Microbiology	Reviewer:	Maria Jose Lopez-Barragan and Natalia Pripuzova	Y/N
• Facility	Reviewer:	Thuy Nguyen	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad	N
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Nicole Garrison	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL 505 b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO	
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments	

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☒ YES Date if known: July 2017 ☐ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments: No issues	☐ Review issues for 74-day letter
<u>APPLICATIONS IN THE PROGRAM (PDUFA V)</u> <u>(NME NDAs/Original BLAs)</u> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ann T. Farrell, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments: This application will go to ODAC.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

KRISTOPHER KOLIBAB
01/03/2017

MARA B MILLER
01/03/2017

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

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

Application: BLA 761060

Application Type: New BLA

Drug Name(s)/Dosage Form(s): Mylotarg, lyophilized cake or powder, 5mg/vial intravenous

Applicant: Pfizer

Receipt Date: November 2, 2016

Goal Date: September 2, 2017

1. Regulatory History and Applicant's Main Proposals

Pfizer submitted a biologics license application on November 2, 2016 under section 351(a) of the Public Health Service Act to market Mylotarg, a CD33-directed antibody-drug conjugate. Pfizer is seeking to market Mylotarg for the treatment of adult patients with previously untreated, de novo acute myeloid leukemia and treatment of patients with acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

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

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required

Selected Requirements of Prescribing Information

• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES

Selected Requirements of Prescribing Information

14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

Selected Requirements of Prescribing Information

(insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 35. All text in the BW should be **bolded**.

Comment:

- YES** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

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

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

KRISTOPHER KOLIBAB
11/17/2016

MARA B MILLER
11/17/2016