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APPLICATION NUMBER:

761053Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

PMR # 3194-1

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

NDA/BLA # BLA 761053
Product Name: Ocrevus (ocrelizumab)

PMR/PMC Description: Conduct a two-part study of ocrelizumab in pediatric patients with relapsing multiple sclerosis (RMS) at least 10 years and less than 17 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ocrelizumab in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine a dose of ocrelizumab that will result in PK and PD effects that are comparable to those of a 600 mg dose (300 mg given twice 14 days apart) in adult patients with RMS. Safety assessments will continue for at least 2 years after the last dose of ocrelizumab. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab compared to an appropriate comparator.

PMR/PMC Schedule Milestones:	Draft Protocol Submission	02/2019
	Final Protocol Submission:	09/2019
	Study Completion:	07/2023
	Final Report Submission:	01/2024
	Other:	MM/DD/YYYY

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

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

This is a PREA study. Ocrevus is ready to be approved in adults.

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

This is a PREA study. The goal is to study the safety and efficacy of Ocrevus in pediatric patients, 10 to 17 years of age, with relapsing-remitting multiple sclerosis.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Conduct a two-part study of ocrelizumab in pediatric patients with relapsing multiple sclerosis (RMS) at least 10 years and less than 17 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ocrelizumab in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine a dose of ocrelizumab that will result in PK and PD effects that are comparable to those of a 600 mg dose (300 mg given twice 14 days apart) in adult patients with RMS. Safety assessments will continue for at least 2 years after the last dose of ocrelizumab. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab compared to an appropriate comparator.

Required

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

Continuation of Question 4

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

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials

- ☐ Immunogenicity as a marker of safety

- ☒ Other (provide explanation)

This is a PREA study of pharmacokinetics, pharmacodynamics, efficacy, and safety.

Agreed upon:

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

☐ Other

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template
PMR # 3194-2

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

NDA/BLA # BLA 761053
Product Name: Ocrevus (ocrelizumab)

PMR/PMC Description: Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to Ocrevus (ocrelizumab) to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study should be followed for a minimum of 5 years or until death following their first exposure to Ocrevus. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>08/31/2017</u>
	Final Protocol Submission:	<u>11/30/2017</u>
	Study Completion:	<u>11/30/2029</u>
	Final Report Submission:	<u>11/30/2030</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The application is ready to be approved. The information that is currently available about malignancy risk after exposure to ocrelizumab can be included in the labeling. Additional long-term data are needed.

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

There is a signal for breast cancer and malignancies overall in the BLA database. Additional long-term information is needed to further characterize the risk. The goal of the study is to determine the incidence and mortality rates of breast cancer and all malignancies after exposure to ocrelizumab.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to Ocrevus (ocrelizumab) to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study should be followed for a minimum of 5 years or until death following their first exposure to Ocrevus. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

-
- ☐ Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR # 3194-3

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

NDA/BLA # BLA 761053
Product Name: Ocrevus (ocrelizumab)

PMR/PMC Description: Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>7/31/2017</u>
	Final Protocol Submission:	<u>10/31/2017</u>
	Study Completion:	<u>10/31/2028</u>
	Final Report Submission:	<u>10/31/2029</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Pregnancy registries are conducted post-marketing to obtain safety data on drug use during pregnancy including maternal and infant outcomes. Historically, pregnancy registries are not conducted during the pre-marketing period, because except in unusual circumstances, it is ethically and medically important to demonstrate safety and efficacy in nonpregnant women before studying the drug in pregnant women.

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

There are no adequate data on the serious risk of adverse maternal, fetal, and infant outcomes associated with use of ocrelizumab in pregnant women. The goal of the pregnancy registry is to obtain data on pregnancy and infant outcomes after ocrelizumab exposure during pregnancy to inform prescribing for and counseling of women affected by multiple sclerosis that are pregnant and of childbearing potential.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Required

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

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
-

Agreed upon:

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

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template
PMR # 3194-4

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

NDA/BLA # BLA 761053
Product Name: Ocrevus (ocrelizumab)

PMR/PMC Description: Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3194-3 (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to ocrelizumab during pregnancy compared to an unexposed control population.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>7/31/17</u>
	Final Protocol Submission:	<u>10/31/17</u>
	Study Completion:	<u>3/31/2023</u>
	Final Report Submission:	<u>3/31/2024</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Pregnancy studies are conducted post-marketing to obtain safety data on drug use during pregnancy including maternal and infant outcomes. Historically, pregnancy studies are not conducted during the pre-marketing period, because except in unusual circumstances, it is ethically and medically important to demonstrate safety and efficacy in nonpregnant women before studying the drug in pregnant women.

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

There are no adequate data on the serious risk of adverse maternal, fetal, and infant outcomes associated with use of ocrelizumab in pregnant women. The goal of this outcomes study is to obtain data on pregnancy and infant outcomes after ocrelizumab exposure during pregnancy to inform prescribing for and counseling of women affected by multiple sclerosis that are pregnant and of childbearing potential.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3194-3 (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to ocrelizumab during pregnancy compared to an unexposed control population.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

- ☐ Other

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

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

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

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

The application is to be approved and an adequate assessment of the potential for OCREVUS to adversely affect the developing organism (including immune function using the TDAR assay) has not been conducted.

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

An expanded pre- and postnatal development study in nonhuman primates is required to identify an unexpected, serious risk of adverse fetal, and infant outcomes associated with use of Ocrevus, in accordance with guidance set forth in ICH S5(R2):*Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility* (2005). The prenatal and postnatal development in nonhuman primate conducted by the sponsor was not adequate, due to lack of results of the immunotoxicity assessment (TDAR) of the offspring and sufficient data to document comparability of the product tested to the to-be-marketed product.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An expanded pre-and postnatal development study (including T-cell dependent antibody response [TDAR]) of Ocrevus (ocrelizumab) in nonhuman primate.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3194-6

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Perform a shipping study to confirm validation of the commercial ocrelizumab drug product shipping conditions. The study will be performed using representative shipping routes and drug product that has been stored for an extended period. The study will include testing of pre- and post-shipping samples for product quality (purity by SE-HPLC, reduced and non-reduced CE-SDS, IE-HPLC, sub-visible particles, visible particles, clarity/opalescence, and potency) and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study Completion:	N/A
	Final Report Submission:	08/31/2017
	Other:	N/A

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

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

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

Data provided in the BLA were from a simulated transport study and did not consider the potential stability issues caused by the degradation of the polysorbate 20 excipient in this drug product. The additional studies provide assurance of the safety and quality of the product when the drug product is shipped in the commercial shipping configuration.

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

Shipping validation studies did not evaluate the impact to drug product under the final commercial shipping conditions or through the shelf life, which is linked to issues with polysorbate 20 degradation. This study will provide validation of the commercial shipping conditions, including a direct assessment of product quality parameters pre- and post-shipment.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

Perform a shipping study to confirm validation of the commercial ocrelizumab drug product shipping conditions. The study will be performed using representative shipping routes and drug product that has been stored for an extended period. The study will include testing of pre- and post-shipment samples for product quality (purity by SE-HPLC, reduced and non-reduced CE-SDS, IE-HPLC, sub-visible particles, visible particles, clarity/opalescence, and potency) and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3194-7

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Confirm validation of the Antibody-Dependent Cellular Cytotoxicity assay (Method Q12764). The validation study will be performed to demonstrate suitability of the method to be used as a potency assay for drug substance release testing.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study Completion:	N/A
	Final Report Submission:	06/30/2017
	Other:	N/A

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

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

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

Qualification and partial validation data and the ocrelizumab testing data area available for these assays and provide some support for the use of the methods for their purposes. The additional testing included in the lot release and stability specifications further support the acceptability of the use of the current methods to control the quality of the drug substance and drug product.

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

The assays that have been added to the release or stability specifications during the review cycle have been qualified or partially validated to be suitable for their current purpose. However, these analytical methods have not been fully validated for accuracy, precision, specificity, quantitation limit, linearity, and range, and robustness with respect to purity, impurities, and potency. Method validation should be performed to ensure the suitability of the lot release and stability tests.

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

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

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

Describe the agreed-upon study:

Method validation will be performed for the ADCC, CE-glycan, RP-UHPLC, and polysorbate 20 assays. If the current polysorbate 20 assay is not found to be suitable for stability testing, an alternative assay will be developed.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

PMC # 3194-8

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Confirm validation of the Capillary Electrophoresis Glycan Analysis assay (Method Q12756). The validation study will be performed to demonstrate suitability of the method to be used to assess levels of high-mannose 5 glycan (Man-5) for drug substance release testing.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study Completion:	N/A
	Final Report Submission:	06/30/2017
	Other:	N/A

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

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

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

Qualification and partial validation data and the ocrelizumab testing data area available for these assays and provide some support for the use of the methods for their purposes. The additional testing included in the lot release and stability specifications further support the acceptability of the use of the current methods to control the quality of the drug substance and drug product.

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

The assays that have been added to the release or stability specifications during the review cycle have been qualified or partially validated to be suitable for their current purpose. However, these analytical methods have not been fully validated for accuracy, precision, specificity, quantitation limit, linearity, and range, and robustness with respect to purity, impurities, and potency. Method validation should be performed to ensure the suitability of the lot release and stability tests.

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

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

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

Describe the agreed-upon study:

Method validation will be performed for the ADCC, CE-glycan, RP-UHPLC, and polysorbate 20 assays. If the current polysorbate 20 assay is not found to be suitable for stability testing, an alternative assay will be developed.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3194-9

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Confirm validation of the Reversed-Phase Ultra-High-Performance Liquid Chromatography assay (Method Q13406). The validation study will be performed to demonstrate suitability of the method to be used to assess levels of Fc oxidation for drug substance release testing.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study Completion:	N/A
	Final Report Submission:	06/30/2017
	Other:	N/A

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

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

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

Qualification and partial validation data and the ocrelizumab testing data area available for these assays and provide some support for the use of the methods for their purposes. The additional testing included in the lot release and stability specifications further support the acceptability of the use of the current methods to control the quality of the drug substance and drug product.

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

The assays that have been added to the release or stability specifications during the review cycle have been qualified or partially validated to be suitable for their current purpose. However, these analytical methods have not been fully validated for accuracy, precision, specificity, quantitation limit, linearity, and range, and robustness with respect to purity, impurities, and potency. Method validation should be performed to ensure the suitability of the lot release and stability tests.

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

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

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

Describe the agreed-upon study:

Method validation will be performed for the ADCC, CE-glycan, RP-UHPLC, and polysorbate 20 assays. If the current polysorbate 20 assay is not found to be suitable for stability testing, an alternative assay will be developed.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3194-10

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Confirm validation of the Polysorbate 20 assay (Method SAM-0106429) or develop, validate, and implement an alternative assay to evaluate Polysorbate 20. The validation study will be performed to demonstrate suitability of the method for use in detecting degradation of Polysorbate 20 during drug product storage and to be included in the drug product release specifications. The final validation report and updated specifications, if applicable, will be submitted to the BLA.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study Completion:	N/A
	Final Report Submission:	05/31/2017
	Other:	N/A

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

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

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

Qualification and partial validation data and the ocrelizumab testing data area available for these assays and provide some support for the use of the methods for their purposes. The additional testing included in the lot release and stability specifications further support the acceptability of the use of the current methods to control the quality of the drug substance and drug product.

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

The assays that have been added to the release or stability specifications during the review cycle have been qualified or partially validated to be suitable for their current purpose. However, these analytical methods have not been fully validated for accuracy, precision, specificity, quantitation limit, linearity, and range, and robustness with respect to purity, impurities, and potency. Method validation should be performed to ensure the suitability of the lot release and stability tests.

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

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

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

Describe the agreed-upon study:

Method validation will be performed for the ADCC, CE-glycan, RP-UHPLC, and Polysorbate 20 assays. If the current polysorbate 20 assay is not found to be suitable for stability testing, an alternative assay will be developed.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3194-11

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Manufacture, qualify, and implement new primary and secondary reference standards that are representative of the pivotal clinical study materials. The qualification protocol will be submitted as a PAS, and the final qualification report will be submitted to the BLA.

PMC Schedule Milestones:	Final Protocol Submission:	05/31/2017
	Study Completion:	N/A
	Final Report Submission:	3/30/2018
	Other:	N/A

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

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

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

The current primary and working reference standards were manufactured from an ocrelizumab lot that is not representative of the pivotal study material; however, given the current use of the reference standards, minimal impact to product safety and efficacy are expected, and this reference is adequate for interim use and approval of the BLA.

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

The reference standards, which are used for release and stability testing of drug substance and drug product, should represent the link between commercial product and clinical experience. However, the current ocrelizumab reference standard is not representative of the pivotal clinical study material, specifically with respect to potency aspects of antibody effector function. New primary and working reference standards should be qualified and implemented to ensure minimal drift in product quality attributes over the lifetime of the product.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

Manufacture, qualify, and implement new primary and secondary reference standards that are representative of the pivotal clinical study materials. The qualification protocol will be submitted as a PAS, and the final qualification report will be submitted to the BLA.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3194-12

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study Completion:	N/A
	Final Report Submission:	05/31/2019
	Other:	N/A

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

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

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

The results from the extractables and leachables studies that have been performed and the clinical studies indicate that the presence of leachates from the ocrelizumab commercial container closure system does not appear to be a significant safety or product quality issue. However, a comprehensive real-time leachable study through the end of drug product expiry period was not performed.

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

The leachables study for ocrelizumab is currently incomplete. The real-time study that was performed included evaluation of only the compounds that were identified in extractables studies, rather than all potential leachables, and the study did not include a comprehensive set of test methods, i.e., methods to detect volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals. Each of these types of potential leachables should be assessed to enable a risk evaluation of potential impact to safety and product quality.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3194-13

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

BLA # 761053
Product Name: Ocrevus (ocrelizumab)

PMC Description: Confirm that the updates to the ocrelizumab drug substance manufacturing process and controls lead to the manufacturing of drug substance with critical product quality attributes consistent with those of the drug substance used to manufacture pivotal clinical study drug product.

PMC Schedule Milestones:	Final Protocol Submission:	<u>04/30/2017</u>
	Study Completion:	<u>N/A</u>
	Final Report Submission:	<u>03/30/18</u>
	Other:	<u>N/A</u>

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

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

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

This PMC would be a pre-approval requirement for a standard product; however, given the breakthrough therapy status of this product, consideration was given to the changes to the manufacturing process, materials and process controls, and release specifications that were made during the review cycle. The manufacturing changes should result in a process that generates drug substance of the appropriate quality, and the specification changes ensure that product of appropriate quality (i.e., representative of the pivotal clinical study material) is released to the market.

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

While the materials controls and manufacturing changes should result in a process that generates drug substance of the appropriate quality, the applicant has not demonstrated that these adjustments will result in a manufacturing process that consistently delivers acceptable product. This study will provide some verification that the corrective actions implemented were successful.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

Confirm that the updates to the ocrelizumab drug substance manufacturing process and controls lead to the manufacturing of drug substance with critical product quality attributes consistent with those of the drug substance used to manufacture pivotal clinical study drug product.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

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/s/

SALLY U YASUDA
03/28/2017

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

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

Memorandum

Date: March 16, 2017

To: Billy Dunn, MD, Director
Division of Neurology Products (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, DNP

Jacqueline Ware, PharmD, Chief Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

Subject: **BLA 761053**
OPDP labeling comments for OCREVUS (ocrelizumab) injection, for intravenous use

In response to DNP's consult request dated June 7, 2016, OPDP has reviewed the proposed Package Insert (PI), Medication Guide, and carton and container labeling for Ocrevus.

PI

OPDP's comments are based on the substantially complete version of the draft PI received from DNP (Jacqueline Ware) on March 2, 2017, and are provided below.

Medication Guide

The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the proposed Medication Guide under a separate cover on March 16, 2017.

Carton and Container Labeling

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 31, 2016, and we do not have any comments.

If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments.

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/s/

ALINE M MOUKHTARA
03/16/2017

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

PATIENT LABELING REVIEW

Date: March 16, 2017

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon Mills, BSN, RN, CCRP
Acting Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Aline Moukhtara, RN, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): OCREVUS (ocrelizumab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761053

Applicant: Genentech, Inc.

1 INTRODUCTION

On April 28, 2016, Genetech, Inc. submitted for the Agency's review the second and final part of a rolling submission for an original Biologics License Application (BLA) 761053, for the use of OCREVUS (ocrelizumab) injection as a treatment for patients with relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

On December 16, 2016, the Agency received a major amendment to this application and extended the goal date to March 28, 2017 to provide for a full review of the submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on May 5, 2016, and June 7, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OCREVUS (ocrelizumab) injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft OCREVUS (ocrelizumab) injection MG received on April 28, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 2, 2017.
- Draft OCREVUS (ocrelizumab) injection Prescribing Information (PI) received on April 28, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 2, 2017.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
03/16/2017

ALINE M MOUKHTARA
03/16/2017

SHARON R MILLS
03/16/2017

LASHAWN M GRIFFITHS
03/16/2017

LABEL AND LABELING REVIEW AMENDMENT

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:	February 14, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761053
Product Name and Strength:	Ocrevus (ocrelizumab) Injection 30 mg/mL
Total Product Strength:	300 mg/10 mL
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Roche/Genentech
Submission Date:	April 28, 2016; July 26, 2016
OSE RCM #:	2016-1212
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
OMEPRM Acting Deputy Director:	Lubna Merchant, MS, PharmD

REASON FOR AMENDMENT:

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].

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:	October 18, 2016
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761053
Product Name and Strength:	Ocrevus (ocrelizumab) Injection 30 mg/mL
Total Product Strength:	300 mg/10 mL
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Roche/Genentech
Submission Date:	April 28, 2016; July 26, 2016
OSE RCM #:	2016-1212
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ocrevus (BLA 761053), the Division of Neurology Products (DNP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed container labels, carton labeling, Prescribing Information (PI), and Medication Guide identified the following areas of needed improvement which may contribute to medication errors:

1. Section 2 Dosage and Administration and Section 16 How Supplied/Storage and Handling in the PI uses the prohibited abbreviation 'IV'.
2. Section 2 Dosage and Administration in the PI uses negative statements and lacks clarity in the dosing, preparation and administration of the product.
3. The carton and container labels do not prominently display the route of administration.
4. We note that the PI labeling, carton labeling and container label use the terminology (b)(4) which is inconsistent with the Agency's current thinking. We discussed with the Office of Biotechnology Products (OBP) who agrees that the terminology utilized should be revised to "single-dose vial".

We note that in the PI Section 2.6 Preparation for Administration includes redundant storage information which may cause confusion regarding the stability of the infusion solution. We discussed with the Office of Biotechnology Products (OBP) who agrees that the information should be revised. We defer to the Office of Pharmaceutical Quality (OPQ) to address this issue in their review.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 in order to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

We determined that there are areas within the Prescribing Information, container label, and carton labeling that can be improved upon to reduce the risk of medication errors and increase clarity and prominence of key information. We provide recommendations below in Section 4.1 for the division and Section 4.2 for Roche to address our concerns. We advise these recommendations are implemented prior to approval of BLA 761053.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 2 Dosage and Administration and Section 16 How Supplied/Storage and Handling

- i. We recommend removing all instances of the abbreviation “IV” used in these sections. The abbreviation “IV” can be misinterpreted as other routes of administration and may pose risk for medication error. Revise this abbreviation to reflect the intended meaning (e.g. intravenous) to prevent misinterpretation and confusion.

2. Section 2 Dosage and Administration, 2.1 Administration

- i. We recommend deleting the sentence (b)(4)
[REDACTED] This statement could be
misinterpreted (b)(4)
[REDACTED]^a We recommend this revision (b)(4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]^b

^a Institute for Safe Medication Practices. (b)(4)
[REDACTED]. ISMP Med Saf Alert Acute Care. (b)(4)

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize

3. Section 2 Dosage and Administration, 2.2 Recommended Dose

- i. We recommend revising the presentation of the initial dose of Ocrevus to improve clarity. The initial dose is (b) (4) divided into two separate infusions of 300 mg given two weeks apart. We are concerned (b) (4) Therefore, the dose should be displayed as dose per day (b) (4) to avoid confusion.^c We recommend that the statement (b) (4) is revised (b) (4)
 - ii. The header in Table 1 states (b) (4) " and (b) (4) may lead to dosing error". Revise the header to read (b) (4)
- ### 4. Section 3 Dosage Forms and Strengths
- i. Revise the phrase (b) (4) to "single dose vial"^d. We recommend this revision to accurately reflect the package type.

4.2 RECOMMENDATIONS FOR ROCHE

We recommend the following be implemented prior to approval of BLA 761053:

A. Carton Labeling and Container Labels

Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^dGuidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

1. Update the labeling to include the conditionally acceptable proprietary name, Ocrevus.
2. The route of administration is not adequately prominent on the principal display panel (PDP) and may lead to wrong route errors. Consider revising the display of the statement “For Intravenous Infusion (b) (4)” to increase the prominence of the route of administration (e.g., increased font size).
3. Revise the phrase (b) (4) to “Single Dose Vial”^e. We recommend this revision to accurately reflect the package type.

^e Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Ocrevus that Roche submitted on April 28, 2016.

Table 2. Relevant Product Information for Ocrevus	
Initial Approval Date	N/A
Active Ingredient	ocrelizumab
Indication	(b) (4)
Route of Administration	Intravenous infusion
Dosage Form	Injection, solution
Strength	300 mg/10 mL (30 mg/mL)
Dose and Frequency	(b) (4)
How Supplied	(b)(4) glass vial
Storage	(b) (4) Do not freeze or shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 8, 2016, we searched the L:drive and AIMS using the terms, Ocrevus and ocrelizumab, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews that are relevant to the current review.

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/s/

EBONY A WHALEY
02/14/2017

LOLITA G WHITE
02/14/2017

LUBNA A MERCHANT
02/14/2017

**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 761053

Application Type: New BLA

Drug Name(s)/Dosage Form(s): OCREVUS (ocrelizumab) injectable solution

Applicant: Genentech

Receipt Date: 04/28/2016

Goal Date: PDUFA 03/28/17

1. Regulatory History and Applicant's Main Proposals

NEW BLA OCREVUS (OCRELIZUMAB) PRIORITY REVIEW DESIGNATION

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

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

Selected Requirements of Prescribing Information

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.

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: *The horizontal line can be extended longer to cover the width of the page*

- 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: *The horizontal line does not extend over the bullets*

- 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:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *The Adverse Reactions section does not reference the section for RMS and PPMS indications*

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

Heading	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

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

* RMC only applies to 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

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

Comment:

- N/A** 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

Selected Requirements of Prescribing Information

“**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:

- N/A** 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:

- N/A** 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:

Selected Requirements of Prescribing Information

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 (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:
- N/A** 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:
- NO** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: In TOC, 14.1 Primary Progressive Multiple Sclerosis (PPMS) should be numbered 14.2
- 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:

- NO** 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: *Does this need to be edited?*

Selected Requirements of Prescribing Information

2.5 Dose Modifications

In the case of IRRs during any infusion, see the following dose modifications. Additional information on IRRs can be found in Warnings and Precautions (5.1).

For Section 5.1 Missing Bracket at the end (94):

For premedication to reduce frequency and severity of IRRs [see Dosage and Administration (2.3).

- 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

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 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

- NO** 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: *It has "clinical practice" instead of practice.(167)*

Selected Requirements of Prescribing Information

Because clinical trials are conducted under widely varying conditions, adverse reactions 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 clinical practice.

- 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:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 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:

- YES** 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/

REBECCA N LOPEZ
02/07/2017

Clinical Inspection Summary - Addendum

Date	12/8/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Nahleen Lopez, Pharm.D., Regulatory Project Manager DNP Lawrence Rodichok, M.D., Medical Officer DNP
BLA #	761053
Applicant	Genentech, Inc.
Drug	ocrelizumab
NME	Yes
Therapeutic Classification	Monoclonal antibody
Proposed Indication(s)	Treatment of relapsing forms of multiple sclerosis and primary progressive multiple sclerosis
Consultation Request Date	6/8/2016
Summary Goal Date	10/21/2016
Action Goal Date	12/1/2016
PDUFA Date	12/28/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This Clinical Inspection Summary (CIS) Addendum provides a summary of the inspection of the contract research organization (CRO), (b) (4). This CRO inspection was completed after the initial CIS was finalized. The overall assessment of findings and recommendations has not changed.

For BLA 761053, the sponsor (Genentech Inc.), CRO (b) (4), and five clinical investigator sites were inspected.

During the sponsor inspection, the termination of Site (b) (4), due to GCP issues was discussed with the field investigator. The sponsor had previously informed the review division of this site termination. The sponsor stated that they performed efficacy analyses excluding this site and confirmed that these analyses did not change the statistical interpretation of the study.

Regulatory violations were identified for (b) (4) the CRO responsible for clinical and medical monitoring of Protocol (b) (4). Regulatory violations included failure to ensure proper monitoring of a clinical investigation. Based on these findings, we recommend that the review division conduct sensitivity analyses excluding Sites (b) (4) and #233958 (Huang in Ohio, US). (b) (4) monitors responsible for monitoring in 2012-2013 did not identify all six of the subjects enrolled into study (b) (4) at Site (b) (4).

in (b)(4), not meeting all eligibility criteria until a remonitoring visit (b)(4). The same (b)(4) monitors were responsible for one other site in (b)(4) and four sites in Croatia. The review division should consider asking the sponsor if additional remonitoring or audits were conducted by the sponsor and/or CRO for these 6 sites in (b)(4) and Croatia regarding assessment of eligibility criteria adherence, protocol violations and any newly identified adverse events. If additional remonitoring/reaudits were performed at all 6 sites in (b)(4) and Croatia, the sponsor should provide a summary of findings including subject records audited/remonitored, and aspects of study conduct (such as assessment of eligibility criteria adherence, protocol violations, safety, etc.) looked at during the audits/remonitoring visits.

The clinical investigator inspections revealed regulatory violations for three of the clinical investigator sites (Huang, Selmaj, and De Seze). Regulatory violations included failure to adhere to the protocol exemplified by study drug administration errors, potential unblinding of investigators, and failure to review laboratory results prior to study drug administration. At one site (Huang), an investigator performing assessments for secondary and exploratory endpoints (MCFCS, LCVA, and SDMT) had access to unblinded study data through data entry of concomitant medications, adverse events, and vital signs as well as conducting follow-up telephone calls to subjects. Because of this access to unblinded study data, there is a potential that investigators performing other assessments, including primary efficacy assessments such as the EDSS, could have been unblinded. The delegation of both blinded and unblinded tasks to one individual appears to have been an oversight and was not noted to have occurred at the clinical investigator sites that were inspected. The potential unblinding of study drug assignment could impact the validity and reliability of the submitted data from this site to determine the primary safety and efficacy analyses. Therefore, we recommend that the review division perform sensitivity analyses for data from this site.

Additionally, at one site (Selmaj) EDSS assessments (primary efficacy endpoint) for Protocol WA25046 were not entered into the computer tablet at the time the assessments were completed, as specified in the protocol, for thirteen of nineteen randomized subjects. For these EDSS data entries, there are no source documents available to verify data integrity. Due to issues regarding data integrity for Protocol WA25046, we recommend that the review division perform sensitivity analyses excluding this site.

A Form FDA 483 was issued for one clinical investigator site (Selmaj); this inspection has been preliminarily classified as Official Action Indicated (OAI). Establishment Inspection Reports (EIRs) have been received and reviewed for three other clinical investigator inspections, the sponsor inspection, and the CRO inspection. Two clinical investigator inspections (Huang, De Seze) have been classified as Voluntary Action Indicated (VAI), one clinical investigator inspection (Zbrojkiewicz) has been classified as No Action Indicated (NAI), the sponsor inspection has been classified as NAI, and the CRO inspection has been classified as VAI. The other clinical investigator inspection has been preliminarily classified as NAI.

We would recommend that the review division ask the sponsor the following questions. Answers to these questions may help in the overall interpretation of study findings for WA21093.

1. The FDA inspection of (b) (4) conducted on (b) (4) noted that (b) (4) CRAs failed to identify 6 of 6 subjects enrolled at Site (b) (4) for Study (b) (4) who did not meet eligibility criteria. This was discovered during a (b) (4) for-cause monitoring visit of this site conducted in (b) (4). These CRAs were also responsible for the monitoring of one other site in (b) (4) as well as four sites in Croatia. Based on this information, were any measures taken (e.g. additional remonitoring/audits) to determine whether subjects at these other sites in (b) (4) and Croatia met eligibility criteria for Study WA21093? If additional remonitoring/reaudits were performed at all 6 sites in (b) (4) and Croatia, the sponsor should provide a summary of findings including subject records audited/remonitored, and aspects of study conduct (such as assessment of eligibility criteria adherence, protocol violations, safety, etc.) looked at during the audits/remonitoring visits.
2. The FDA inspection of Site #208392 (Selmaj/Poland) conducted 9/12 – 9/23/2016, noted issues with data entry (b) (4). Specifically, for 13 of 19 subjects enrolled in Study WA25046, data was entered (b) (4) during or after the infusion of study drug with no source documents available to verify data entry. FDA was unable to determine if similar issues occurred at this site for Study WA21093, however, this site was not listed among the 37 sites entering data (b) (4) from paper documents. Based on this information, were any measures taken to verify that source documents existed for all data entered (b) (4) at a later time?

II. BACKGROUND

See Clinical Inspection Summary in DARRTS (10/21/2016).

III. RESULTS:

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Site #233958 Deren Huang, M.D., Ph.D. Neurology and Neuroscience Assoc., 701 White Pond Drive, Suite 300 Akron, OH 44320	WA21093 Subjects: 17	7/26/2016 to 8/4/2016	Voluntary Action Indicated (VAI)
Site #242600 Angelica Carbajal Ramirez, M.D. Mexico Centre for Clinical Research, Amores 709 Col. Del Valle Mexico DF 3100 Mexico	WA21093 Subjects: 8	9/19/2016 to 9/23/2016	No Action Indicated (NAI)*
Sites #252185, #208392 Krzysztof Selmaj, M.D. Centrum Neurologii Krzysztof Selmaj Ul. Tylna 12 LODZ 90-324 Poland	WA21093 Subjects: 70 WA25046 Subjects: 19	9/12/2016 to 9/23/2016	Official Action Indicated (OAI) Pending
Site #208241 Jerome De Seze, M.D. Hôpital de Hautepierre Avenue Molière Service de Pédiatrie 2 Cedex 67098 Strasbourg France	WA25046 Subjects: 17	9/5/2016 to 9/9/2016	Voluntary Action Indicated (VAI)
Site #208664 Janusz Zbrojkiewicz, M.D. Neuro-Medic Medykow 22 40-752 Katowice, Poland	WA25046 Subjects: 7	9/26/2016 to 9/28/2016	No Action Indicated (NAI)
Genentech, Inc. 1 DNA Way South San Francisco, CA 94080- 4990	WA21093 WA25046	9/12/2016 to 9/16/2016	No Action Indicated (NAI)
(b) (4)	(b) (4)	(b) (4)	Voluntary Action Indicated (VAI)

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be 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.

1. **Clinical Investigator:** Jerome De Seze, M.D.; France; Site #208241

See Clinical Inspection Summary in DARRTS (10/21/2016). Based on the inspectional findings of study drug dispensing and administration errors in two of seventeen subjects enrolled at this site, the inspection classification was upgraded from NAI to VAI.

2. **CRO:** [REDACTED] (b) (4)

This CRO was contracted by the sponsor to provide clinical and medical monitoring for Protocol [REDACTED] (b) (4). This particular [REDACTED] (b) (4) site, [REDACTED] (b) (4) is the location of global trial documents. The majority of the individual clinical site specific records were not stored at this site. Field investigators could request specific records if needed during the inspection.

Documentation was reviewed during this inspection for organization and personnel including, but not limited to, review of written agreements with the sponsor; qualifications, experience, and training of monitors; monitoring procedures; and SOPs. Monitoring reports for nine sites [REDACTED] (b) (4) and 232242/[REDACTED] (b) (4) [REDACTED] 208873 and 252185/Poland; 233958/U.S.; 209805, 209809, 209776, and 209810/Croatia) were reviewed. Clinical investigator inspections had been conducted for three of these sites (208873/252185, Dr. Selmaj; 233958, Dr. Huang).

Monitoring deficiencies were observed during the inspection and the firm was issued a Form FDA 483:

Failure to ensure proper monitoring of a clinical investigation. Specifically,

1. The sponsor had informed the review division about serious GCP issues (including pregnancy) occurring at Site [REDACTED] (b) (4) which led to the sponsor terminating this site (see Clinical Inspection Summary 10/21/2016). While performing a for-cause monitoring visit at this site in [REDACTED] (b) (4), [REDACTED] (b) (4) noted that all six of the subjects enrolled into the study did not meet eligibility criteria. The monitoring reports from 2012 and 2013 had indicated that all subjects had met eligibility criteria. The CRAs responsible for monitoring this site in 2012 and 2013 also monitored one other site in [REDACTED] (b) (4) and four sites in Croatia. The field investigators asked whether these other sites had additional monitoring visits to determine whether there were any issues with subjects not meeting eligibility criteria but the field investigators did not receive adequate answers. The subjects from Site [REDACTED] (b) (4)

(b)(4)

2. For Site 233958 (Dr. Huang), one of the two approved blinded examining designees had access to unblinded source data while performing some blinded assessments (see Clinical Inspection Summary 10/21/2016). (b)(4) conducted monitoring visits in 2012 and 2013, at the time this person was conducting blinded assessments while having access to unblinded data, and this issue was not identified. (b)(4) conducted a monitoring visit in April 2014 at which time this issue was identified.

The field investigators asked whether monitors verified the source and the time EDSS scores were documented (b)(4) (see Clinical Inspection Summary 10/21/2016). The CRO provided a list of 37 sites that used manual or paper based documentation of the EDSS scores but did not provide information regarding verification of source documents or the time EDSS scores were documented.

Due to (b)(4) monitoring deficiencies identified for Protocol (b)(4) and consistent with prior advice (see Clinical Inspection Summary 10/21/2016), we recommend that the review division perform additional sensitivity analyses excluding sites (b)(4) and 233958 (U.S./Huang).

CC:

Central Document Room/BLA #761053
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DNP/Medical Officer/Lawrence Rodichok
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/s/

CARA L ALFARO
12/08/2016

SUSAN D THOMPSON
12/08/2016

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo for Ocrelizumab
Template Version: 2016-02-11**

Date:	November 15, 2016 (revision)
Reviewer(s):	Elisa R. Braver, PhD Division of Epidemiology I
Team Leader:	Lockwood Taylor, PhD, MPH Division of Epidemiology I
Acting Deputy Director:	Simone Pinheiro, ScD, MSc Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Ocrelizumab (Ocrevus)
Drug Name(s):	Ocrelizumab
Application Type/Number:	BLA 761053
Applicant/sponsor:	Genentech (working with F. Hoffmann-La Roche)
OSE RCM #:	2016-1310

EXECUTIVE SUMMARY (place "X" in appropriate boxes)

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Ocrelizumab (OCR) is a new therapeutic biologic product (new molecular entity) that has been submitted for FDA priority approval. OCR is a recombinant, humanized monoclonal antibody that targets CD20-expressing B-cells (B lymphocytes). The drug aims to modulate the immune system by reducing the number and function of B-cells, which are involved in the pathophysiology of multiple sclerosis. OCR is intended to treat relapsing-remitting multiple sclerosis (RMS) and primary progressive MS (PPMS). In RMS, patients experience relapses where their symptoms worsen and the disease subsequently goes into remission. In PPMS, the disease keeps worsening and patients do not have remissions.

The goal of treatment with OCR is to reduce the likelihood of either disease progression or disease relapses. If the drug is approved, patients will receive intravenous infusions every 24 weeks for as long as health care providers deem the treatment to be appropriate. Currently, there are no treatments for PPMS, so, if approved, OCR likely will be a first-line therapy. OCR also is likely to be first-line therapy for RMS if approved. The PDUFA action date is in December 2016.

1.2. Describe the Safety Concern

A malignancy signal for OCR appeared during clinical trials to treat MS. Higher numbers of all malignancies, and all breast cancers specifically, were observed among OCR-treated patients than either placebo controls or interferon-treated participants in MS trials; however, it is unclear whether this happened by chance or reflects carcinogenic effects from OCR.

A total of 19 OCR-treated MS patients developed malignancies during the randomized clinical trials in the development program, including 4 with non-melanoma skin cancers and 15 with other cancers, compared with 4 MS patients in the placebo group or interferon-beta-1a comparator arms of the clinical trials. The only cluster that could be identified was 6 breast cancer cases in the OCR treatment arm compared with zero among comparison MS patients in trials. An additional 3 breast cancer cases were diagnosed among patients treated with OCR during the open-label extension period of the trials.

Breast cancer

One clinical trial conducted for PPMS included 486 OCR-treated patients and 239 placebo controls. Two clinical trials (pooled) were conducted for RMS and included 825 OCR-treated patients and 826 patients treated with interferon beta-1a. The RMS trials lasted for 96 weeks, while the PPMS trials lasted for 120 weeks. All three clinical trials had extension periods of open-label follow-up.

- Of the 9 breast cancer cases among OCR-treated patients, 2 occurred among women younger than age 45, 3 occurred among women ages 45-49, and 4 occurred among women age 50 or older. Three of the 9 breast cancer cases were diagnosed after the end of the clinical trials. A 44-year-old patient was in the interferon comparator group, but switched to OCR during the open-label extension of the clinical trials prior to diagnosis of her breast cancer.

- The two youngest breast cancer cases were a 29-year-old patient with invasive ductal breast carcinoma diagnosed at Stage I and a 44-year-old patient with breast cancer with no stage reported.
- Based on 2 breast cancer cases, the breast cancer incidence rate among female patients younger than age 45 was 9 per 10,000 woman-years (95% CI: 1.1-32.4). Based on 6 breast cancer cases, the breast cancer incidence rate for female patients ages 45 or older was 49.8 per 10,000 woman-years (95% CI: 18.3-108.4). One breast cancer case is still being reviewed and is not included in the incidence rates.
- Of the 9 breast cancer cases, 1 was diagnosed at Stage IV (invasive ductal breast cancer); 2 were diagnosed at Stage III (breast cancer) or IIIA (invasive ductal breast carcinoma); 4 were diagnosed at Stage I or Stage IA (breast cancer or invasive ductal breast carcinoma); and 2 were missing information on stage.
 - If OCR primarily is a tumor promoter, then we cannot exclude the possibility that OCR acted on initiated pre-malignant cells and contributed to completing their transformation to malignancies. OCR also might have accelerated the growth of existing tumors, including those diagnosed at Stages III and IV.
- In terms of cumulative dosage and occurrence of breast cancer, the following was reported by the sponsor (note: data are not yet available for the 9th case of breast cancer).
 - 1 breast cancer (age <45) after receiving 1st 600 mg dose of OCR
 - 2 breast cancers (ages 45+) after 3rd dose
 - 1 breast cancer (age 45+) after 5th dose
 - 2 breast cancers (ages 45+) after 6th dose
 - 1 breast cancer (age <45) after 7th dose
 - 1 breast cancer (age 45+) after 8th dose
- The sponsor did not present time to breast cancer diagnosis from initial exposure to OCR. Because there were drop-outs from the clinical trial but follow-up continued after stopping the drug, the cumulative dosage can provide only the minimum amount of the time between initial exposure and breast cancer diagnosis. Based solely upon cumulative dosage, the breast cancer diagnosis times were as follows.
 - 2 weeks or longer (1st dose) (one case),
 - 48 weeks or longer (3rd dose) (two cases),
 - 96 weeks or longer (5th dose) (one case),
 - 120 weeks or longer (6th dose) (two cases),
 - 144 weeks or longer (7th dose) (one case),
 - 168 weeks or longer (8th dose) (one case).

All cancers

- Among OCR-treated patients, malignancy events (one event counted per person) included 9 breast cancers, 2 melanomas, 1 endometrial cancer, 1 anaplastic large-cell lymphoma, 6 basal

cell skin cancers, 2 squamous cell skin cancers, 1 renal cancer, 1 malignant fibrous histiocytoma, 1 pancreatic cancer, 1 papillary thyroid cancer, 1 esophageal adenocarcinoma, and 1 colon adenocarcinoma.

- Of all malignancies excluding non-melanoma skin cancers (NMSC) among OCR-treated patients, 3 occurred in patients younger than age 45. The corresponding cancer incidence rate among patients younger than age 45 was 800 per 10,000 person-years (95% CI: 160-2,330). A total of 15 cancers (excluding NMSC) occurred among patients age 45 or older, and the corresponding cancer incidence rate was 7,800 per 10,000 person-years (95% CI: 4,360-12,850).

Both FDA and the sponsor have recognized that the potential malignancy risk is a safety concern. We do not know if OCR is an initiator, promoter, neither, or both. Neither carcinogenicity nor mutagenicity tests were submitted with the original drug application. The sponsor has pointed out that antibodies normally do not interact with the DNA inside cells. One possibility is that the mechanism of action might be related to alteration of the immune response.

Dr. Bindu Kanapuru, Medical Officer with the Division of Hematology Products, reviewed the data at the request of the Division of Neurology Products (DNP) and recommended post-marketing evaluation as “necessary to make a definitive conclusion about ocrelizumab and malignancy risk in patients with MS” and also stated that the imbalance in breast cancer diagnoses should be included in the proposed labeling for OCR.

Dr. Gwynn Ison, Medical Officer with the Division of Oncology Products, also received a consult request and pointed out that requiring malignancy warnings would be consistent with the agency’s previous actions for drugs with a malignancy signal, including olaparib (Lynparza)^a and alemtuzumab (Lemtrada).^b She also stated that the sponsor should collect the following information on malignancies among OCR-treated patients in the future:

“Specific guidance should be given to the Sponsor on the information collected going forward, but should include, at a minimum, the pathological cancer diagnosis, stage at diagnosis, time on therapy with ocrelizumab at the time of cancer diagnosis, and action taken with ocrelizumab therapy at that point (continue vs. discontinue). For breast cancer cases, specifically, details collected should include stage at diagnosis and hormonal status of the tumor (to include ER/PR status and HER2 status).”

Signal Assessment Meeting held on September 29, 2016

Section 2 below, which evaluates the FDA-supported Active Risk and Identification Analysis (ARIA) System, is guided by conclusions reached during a Signal Assessment Meeting held on September 29, 2016 in which the DNP and Division of Epidemiology (DEPI) participated and a follow-up meeting held on November 3, 2016. The group consensus was that both short-term and long term evaluations of OCR-related cancer risk are needed and that ARIA is insufficient to evaluate the long-term risk of OCR-related cancer, primarily due to the relatively short periods of enrollment of patients in the data partners’

^aFDA-approved label for olaparib:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf

^b FDA-approved label for alemtuzumab:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103948s5139lbl.pdf

insurance plans. In particular, DNP has said that physicians and patients need to understand the magnitude of the malignancy risk over time and whether countermeasures may be needed to address malignancy risk. One of the concerns raised during discussions is that the relative risk for malignancy may increase over time with long-term product use. Quantifying adverse effects of OCR on malignancy incidence rates will inform labeling for OCR and will help inform FDA and the sponsor about whether further measures are needed for patient safety. The sponsor included a proposal for a postmarketing requirement (PMR) for epidemiologic research to examine the malignancy signal in its biologic licensing application. The FDA is planning a PMR for malignancy with an adequate length of follow-up and currently is considering inclusion of the potential malignancy risk on the label.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of this memo is to evaluate whether ARIA is sufficient to evaluate the long-term OCR-related malignancy risk, including the risk of breast cancer. A postmarketing assessment of the malignancy safety signal is needed to evaluate the potential OCR-related malignancy risk, inform labeling, and determine whether further regulatory measures are needed to address safety risks of OCR if it is approved to treat MS. The purpose of the assessment is to evaluate and quantify the short-term and long-term potential associations between OCR and the risk of breast cancer and all malignancies combined with and without non-melanoma skin cancers among OCR-treated MS patients. Risk and protective factors for malignancy will be investigated among MS patients treated with OCR compared with other drugs used to treat MS.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The sample size for a proposed PMR still is under discussion. Formal sample size calculations have not yet been performed to determine how many patients and person-years are necessary. One option under consideration is requiring that the study be sufficiently powered to detect a relative risk of 2.0 for breast cancer among women of all ages; however, this will depend on how feasible it will be to enroll a study population of sufficient size.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

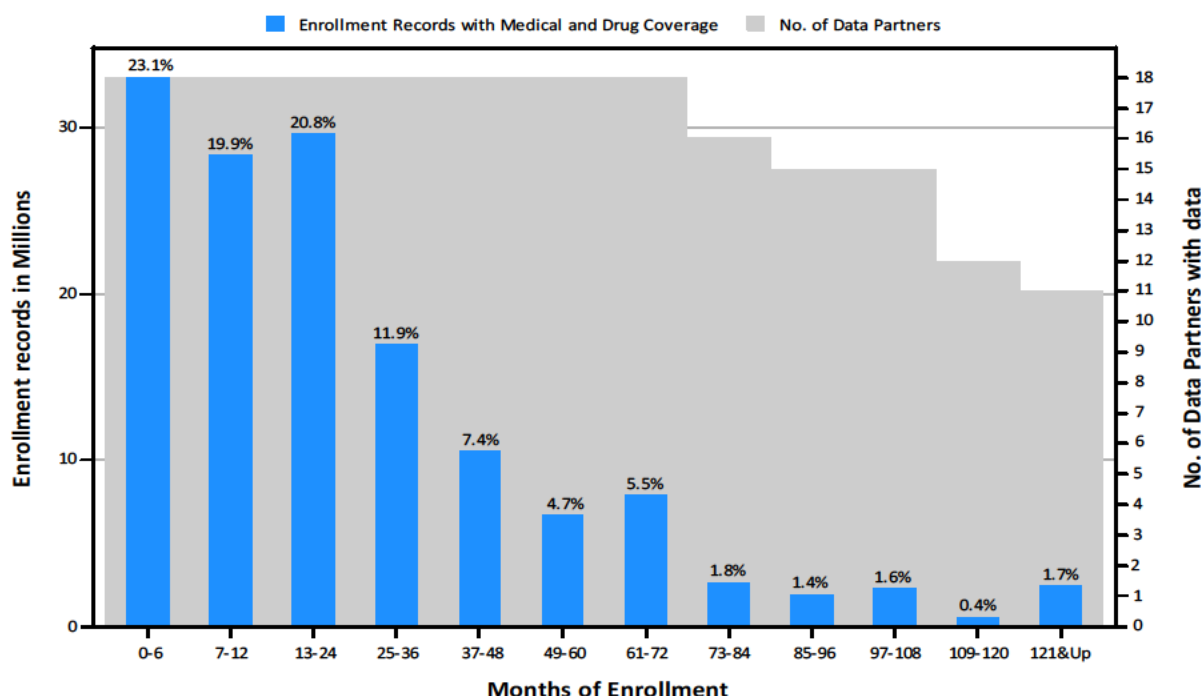
2.1 Population

Adults with relapsing MS or primary progressive MS who are followed continuously for more than three years following initiation of OCR exposure are the study population. DEPI and DNP have discussed the follow-up period, and DNP preferred requiring a minimum of 5 years of patient follow-up, given the timing of the signal observed in the trials (<3 years), despite potentially lengthy latency periods for breast cancer and other malignancies.

2.2 Is ARIA sufficient to assess the intended population?

No. The primary reason for the insufficiency determination is that a cohort of new OCR users could be constructed, but an insufficient proportion of them could be continuously followed to ascertain incidence of malignancies for longer than three years within the database of an individual data partner. The figure below indicates the distribution of lengths of enrollment among all patients insured by Sentinel data partners. Only 36% of the population is enrolled for longer than 2 years, which makes long-term studies of patients infeasible. If OCR is a tumor promoter, then an increased cancer risk could possibly be detected during the time span of a typical clinical trial for MS, but some promoters of solid tumors take longer than a few years to develop. If OCR is a tumor initiator, malignancies would likely take significantly longer to develop, based on experience with other carcinogens.^c

Figure 3: Number of Enrollment Records by Length of Enrollment and Number of Contributing Data Partners
(Total number of records = 142,841,279)



3 EXPOSURES

^c James V. Lacey, Graham A. Colditz, and David Schottenfeld. Exogenous Hormones. *Cancer Epidemiology and Prevention*. Third edition. 2006 and 2009. <http://dx.doi.org/10.1093/acprof:oso/9780195149616.003.0024>; Laurel A. Habel and Gary D. Friedman. Pharmaceuticals Other Than Hormones. *Cancer Epidemiology and Prevention*. Third edition. 2006 and 2009. <http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195149616.001.0001/acprof-9780195149616-chapter-25>; Herbst AL, Cole P, Colton T, Robboy SJ, Scully RE. Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. *Am J Obstet Gynecol*. 1977 May 1;128(1):43-50; Triebig G. Implications of latency period between benzene exposure and development of leukemia—a synopsis of literature. *Chem Biol Interact*. 2010 Mar 19;184(1-2):26-9; Clin B; "RecoCancerProf" Working Group, Pairon JC. Medical follow-up for workers exposed to bladder carcinogens: the French evidence-based and pragmatic statement. *BMC Public Health*. 2014 Nov 6;14:1155. doi: 10.1186/1471-2458-14-1155.

3.1 Treatment Exposure(s)

Intravenous infusion of OCR in an outpatient clinic; dosing once every 24 weeks (initial doses are split and administered two weeks apart); 600 mg per dose.

3.2 Comparator Exposure(s)

MS comparator drugs are to be determined. They may be self-administered orally or by subcutaneous injection or other methods.

3.3 Is ARIA sufficient to identify the exposure of interest?

Possibly. ARIA will be sufficient to identify OCR administered as an intravenous infusion in clinical settings. However, identifying the comparator exposures may be more challenging if they are self-administered, such as subcutaneous injections or oral administration. Prescription data would be available, but whether patients took the prescribed comparator medications would not be known.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes for the malignancy safety signal are all malignancies combined, breast cancer, and all malignancies combined excluding non-melanoma skin cancers.

4.2 Is ARIA sufficient to assess the outcome of interest?

No. The outcome of interest precludes use of ARIA to assess the intended population due primarily to two reasons including unavailability of long-term follow-up for a large proportion of participants and lack of histological information on code-only based algorithms.

Malignancies can take many years to develop following exposure to a carcinogen although they can develop sooner if the carcinogen is a promoter. During the SAM, it was decided that the average follow-up in Sentinel would be insufficient to evaluate the long-term OCR-related cancer risk. This was discussed in greater detail under “study population.”

Another important concern is that code-only based algorithms do not provide adequate histological information. Analyzing characteristics of individual malignancies is important for understanding the malignancy signal observed in clinical trials. For example, breast cancer can arise in multiple locations in the breast (ducts, lobes, other tissues, inflammatory) and can be non-invasive, invasive, recurrent, or metastatic. Breast cancers are classified by grade (well-differentiated, moderately differentiated, and poorly differentiated) and by other characteristics relevant to treatment (estrogen receptors, progesterone receptors, presence of a growth promoting protein known as called HER2/neu). The insurance claims codes of the ARIA data partners do not indicate tumor stage, grade, and other characteristics that would be helpful in understanding the potential effects of OCR treatment on the risk of breast cancer. This is a concern although previous studies not conducted within Sentinel data partners suggest that the positive predictive values (PPV) for breast cancer are likely to be acceptable in electronic healthcare databases: 71-85% (Sensitivity=46-87%)^d or 83-93% (Sensitivity=80-87%).^e

^d Setoguchi S et al. (2007) Agreement of diagnosis and its date for hematologic malignancies and solid tumors between

An additional consideration is that the modulation of the immune system may give rise to cancers in multiple body regions. As a result, all malignancies might need to be validated to better understand the effects of OCR because the PPVs for them are unknown or have been shown to be less than optimal in non-Sentinel databases. These include common malignancies such as lung cancer (PPV=45-76%; Sensitivity=56-87%)^d and colorectal cancer (PPV=45-71%; Sensitivity=67-88%).^e

5 COVARIATES

5.1 Covariates of Interest

Patient characteristics, including duration of disease, disease severity, prior MS treatments, and demographic data, will need to be examined. In addition, risk factors for breast cancer and all malignancies should be collected. Possible covariates could include body mass index, alcohol use, smoking, family history of breast cancer, hormone treatment following menopause, and reproductive history. These covariates are important to analyze because if risk factors for malignancy were more common among OCR-treated MS patients than among MS patients treated with other drugs, the risk factors could result in an increased risk of malignancy that was unrelated to the drug.

5.2 Is ARIA sufficient to assess the covariates of interest?

No. Insurance claims data and electronic medical records generally do not contain enough information on disease severity and prior treatment, nor do they necessarily have information on risk factors for malignancy. Smoking, alcohol use, body mass index, family history of breast cancer, prior hormone treatment following menopause during a time period before the lookback period for the study, and reproductive history are captured inconsistently by clinicians within the same data partner and across data partners.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Propensity scores or other pharmacoepidemiologic methods may be needed to account for the different likelihoods of being prescribed OCR versus comparator MS drugs.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. The statistical methods and study design would be sufficient.

7 NEXT STEPS

ARIA is insufficient to evaluate the safety of OCR in the post-marketing setting as a result of concerns about its adequacy in assessing the study population, outcomes, and confounding factors. PMR language still is being developed. Currently, DNP and DEPI are considering a requirement that could include the following language (subject to change).

Medicare claims and cancer registry data. *Cancer Causes and Control*; 18:561-569.

^e Nattinger AB, Laud PW, Bajorunaite R, et al: An algorithm for the use of Medicare claims data to identify women with incident breast cancer. *Health Serv Res* 39:1733-1749, 2004.

Perform a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to Ocrevus, with the primary objective of evaluating the short-term and long-term risks for breast cancer and all malignancies (including and excluding non-melanoma skin cancers). The sponsor should identify and justify two appropriate comparator populations with multiple sclerosis with which observed incidence rates among Ocrevus-treated patients will be compared. The Sponsor will propose an adequate number of multiple sclerosis patients treated with Ocrevus to be enrolled and followed for a minimum of 5 years for evaluating the risks of breast cancer and all malignancies (b) (4)

The study protocol must demonstrate the ability to follow patients continuously for a long period and have data on prescriptions, health outcomes, and risk factors for malignancy. Information on characteristics of the malignancy such as tumor grade, stage, malignancy type, and hormonal status of breast tumors must be collected. In their protocol, the Sponsor must propose an interim analysis to evaluate short-term malignancy risks prior to completion of the full follow-up period for all enrolled participants. The Sponsor also must propose a detailed plan for patient retention following enrollment to minimize loss to follow-up.

Discussions with DNP have resulted in decisions on specific requirements for the PMR, including the duration of follow-up and other requirements. DEPI is considering a parallel capability development project in which the incidence rates of malignancies among new users of OCR with multiple sclerosis would be compared with those of new users of other drugs for multiple sclerosis through using data from Sentinel data partners. The purpose of the capability development project would be to better understand the circumstances in which Sentinel data might contribute to evaluating short-term risks of malignancy when malignancy signals are observed during clinical trials. If this project goes forward, medical chart reviews will be planned.

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/s/

ELISA R BRAVER

11/16/2016

Approved by Michael Nguyen and Bob Ball

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11/16/2016

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Center for Drug Evaluation and Research
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Division of Pediatric and Maternal Health Memorandum

Date: November 10, 2016 **Date consulted:** September 23, 2016

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

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

To: Division of Neurology Products (DNP)

Drug: Ocrelizumab

BLA: 761053

Applicant: Genentech

Subject: Postmarketing Requirement (PMR) Language

Indication(s) Treatment for relapsing forms of multiple sclerosis and primary
progressive multiple sclerosis

Materials Reviewed:

- BLA 781053
 - Cover Letter, April 4, 2016
 - Draft Labeling, July 26, 2016
 - Ocrelizumab Pregnancy Surveillance Study Synopsis

Consult Question: “We note that the Sponsor proposes

(b) (4)

Please comment on whether you recommend a traditional registry or an alternative. If you recommend an alternative, please recommend language for a PMR.”

PURPOSE

DNP is requesting that DPMH review the sponsor’s proposed ocrelizumab pregnancy study to fulfill the postmarketing requirement (PMR) and to recommend appropriate PMR language.

DNP currently has the following PMR language:

Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed through at least the first year of life.

The sponsor seeks to conduct an observational study based on healthcare claims databases/population registries. It is not designed as a prospective pregnancy exposure registry study. DPMH

(b) (4)

recommends that a prospective pregnancy exposure registry be conducted concomitantly. The two study designs would complement each other in a manner that ameliorates some of the disadvantages to each while maximizing the yield of information for ocrelizumab use during pregnancy.

BACKGROUND

Drug Characteristics

Ocrelizumab is a recombinant, humanized monoclonal antibody that selectively targets CD20-expressing B cells. Ocrelizumab binds to CD20 with high affinity and selectively depletes CD20-expressing B cells, while preserving the capacity for B-cell reconstitution and preexisting humoral immunity. Selective B-cell depletion is achieved via several mechanisms including antibody-dependent cellular phagocytosis (ADCP), antibodydependent cell-mediate cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.

Terminal half-life = 26 days

Regulatory History

Breakthrough Therapy Designation was granted to ocrelizumab for the treatment of primary progressive multiple sclerosis (PPMS) on February 1, 2016.

Nonclinical Studies

Animal reproduction studies have not demonstrated adverse developmental effects, aside from the depletion of B-cells in fetuses of treated pregnant cynomolgus monkeys.

PROPOSED PMR STUDY SYNOPSIS

(b)(4)



Reviewer Comment:

The proposed study should only be considered acceptable to complement a well-designed prospective pregnancy exposure registry, and should aim to capture as many reports of pregnancy exposure to ocrelizumab as possible, both prospectively and retrospectively.

DISCUSSION

A well-designed, prospective pregnancy exposure registry remains the Agency's preferred method for post-marketing data collection in pregnant women due to the prospective method of data collection, which minimizes the biases of retrospective data collection.¹ In addition, pregnancy registries allow collection of patient level detailed data on potential confounders. However pregnancy registries are limited by their lack of power to assess specific (rare) birth defects and the long duration that may be needed to accumulate data.

Claims-database observational studies have the ability to detect specific birth defects, but are limited by assumed exposure via pharmacy dispensing, inconsistent data variables between sources, confounding by unmeasured factors, and lack of adequate information on spontaneous and elective abortions.

As the sponsor is aware, the concept of complementary study designs to meet the challenges related to pregnancy registries arose in discussions at the recent workshop on pregnancy registries. In May 2014, DPMH, in collaboration with the Office of Surveillance and Epidemiology and the Office of Women's Health, convened the public workshop on pregnancy registry studies entitled, "Study Approaches and Methods to Evaluate the Safety of Drugs and Biological Products during Pregnancy in the Post-Approval Setting". Perspectives were sought from an expert panel regarding the challenges in designing and implementing pregnancy registries and other methods of evaluating the post-approval safety profile of drugs and biological products in pregnant women. Key conclusions from the meeting included: 1) the combined use of a pregnancy registry study and a complementary study with a different study design (e.g., retrospective cohort or case-control) that relies on large databases to address the potential low enrollment in a registry, improve data collection and maximize information obtained to assess risks of products used during pregnancy, 2) consideration of modifications to future pregnancy registry studies (e.g., utilizing an internal matched-control comparator group, pre-specifying the outcome of interest), and 3) improving awareness of the availability of pregnancy registry studies amongst healthcare providers and patients.

Based on the key conclusions of the public workshop, DPMH recommends a two study approach (a well-designed, prospective pregnancy exposure registry and a

¹ FDA Guidance for Industry Establishing Pregnancy Exposure Registries, 2005.

complementary study of some form) for collection of safety information during pregnancy.

RECOMMENDATION

DPMH

(b) (4)

recommends that a prospective pregnancy exposure registry be conducted in addition to the proposed study. The two studies maximize the yield of information for ocrelizumab use during pregnancy. Therefore, DPMH recommends the following PMR language:

Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

And

An additional study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to ocrelizumab during pregnancy compared to an unexposed control population.

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/s/

TAMARA N JOHNSON
11/10/2016

LYNNE P YAO
11/10/2016

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

FINAL LABEL AND LABELING REVIEW

Date:	November 2, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products
Through:	Milos Dokmanovic, PhD, Quality Reviewer Division of Biotechnology Review and Research I
Application:	BLA 761053/0
Product:	Ocrevus (ocrelizumab)
Applicant:	Genentech, Inc.
Submission Dates:	April 28; October 31, 2016

Recommendations:

We provided recommendations for the prescribing information to be communicated during labeling negotiations. The container label and carton labeling submitted on October 31, 2016 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 761053/0 Ocrevus (ocrelizumab) on April 4, 2016. The Applicant submitted proposed labeling on April 28, 2016, which is the subject of this review. Table 1 lists the proposed characteristics of Ocrevus (ocrelizumab).

Table 1: Proposed Product Characteristics of Ocrevus (ocrelizumab).

Proprietary Name:	Ocrevus
Proper Name:	ocrelizumab
Indication:	(b)(4)
Dose:	(b)(4)
Route of Administration:	Intravenous infusion
Dosage Form:	Injection
Strength and Container-Closure:	300 mg/10 mg single-dose vial
Storage and Handling:	<p>Store OCREVUS vials at 2°C–8°C (36°F–46°F). Keep the vial in the outer carton to protect from light. Do not freeze or shake.</p> <p>If not used immediately, store up to 24 hours in the refrigerator at 2°C–8°C (36°F–46°F) and 8 hours at room temperature up to 25°C (77°F), which includes infusion time.</p>

Materials Reviewed:

- Prescribing Information
- Container Label
- Carton Labeling

Start of Sponsor Material



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label: *This product has a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.*

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

(2) The name, address, and license number of manufacturer; *conforms.*

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

(4) The expiration date; *conforms.*

(5) The recommended individual dose, for multiple dose containers; *not applicable, single-dose vial.*

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

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label; *conforms.*

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

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose.

Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms. We concur with DMEPA's request to add the conditionally acceptable proprietary name, Ocrevus.*

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

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

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

The Applicant provided a photo of a labeled vial that illustrated adequate area for visual inspection and also confirmed there is no text on the ferrule and caps over seal.

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

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

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

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

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms.*

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

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

- I. 21 CFR 201.50 Statement of identity; *conforms*.
- J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.
- K. 21 CFR 201.55 Statement of dosage; *not applicable as this appears on the carton labeling*.
- L. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

Start of Sponsor Material



(b)(4)

End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

- a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms. We concur with DMEPA's request to add the conditionally acceptable proprietary name, Ocrevus*
- b) The name, addresses, and license number of manufacturer; *conforms.*
- c) The lot number or other lot identification; *conforms.*
- d) The expiration date; *conforms.*
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms.*
- f) The number of containers, if more than one; *not applicable, only one vial per carton.*
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms.*
- h) The recommended storage temperature; *conforms. However we recommended revising to include "refrigerator".*

OBP Request: Revise the storage information to read "Storage: Refrigerate at 2°C to 8°C (36°C to 46°F) in original carton to protect from light. Do Not Freeze. Do Not Shake".

Note: We request this revision for both the container label and carton labeling.

Applicant revised as requested.
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable, single-dose vial.*

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

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

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

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

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

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

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

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

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

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Ocrevus (ocrelizumab) is a monoclonal antibody, therefore, exempt.*

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

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

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

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

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

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*. *However, we recommend revising the package type term.*

OBP Request: Revise the package type term (b)(4) to "Single Dose Vial". See the Agency's current thinking on this topic. (Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf> *Applicant revised as requested.*

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

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

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

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

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

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

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

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

OBP Request: Revise the list of ingredients to alphabetical order per USP General Chapters: <1091> Labeling of Inactive Ingredients and include the amounts in milligrams.

Each mL of solution contains 30 mg ocrelizumab, glacial acetic acid (x mg), polysorbate 20 (x mg), sodium acetate trihydrate (x mg), and trehalose dihydrate (x mg) at pH 5.3
Applicant revised as requested.

Prescribing Information

The section below describes our recommendations for the prescribing information to be communicated during labeling negotiations.

A. Highlights of Prescribing Information

1. Dosage Forms and Strengths

- a. We requested revising the package type term here and throughout the PI. See the Agency's current thinking:
<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm468228.pdf>

Injection: 300 mg/10 mL (30 mg/mL) in a single-dose (b)(4) vial

B. Full Prescribing Information

1. Dosage and Administration

- a. We organized this section to ensure information appeared in the correct subsection (i.e. dosage, preparation, administration). Additionally, we deleted duplicate information.
- b. We revised the diluent to the appropriate name and dosage form.

0.9% Sodium Chloride Injection

2. Dosage Forms and Strengths

- a. We requested revising the package term here and throughout the PI.

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm468228.pdf>

Injection: 300 mg/10 mL (30 mg/mL) clear or slightly opalescent, and colorless to pale brown solution in a single-dose (b)(4) vial.

4. Description

- a. We revised the list of ingredients to include the amounts in mg per mL.
- b. We revised the list of inactive ingredients to alphabetical order per USP General Chapters: <1091> Labeling of Inactive Ingredients.
- c. We deleted the vial size (b)(4) because this information is not helpful for healthcare practitioners and is potentially confusing.

5. How Supplied/Storage and Handling

- a. We revised by deleting duplicate information.
- b. We deleted the vial size (b)(4) because this information is not helpful for healthcare practitioners and is potentially confusing.
- c. We deleted a statement (b)(4)
(b)(4) This is standard practice for healthcare practitioners for all drugs and biologics. Therefore, this statement is not needed in the PI.

C. Medication Guide

1. We revised the manufacturer information
 - a. The licensed manufacturer must appear in the labeling per 21 CFR 610.61(b). You may label a distributor name and address provided the licensed manufacturer appears in the labeling per 21 CFR 610.64.

(b)(4) -Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No. 1048

Conclusions:

The prescribing information, container label, and carton labeling for Ocrevus (ocrelizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 August 1, 2016 to November 30, 2016]. We provided recommendations for the prescribing information to be communicated during labeling negotiations. The container label and carton labeling submitted on October 31, 2016 are acceptable (see below).

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/s/

JIBRIL ABDUS-SAMAD
11/02/2016

MILOS DOKMANOVIC
11/02/2016

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:	November 1, 2016
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761053
Product Name and Strength:	Ocrevus (ocrelizumab) Injection 30 mg/mL
Submission Date:	October 31, 2016
Applicant/Sponsor Name:	Genentech
OSE RCM #:	2016-1212-1
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised carton labeling and container label for Ocrevus (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

2 CONCLUSION

The revised carton labeling and container label for Ocrevus is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Whaley E. Label and Labeling Review for Ocrevus (BLA 761053). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 OCT 18. 9 p. OSE RCM No.: 2016-1212.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 31, 2016

A. Container labels



B. Carton labeling



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/s/

EBONY A WHALEY
11/01/2016

LOLITA G WHITE
11/01/2016

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:	October 18, 2016
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761053
Product Name and Strength:	Ocrevus (ocrelizumab) Injection 30 mg/mL
Total Product Strength:	300 mg/10 mL
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Roche/Genentech
Submission Date:	April 28, 2016; July 26, 2016
OSE RCM #:	2016-1212
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ocrevus (BLA 761053), the Division of Neurology Products (DNP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed container labels, carton labeling, Prescribing Information (PI), and Medication Guide identified the following areas of needed improvement which may contribute to medication errors:

1. Section 2 Dosage and Administration and Section 16 How Supplied/Storage and Handling in the PI uses the prohibited abbreviation 'IV'.
2. Section 2 Dosage and Administration in the PI uses negative statements and lacks clarity in the dosing, preparation and administration of the product.
3. The carton and container labels do not prominently display the route of administration.
4. We note that the PI labeling, carton labeling and container label use the terminology (b)(4) which is inconsistent with the Agency's current thinking. We discussed with the Office of Biotechnology Products (OBP) who agrees that the terminology utilized should be revised to "single-dose vial".

We note that in the PI Section 2.6 Preparation for Administration includes redundant storage information which may cause confusion regarding the stability of the infusion solution. We discussed with the Office of Biotechnology Products (OBP) who agrees that the information should be revised. We defer to the Office of Pharmaceutical Quality (OPQ) to address this issue in their review.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 in order to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

We determined that there are areas within the Prescribing Information, container label, and carton labeling that can be improved upon to reduce the risk of medication errors and increase clarity and prominence of key information. We provide recommendations below in Section 4.1 for the division and Section 4.2 for Roche to address our concerns. We advise these recommendations are implemented prior to approval of BLA 761053.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 2 Dosage and Administration and Section 16 How Supplied/Storage and Handling

- i. We recommend removing all instances of the abbreviation “IV” used in these sections. The abbreviation “IV” can be misinterpreted as other routes of administration and may pose risk for medication error. Revise this abbreviation to reflect the intended meaning (e.g. intravenous) to prevent misinterpretation and confusion.

2. Section 2 Dosage and Administration, 2.1 Administration

- i. We recommend deleting the sentence (b)(4)
[REDACTED] This statement could be
misinterpreted (b)(4)
[REDACTED]^a We recommend this revision (b)(4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]^b

^a Institute for Safe Medication Practices. (b)(4)
[REDACTED]. ISMP Med Saf Alert Acute Care (b)(4)

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize

3. Section 2 Dosage and Administration, 2.2 Recommended Dose

- i. We recommend revising the presentation of the initial dose of Ocrevus to improve clarity. The initial dose (b) (4) divided into two separate infusions of 300 mg given two weeks apart. We are concerned (b) (4). Therefore, the dose should be displayed as dose per day (b) (4) to avoid confusion.^c We recommend that the statement (b) (4) is revised (b) (4).
 - ii. The header in Table 1 states (b) (4) and (b) (4) may lead to dosing error”. Revise the header to read (b) (4) to be reflective of the dose per day and to prevent misinterpretation and wrong dose errors.
4. Section 3 Dosage Forms and Strengths
- i. Revise the phrase (b) (4) to “single dose vial”^d. We recommend this revision to accurately reflect the package type.

4.2 RECOMMENDATIONS FOR ROCHE

We recommend the following be implemented prior to approval of BLA 761053:

A. Carton Labeling and Container Labels

Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^dGuidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

1. Update the labeling to include the conditionally acceptable proprietary name, Ocrevus.
2. The route of administration is not adequately prominent on the principal display panel (PDP) and may lead to wrong route errors. Consider revising the display of the statement “For Intravenous Infusion (b) (4)” to increase the prominence of the route of administration (e.g., increased font size).
3. Revise the phrase (b) (4) to “Single Dose Vial”^e. We recommend this revision to accurately reflect the package type.

^e Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Ocrevus that Roche submitted on April 28, 2016.

Table 2. Relevant Product Information for Ocrevus	
Initial Approval Date	N/A
Active Ingredient	ocrelizumab
Indication	- (b)(4) - (b)(4)
Route of Administration	Intravenous infusion
Dosage Form	Injection, solution
Strength	300 mg/10 mL (30 mg/mL)
Dose and Frequency	- (b)(4) - (b)(4)
How Supplied	(b)(4) vial
Storage	(b) (4) (b)(4) Do not freeze or shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 8, 2016, we searched the L:drive and AIMS using the terms, Ocrevus and ocrelizumab, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews that are relevant to the current review.

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/s/

EBONY A WHALEY
10/18/2016

LOLITA G WHITE
10/18/2016

Clinical Inspection Summary

Date	10/20/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, GCPAB/DCCE/OSI Susan Thompson, M.D., Team Leader, GCPAB/DCCE/OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB/DCCE/OSI
To	Nahleen Lopez, Pharm.D., Regulatory Project Manager DNP Lawrence Rodichok, M.D., Medical Officer DNP
BLA #	761053
Applicant	Genentech, Inc.
Drug	ocrelizumab
NME	Yes
Therapeutic Classification	Monoclonal antibody
Proposed Indication(s)	Treatment of relapsing forms of multiple sclerosis and primary progressive multiple sclerosis
Consultation Request Date	6/8/2016
Summary Goal Date	10/21/2016
Action Goal Date	12/1/2016
PDUFA Date	12/28/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For BLA 761053, the sponsor (Genentech Inc.) and five clinical investigator sites were inspected. The inspection of the contract research organization (CRO), (b) (4) is pending.

The only issue identified during the sponsor inspection was termination of Site (b) (4) participating in Protocol (b) (4) due to GCP issues. The sponsor had informed the review division of this site termination. The sponsor stated that they performed efficacy analyses excluding this site and confirmed that these analyses did not change the statistical interpretation of the study.

The clinical investigator inspections revealed regulatory violations for three of the clinical investigator sites (Huang, Selmaj, and De Seze). Regulatory violations included failure to adhere to the protocol exemplified by study drug administration errors, potential unblinding of investigators, and failure to review laboratory results prior to study drug administration. At one site (Huang), an investigator performing assessments for secondary and exploratory endpoints (MCFCS, LCVA, and SDMT) had access to unblinded study data through data entry and follow-up telephone calls to subjects. Because of this access to unblinded study data, there is a potential that investigators performing other assessments, including primary efficacy assessments such as the EDSS, could have been unblinded. The potential unblinding of study drug assignment could impact the validity and reliability of the submitted data from this site to determine the primary safety and efficacy analyses. Therefore, we recommend that the review

division perform sensitivity analyses for data from this site.

Additionally, at one site (Selmaj) EDSS assessments (primary efficacy endpoint) for Protocol WA25046 were not entered into the computer tablet at the time the assessments were completed, as specified in the protocol, for thirteen of nineteen randomized subjects. For these EDSS data entries, there are no source documents available to verify data integrity. Due to issues regarding data integrity for Protocol WA25046, we recommend that the review division perform sensitivity analyses excluding this site.

A Form FDA 483 was issued for one clinical investigator site (Selmaj); this inspection has been preliminarily classified as Official Action Indicated (OAI). Establishment Inspection Reports (EIRs) have been received and reviewed for one clinical investigator inspection (Huang), final classification Voluntary Action Indicated (VAI), and the sponsor inspection, preliminarily classified as No Action Indicated (NAI). The other clinical investigator inspections have been preliminarily classified as NAI. Observations noted above are based on the Form FDA 483 and communications with the field investigators.

An inspection summary addendum will be generated to include the CRO inspection results as well as any clinical investigator preliminary classifications that may change upon receipt and review of EIRs.

II. BACKGROUND

Ocrelizumab (BLA 761053), is a new molecular entity (NME) being developed for the treatment of relapsing forms of multiple sclerosis (RMS) and primary progressive MS (PPMS). There are no therapies approved for the treatment of PPMS. Ocrelizumab is a recombinant humanized monoclonal antibody that depletes CD20 expressing B cells.

The sponsor is seeking approval for intravenous infusion of ocrelizumab for the treatment of RMS and PPMS. The sponsor received Breakthrough Therapy designation and this BLA submission is under priority review. Three pivotal Phase 3 trials were submitted to support the efficacy and safety of ocrelizumab in RMS (Protocols WA21092, WA21093) and PPMS (Protocol WA25046). Inspections were performed for clinical sites that enrolled subjects in WA21093 and WA25046 only.

Protocol WA20193

Title: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a in patients with relapsing multiple sclerosis

Subjects: 835 subjects were enrolled at 166 sites in 24 countries

First Subject Randomized: September 20, 2011

Last Subject Randomized: March 28, 2013

This was a randomized, 96-week, double-blind, double-dummy, parallel group, active-

controlled Phase 3 study in patients with RMS. Eligible subjects were randomized (1:1) to ocrelizumab 600 mg by IV infusion every 24 weeks or interferon beta-1a (Rebif®) 44 µg by SC injection three times per week for 96 weeks in the treatment phase.

The primary efficacy endpoint was the annualized relapse rate (ARR) at 96 weeks. Key secondary endpoints include the delay in the 12-week and 24-week confirmed disability progression (CDP). The sponsor reported a statistically significant reduction in ARR in the ocrelizumab group compared to the interferon beta-1a group (ARR 0.155 vs. 0.290, $p < 0.0001$). The sponsor also reported a statistically significant difference in the proportion of subjects with 12 and 24-week CDP favoring the ocrelizumab group (12 week: 11.1% vs. 17.5%, $p = 0.02$, 24-week: 8.6% vs. 13.6.0%, $p = 0.04$).

Protocol WA25046

Title: A Phase 3, multicenter, randomized, parallel-group, double-blinded, placebo-controlled study to evaluate the efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis.

Subjects: 732 subjects were enrolled at 182 sites in 29 countries

First Subject Randomized: March 3, 2011

Last Subject Randomized: December 27, 2012

This was a randomized, parallel-group, double-blind, placebo-controlled study in subjects with PPMS. Eligible subjects were randomized 2:1 to either ocrelizumab 600 mg or placebo. Treatment doses were administered until the last enrolled subject reached 120 weeks of treatment and the planned total number of 253 confirmed disability progression events had occurred.

The primary efficacy endpoint was the time to onset of CDP for at least 12 weeks during the double-blind period. The sponsor reported a statistically significant decrease in the proportion of subjects with CDP at 12 weeks in the ocrelizumab group compared to placebo (30.2% vs. 34.0%, $p = 0.0321$) and at 24 weeks (28.3% vs. 32.7%, $p = 0.0365$).

Inspections of clinical sites were considered essential to verify the data submitted for this application. Clinical sites for inspection were chosen primarily based on the numbers of subjects enrolled at the site and/or site-specific efficacy effect size. The focus of the clinical site inspections was adherence to protocols (e.g. inclusion/exclusion criteria), protocol deviations, documentation of informed consent prior to subject participation, reporting of adverse events, maintenance of the study blind, and verification of the primary and key secondary efficacy endpoints.

III. RESULTS:

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Site #233958 Deren Huang, M.D., Ph.D. Neurology and Neuroscience Assoc., 701 White Pond Drive, Suite 300 Akron, OH 44320	WA21093 Subjects: 17	7/26/2016 to 8/4/2016	VAI
Site #242600 Angelica Carbajal Ramirez, M.D. Mexico Centre for Clinical Research, Amores 709 Col. Del Valle Mexico DF 3100 Mexico	WA21093 Subjects: 8	9/19/2016 to 9/23/2016	Interim classification NAI
Sites #252185, #208392 Krzysztof Selmaj, M.D. Centrum Neurologii Krzysztof Selmaj Ul. Tylna 12 LODZ 90-324 Poland	WA21093 Subjects: 70 WA25046 Subjects: 19	9/12/2016 to 9/23/2016	Interim classification OAI
Site #208241 Jerome De Seze, M.D. Hôpital de Hautepierre Avenue Molière Service de Pédiatrie 2 Cedex 67098 Strasbourg France	WA25046 Subjects: 17	9/5/2016 to 9/9/2016	Interim classification NAI
Site #208664 Janusz Zbrojkiewicz, M.D. Neuro-Medic Medykow 22 40-752 Katowice, Poland	WA25046 Subjects: 7	9/26/2016 to 9/28/2016	Interim classification NAI
Genentech, Inc. 1 DNA Way South San Francisco, CA 94080- 4990	WA21093 WA25046	9/12/2016 to 9/16/2016	Interim classification NAI
(b) (4)	(b) (4)	Inspection pending	Inspection pending

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be 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.

1. **Clinical Investigator:** Deren Huang, M.D., Ph.D.; Akron, OH; Site #233958

For Protocol WA21093, twenty-two subjects were screened (four were re-screened) and seventeen subjects were randomized. Three subjects met criteria for MS relapse during the double-blind phase of the study. At the time of the inspection, seven subjects were continuing treatment in the Open Label Extension phase. One subject discontinued the Open Label Extension phase and entered the Safety Follow-Up phase. Four subjects completed the Safety Follow-Up phase and five discontinued the study without entering and/or completing the Safety Follow-Up phase.

Signed informed consent forms were present for all subjects who were enrolled to participate in the studies prior to participation. Records reviewed included but were not limited to source documents, CRFs, inclusion/exclusion criteria, adverse event reports, concomitant medications, IRB/sponsor/monitor communications, monitoring logs, delegation logs, training records, enrollment logs, financial disclosure, test article accountability, protocol deviations, and primary and secondary efficacy data.

A Form FDA 483 was issued with the observation that the investigation was not conducted in accordance with the investigational plan. This protocol included an Examining Investigator who performed the neurological examination, documented Neurostatus Functional System Scores (FSS), assessed Expanded Disability Status Scale (EDSS) scores, and the Karnofsky Performance Status Scale. The Examining Investigator or a qualified designee was also responsible for performing and documenting results from the Multiple Sclerosis Functional Composite Scale (MSFCS), the Low Contrast Visual Acuity Test (LCVA), and the Symbol Digit Modalities Test (SDMT). The Examining Investigator and qualified designees were to remain blinded to treatment assignment during the double-blind treatment period and to have access only to the assessment data for assessments that they performed.

At this site, one of the two approved blinded examining designees had access to unblinded source data while she was also performing some of the blinded assessments for sixteen of seventeen (94%) randomized subjects. This examining designee was originally delegated the unblinded duties of data entry (concomitant medications, adverse events, and vital signs) and telephone follow-up calls before she was approved to perform blinded assessments on 3/20/2012. These unblinded duties continued until 4/28/2014 when they were removed from the delegation log. A review of records indicated that this examining designee had access to unblinded source data between 5/15/2012 to 9/24/2013 (16 months). The delegated task of blinded assessor was removed from the delegation log for this examining designee on 6/12/2014, and the last blinded assessment performed by this examining designee was on 5/16/2014. The blinded assessments conducted by this designee included the MSFCS, LCVA, and the SDMT. During the inspection, the examining designee stated that she did not discuss the MSFCS, LCVA, or SDMT assessments with any of the EDSS blinded Examining Investigators, this was confirmed by the EDSS Examining Investigators. A Corrective Action Response Form describing this issue was completed by the site. This form states that “the Examining Physicians were not

unblinded but they were reminded of their blinded role”.

The majority of these deviations were discovered during a monitoring visit on 4/15/2014, although the monitoring report did not discuss this issue. This issue was documented in an email sent on 5/27/2014 from the CRO (b) (4) to Dr. Huang; “Examining investigator performing efficacy assessments had access to source documentation and entered data in electronic Case Report Forms for multiple subjects/visits. Examining PI was not blinded to the patient data which resulted in over 50 protocol deviations.” Based on this and other findings, the CRO implemented a Non-Compliance Corrective Action Plan (CAP) at this site. The site began retraining on 4/23/2014 by the study monitor on the blinded versus unblinded roles of study personnel and formal training was completed in 6/2014. The site reported these protocol deviations to the IRB on 6/17/2014; however, due to an issue with uploading of documents, the IRB did not receive or review that submission. These protocol deviations were resubmitted to the IRB on 8/1/2016. In the IRB submission, the site stated that none of the Examining Investigators were unblinded and that they did not have access to the source documents where the paper copies of MSFCS, LCVA, or SDMT assessments were filed.

Dr. Huang responded to the inspectional findings in the Form FDA 483 in a letter dated 8/18/2016. In his response, Dr. Huang took full responsibility for the findings and outlined corrective measures that have been instituted. In his response, he also stated “though this examining designee was not responsible for EDSS assessments, there are four EDSS assessments where she might have had involvement based on the EDSS audit trail”. During the inspection, the field investigator did not find evidence that this examining designee was involved with any EDSS assessments.

Reviewer Comment: The examining designee had access to unblinded data while conducting blinded assessments in sixteen of seventeen subjects at this site. These blinded assessments included the MSFCS, LCVA, and SDMT which were used in secondary and exploratory objectives of this study. Though site personnel stated that Examining Investigators were not unblinded, there is a potential that they could have become unblinded. These protocol deviations are not included in the list of major protocol deviations in the clinical study report.

The inspection assignment requested that the field investigator assess how well the blind was maintained during this clinical trial. Due to differences in types of adverse events between the two study medications, the protocol instructed that subjects were not to discuss adverse events with blinded Examining Investigators. Dr. Huang stated that during the injection/infusion study visits, the physical examinations were performed first by the treating investigator followed by the EDSS assessments done by the blinded assessors. Study drug was administered following the EDSS assessments. Dr. Huang stated that the blinded EDSS could have seen subject injection site reactions if they were visible on the back of the arms, but the injection site reactions that he observed were very slight. There were two main EDSS assessors at this site and these assessors stated that they did not observe any injection site reactions during the double-blind phase of the study.

Reviewer Comment: During the inspection, the field investigator did not find evidence of unblinding due to the occurrence of adverse events. Data listings show that injection site reactions occurred more frequently in subjects receiving interferon beta-1a, and infusion-related reactions occurred more frequently in subjects receiving ocrelizumab. There are, however, subjects who experienced both injection site reactions and infusion-related reactions indicating adverse events occurring during administration of either the placebo injection or infusion.

The examining designee had access to unblinded data while conducting blinded assessments in sixteen of seventeen subjects at this site. Study personnel stated that Examining Investigators were not unblinded, however, there is a potential that they could have become unblinded due to these protocol violations. We recommend that the review division conduct a sensitivity analysis of data from this site.

2. Clinical Investigator: Angelica Carbajal Ramirez, M.D.; Mexico; Site #242600

For Protocol WA21093, twelve subjects were screened, eight subjects were randomized, and eight subjects completed the study. The records of all twelve subjects were reviewed. No significant regulatory violations were noted and no Form FDA 483 was issued. The primary efficacy endpoint data was verifiable and there was no evidence of under-reporting of adverse events.

The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

3. Clinical Investigator: Krzysztof Selmaj, M.D.; Poland; Site #252185 and #208392
Site #208392 is the hospital and Site #252185 is Dr. Selmaj's outpatient clinic. Some subjects were enrolled and randomized into the double-blind phase of the study at one site and then transferred to the other site for the open label extension phase of the study.

For Protocol WA21093, 70 subjects were enrolled and randomized and 67 subjects completed the study. Per data listings, three subjects discontinued due to "withdrawal by subject", "other", and lost to follow-up.

For Protocol WA25046, nineteen subjects were screened and randomized, and seventeen subjects completed the study. Per data listings, one subject discontinued due to "withdrawal by subject" and the other subject (Subject #21404) died due to pancreatic cancer.

Some regulatory violations were noted and a Form FDA 483 was issued with the following observations:

Observation 1: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation

EDSS and MSFCS assessments were to be entered directly into an electronic interface

(b) (4) tablet). Data was to be transmitted from the (b) (4) tablet to a central database that was later transferred to the sponsor. Paper copies of relevant questionnaires were to be provided by the (b) (4) Helpdesk if there was a failure with the device.

For Study WA25046, EDSS and MSFCS assessments for thirteen of nineteen (68%) randomized subjects were entered (b) (4) during or after infusion of study drug. Paper EDSS forms were not maintained by the site for those assessments. For EDSS assessments that were entered (b) (4) after the infusions, entry times ranged from two to forty-five minutes after the end of the infusion. Since infusions were 2.5 hours, the EDSS assessments were entered (b) (4) a minimum of 2.5 hours after assessments were completed up to 3.25 hours after assessments were completed. Additionally, paper EDSS forms that were not provided by the (b) (4) Helpdesk were used seventeen times. There were discrepancies noted between these paper EDSS forms and the (b) (4) data. The most common discrepancy was the subject reported walking range which was noted as zero (0) in the paper EDSS forms for three subjects but recorded as 50 to 150 meters in (b) (4). In one instance (Subject #21406), the score on the paper EDSS was 4.5 and the score in (b) (4) was 3.0. A query from the EDSS expert stated that the calculated EDSS score should be 5.0 based on FSS scores in (b) (4). The examining investigator then confirmed the EDSS score of 3.0 and requested to change pyramidal FSS scores from 4 to 3 and ambulation FSS scores from 3 to 1. An additional observation was that some MSFCS assessments were documented in notes (not forms provided by the helpdesk) and the notes did not always identify the subject, visit/date of the assessment, or the results of all MSFCS assessments.

Reviewer Comments: The field investigator noted the issues (b) (4) while reviewing regulatory documents for Protocol WA25046, after documents had been reviewed for Protocol WA20193. The field investigator had insufficient time to re-review documents for Protocol WA20193 to ascertain whether the same protocol deviations occurring in Protocol WA25046 had occurred in Protocol WA20193.

The primary efficacy endpoint for Protocol WA25046 was the time to confirmed disability progression (CDP). CDP was defined as an increase in EDSS score. The EDSS is based on a standard neurological examination, incorporating seven functional systems with each functional system given a functional system score (FSS). Each FSS is rated on a rating scale with anchored severity scores ranging from 0 to 5 or 6. These FSS ratings are then used in conjunction with observations and information concerning ambulation and use of devices to determine the EDSS score. For thirteen of nineteen randomized subjects, the FSS and EDSS scores were entered (b) (4) either during or after the infusion rather than at the time of the assessments. The site indicated that the assessments were performed prior to the infusion. Since there are no source documents available for the FSS or EDSS, it is not known whether investigators accurately recalled these scores when entering them (b) (4). It seems unlikely that an investigator could accurately remember scores for all seven functional systems and other information to ascertain the EDSS score after assessments were completed.

For the cases where paper EDSS forms were used (but not provided by the helpdesk), there

were discrepancies when compared to (b) (4) data for subject reporting walking range and, in one subject, for the EDSS score.

Observation 2. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan

Per protocol, laboratory reports were to be reviewed prior to administration of study drug. At this site, laboratory results for at least ten subjects enrolled in WA21093 were not reviewed prior to infusion of study drug. Of these, Subject #1939983 did not meet re-treatment criterion related to neutrophils and received infusions of ocrelizumab.

The investigator stated that there were some issues with the receipt of laboratory reports from (b) (4). It was difficult to determine whether the issues were due to not receiving laboratory reports or whether reports were received but not reviewed prior to the infusion.

To maintain the study blind, some laboratory results (e.g. FACS cell counts, absolute neutrophil counts, Ig levels) were blinded. A central laboratory was to provide study investigators and medical monitors with “reflex messages” triggered by critical blinded laboratory results. Investigators notified of their patient’s critical laboratory results were instructed to suspend further treatment with study drug until the subject becomes eligible for re-treatment. Per protocol, “the reflex messages from the central laboratory, together with non-blinded laboratory results, were to be reviewed at every visit before continuing with study treatment”. The reflex messages occurred during the double-blind treatment period until the fifth cycle (first cycle of the open-label extension phase).

Blood was collected from Subject #1939983 for laboratory assessment on 2/16/2015. The laboratory (b) (4) reported the results on 3/4/2015. However, this subject received an infusion of ocrelizumab on 3/2/2015 (open-label extension, week 2). Since the laboratory report was not available until after the infusion was given, the investigator did not review the results prior to the infusion. The laboratory results were blinded – the report states that neutrophil testing was “completed”. It is not known whether (b) (4) sent a reflex message to the site. The monitor noted that this subject did not meet “laboratory retreatment criterion related to neutrophils” (per protocol, absolute neutrophil count < $1.5 \times 10^9/L$). The subject’s neutrophil count on 2/16/2015 was $1.37 \times 10^9/L$.

Reviewer Comments: Laboratory reports were not reviewed for at least ten of seventy subjects enrolled in WA20193 prior to administration of study drug. The field noted one instance where a subject had a low neutrophil count and did not meet retreatment criteria but was administered ocrelizumab. Although laboratory results were not reviewed prior to infusions for at least ten of seventy subjects, there was no evidence of subject harm.

For Protocol WA25046, data integrity cannot be confirmed for EDSS scores entered (b) (4) during or up to three hours after infusions for thirteen of nineteen subjects enrolled. For cases in which paper EDSS forms were available, discrepancies between these forms and (b) (4) were noted for the subject reporting walking range and, for one

subject, the EDSS score. Though similar issues could have been present for Protocol WA20193, there was insufficient time to fully investigate this issue for Protocol WA20193. Due to issues regarding data integrity for Protocol WA25046, we recommend that the review division perform sensitivity analyses excluding this site

4. Clinical Investigator: Jerome De Seze, M.D.; France; Site #208241

For Protocol WA25046, nineteen subjects were screened, seventeen subjects were enrolled, and fifteen subjects completed the study. The records of twelve subjects were reviewed. The primary efficacy endpoint data was verifiable and there was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued. The field investigator noted two instances of study drug administration errors. Due to a drug dispensing error, Subject 47109 (randomized to placebo) received kit number 116770 instead of kit number 116670 for Visit 18, cycle 6, infusion 2/2. Kit number 116770 was meant for Subject 47107, who was randomized to receive ocrelizumab. After the infusion, Subject 47109 experienced a skin reaction that had not been experienced in prior infusions. The drug dispensing error was discovered when the investigators requested the pharmacist to check whether there had been a drug dispensing error. Due to this error, Subject 47109 received ocrelizumab instead of placebo at this visit.

Approximately two weeks later, a similar drug dispensing error was discovered. Subject 47103 (randomized to ocrelizumab) received kit number 115348 instead of kit number 115438 for Visit 21, cycle 7, infusion 2/2. The incorrect kit number (115348) was meant for Subject 47117, who was randomized to receive placebo. This error was noted when kit number 115348 which was to be dispensed for Subject 47117 was noted to be missing. The error was noted in September 2014; however, the drug dispensing error occurred in July 2014. Due to this error, Subject 47103 received placebo instead of ocrelizumab at this visit.

The monitor and sponsor were notified of the error and the incident was to be reviewed by the pharmacist-in-charge to avoid future incidents.

Reviewer Comments: Neither of these study drug administration protocol deviations were noted in the data listing (Listing 4) for protocol violations and/or deviations. The protocol deviation for Subject 47109 was noted in the CSR and in a listing of patients excluded from analysis populations, in this case excluded from the Per Protocol analysis. The protocol deviation for Subject 47103 is not mentioned in the CSR or this listing. However, the study drug administration errors for both subjects are noted in the aex.xpt dataset. Therefore, it appears that the sponsor was made aware of this drug dispensing error. According to the CSR, similar errors occurred in three other subjects at three different sites.

Subject 47109 experienced a “skin reaction” which was noted as an “infusion-related reaction” in the adverse event listing. The skin reaction was treated with an antihistamine and quickly resolved. No other safety issues were reported that resulted from these study

drug administration errors. It is unclear what specific steps were taken by the site to prevent the recurrence of similar drug dispensing errors. It is also unclear whether the subjects were informed of the study drug administration errors.

Drug dispensing errors which resulted in study drug administration errors for two of seventeen enrolled subjects occurred at this site. These errors occurred during one of the infusions at a single study visit. It is unclear from the available inspection data whether any investigators performing efficacy assessments for these two subjects became unblinded due to these study drug administration errors. Due to the potential for unblinding, we recommend that the review division perform a sensitivity analysis excluding these two subjects.

With the exception of these study drug administration errors, the study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

5. Clinical Investigator: Janusz Zbrojkiewicz, M.D.; Poland; Site #208664

For Protocol WA25046, seven subjects were randomized (four of these were re-screened and randomized) and four subjects completed the study. Per data listings, three subjects discontinued due to non-compliance, an adverse event, and lost to follow-up.

A Form FDA 483 was not issued. The field investigator noted that this site also had technical difficulties with (b) (4), the computer tablet used to enter clinical assessments (EDSS, MSFCS, etc.). Five different tablets had to be sent to this site due to the technical difficulties. Not all audit trail information was correct. As an example, the initial entry date for the EDSS assessment for Subject #21607 was 6/9/2010 (before the trial began) while the actual assessment date was 12/22/2014. It is unknown how many other audit trails were affected.

Based upon the summary data available, the study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the indication.

6. Sponsor: Genentech, Inc.; 1 DNA Way; South San Francisco, CA

This inspection covered sponsor practices related to Protocols WA21093 and WA25046. Regulatory documents for three clinical sites (233958, 242600, and 252185) participating in Protocol WA21093 and three clinical sites (208392, 208241, and 208664) participating in Protocol WA25046 were reviewed. Documentation reviewed during this inspection included written agreements with vendors and CROs; registration of studies on ClinicalTrials.gov; monitoring procedures; monitor training; Quality Assurance (QA) including audit plan and QA audits; site selection procedures; site closures due to non-compliance; adverse event reporting and

protocol deviations; data collection and handling; SOPs; financial disclosures; 1572s; IRB approvals; and test article accountability.

Sponsor personnel stated that laboratory results from (b)(4) are faxed to each site for investigator review. Clinical sites receive the fax for investigator review and signature and for subject records. The sites return a fax documenting receipt within 48 hours. If a fax from the site is not received, (b)(4) sends another fax to the site. Sponsor personnel stated that repeated attempts are made if needed; however, he was not aware of any delays or problems regarding sites receiving laboratory results from (b)(4).

During the inspection, the field investigator asked whether any sites had been terminated. The sponsor indicated that (b)(4) participating in Protocol (b)(4) was closed due to serious GCP issues (outlined below). The sponsor communicated the site closure and GCP issues in a 7/28/2016 submission to the BLA. The sponsor was notified that Subject #190433 gave birth to a “still born” child on (b)(6). The pregnancy was estimated to be full-term. Subject #190433 was not administered further infusions but entered the Safety Follow-up phase of the study.

An Issue of Notification of Serious GCP Noncompliance or Misconduct Form was issued to the site by the sponsor. The site’s local ethics committee was informed on 1/29/2016 and (b)(4) performed an Accompanied Site Visit on (b)(4). The For-Cause audit noted 1) investigator oversight and adherence to ICH GCP was inadequate as evidenced by nonadherence of protocol requirements; 2) noncompliance with GCP requirements for the obtaining and documenting of patient informed consent; 3) deficient documentation practices; and 4) site management difficulties not timely or adequately escalated to study team managers. As a result of these findings, the sponsor suspended dosing at this site and initiated procedures to close the site. This site contributed six patients and three events to the analysis of the ARR. Subjects continuing participation in the study have been offered participation at another site.

The GCP violations occurring at Site (b)(4) are being further evaluated by the FDA Office of Scientific Investigations GCP Compliance Oversight Branch.

No other issues, besides GCP issues noted at the foreign site, were identified during this sponsor inspection. The sponsor performed additional efficacy analyses excluding Site (b)(4) with no impact on overall study results. We recommend that the review division confirm the analyses excluding Site (b)(4).

7. **CRO:** (b)(4)

The CRO inspection is schedule to begin October 21, 2016. This Clinical Inspection Summary will be amended to include information from that inspection once available.

CC:

Central Document Room/BLA #761053
DNP /Division Director/Billy Dunn
DNP /Medical Team Leader/John Marler
DNP/Medical Officer/Lawrence Rodichok
DNP /Project Manager/Nahleen Lopez
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan Thompson
OSI/DCCE/GCPAB Reviewer/Cara Alfaro
OSI/ GCPAB Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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

/s/

CARA L ALFARO
10/20/2016

SUSAN D THOMPSON
10/20/2016

KASSA AYALEW
10/21/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
BLA# 761053		Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: OCREVUS Established/Proper Name: ocrelizumab Dosage Form: injectable solution Strengths: 300mg/10mL		
Applicant: Genentech Agent for Applicant (if applicable): N/A		
Date of Application: April 28, 2016 Date of Receipt: April 28, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: 12/28/16		Action Goal Date (if different): 12/01/16
Filing Date: 06/27/16		Date of Filing Meeting: 06/01/16
Chemical Classification (original NDAs only) : N/A <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of patients with relapsing-forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS)		
Type of Original NDA: N/A AND (if applicable) Type of NDA Supplement:N/A		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 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		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i> <ul style="list-style-type: none"> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): 100593

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			X	
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period 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>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>	X	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	X	

<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>	X																	
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X																	
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input type="checkbox"/>	X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><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></p>																				
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/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
If yes , # years requested:																				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>																				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	

<p>already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</p>				
<p>BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<p>Do not check mixed submission if the only electronic component is the content of labeling (COL).</p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹</p> <p>If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA # N/A</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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

Forms and Certifications				
<p><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.</i></p> <p><i>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></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<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</i>				

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...”				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

3

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

4

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

Version: 4/12/2016

Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Date(s): December 5, 2008				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 8, 2015; February 4, 2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): March 11, 2011 for SPA 1 and 2. No agreements were issued on April 25, 2011	<input checked="" type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 06/01/11

BACKGROUND: There are no filing issues, just some information requests for the no filing issues letter along with designating as a priority review.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nahleen Lopez	Y
	CPMS/TL:	Jackie Ware	Y
Cross-Discipline Team Leader (CDTL)	John Marler		Y
Division Director/Deputy	(DD) Billy Dunn/ (Deputy) Eric Bastings		Y
Office Director/Deputy	ODE1 Director: Ellis Unger Deputy: Robert Temple		Y
ADRA	Colleen Locicero		Y
Clinical	Reviewer:	Lawrence Rodichok	Y
	TL:	John Marler	Y
Clinical Safety	Reviewer:	Gerard Boehm	Y
	TL:	Sally Yasuda	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Jagan Parepally	Y
	TL:	Angela Men	Y
Pharmacometrics (DPM)	Reviewer:	Xiaofeng Wang	Y
	TL:	Kevin Krudys	Y
Genomics	Reviewer:		
Biostatistics	Reviewer:	Sharon Yan	Y
	TL	Kun Jin	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Barbara Wilcox	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Linan Ha	Y
	Reviewer:	Milos Dokmanovic	Y
	RBPM:	Melinda Bauerlien	N
(CMC) Micro:	TL:	Patricia Hughes	Y
	DS (Drug Substance) Reviewer:	Reyes Candau-Chacon	Y
	DP (Drug Product) Reviewer:	Bo Chi	Y
• Process	Reviewer:	N/A	
• Microbiology	Reviewer:	N/A	
• Facility	Reviewer:	Ruth Moore	Y
	TL:	Zhihao (Peter) Qiu	Y
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	Tracy Peters	Y
• Labeling (CMC)	Reviewer:	Jibril Abdus-Samad	Y
• Other (e.g., Branch Chiefs, EA Reviewer)	N/A		
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sarai Aman	Y
	TL:	Marcia Britt Williams	Y
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Aline Moukhtara	Y
	TL:	Mathilda Fienkeng	Y
OSE	RPM:	Corwin Howard	Y
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Ebony Whaley	N
	TL:	Lolita White/Danielle Harris	N
OSE/DRISK (REMS)	Reviewer:	Jasminder Kumar	N
	TL:	Jamie Wilkins Parker	N

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
OSE/OPE/DEPI	Reviewer:	Elisa Braver	N
	TL:	Lockwood Taylor	N
OSE/OPE/DPV	Reviewer:	Danijela Stojanovic	N
	TL:	Corinne Kulick	N

OSI	PM:	Cara Alfaro	Y
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:	Susan Thompson/Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none">• 505 b)(2) filing issues:<ul style="list-style-type: none">○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., 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):</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none">• Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none">• Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> No comments</p>

CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: N/A	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: N/A <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: Division Director stated at filing meeting that no AC would be needed.
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments: Comments were placed in filing letter as IR</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</u></p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Robert Temple, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 27, 2016 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: 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/

REBECCA N LOPEZ

08/18/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Consult Safety Review for Ocrelizumab

Date:	July 18, 2016
Reviewer(s):	Elisa R. Braver, PhD Division of Epidemiology I
Team Leader	Lockwood Taylor, PhD Division of Epidemiology 1
Acting Deputy Director	Simone P Pinheiro, ScD MSc Division of Epidemiology 1
Drug Name(s):	Ocrelizumab
Subject	Consult Safety Review for Ocrelizumab
Application Type/Number:	BLA 761053
Applicant/sponsor:	Genentech (working with F. Hoffmann-La Roche)
OSE RCM #:	2016-1310

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EXECUTIVE SUMMARY

The purpose of this review is to answer three questions posed by Division of Neurology Products (DNP) to Division of Epidemiology (DEPI) regarding the Sponsor's analyses of a malignancy signal for ocrelizumab (OCR). OCR is undergoing priority review for FDA approval for its use in treatment of multiple sclerosis (MS). This review also proposes potential post-marketing requirement (PMR) language to further assess the safety signal. The questions are listed below, together with DEPI's responses.

1. **QUESTION:** Evaluate the two sources cited by Genentech (PBER, Frisell, ARTIS assessment) which they claim found no additional risk of malignancy with Rituximab (RT).

ANSWER: No conclusions on breast cancer risk in relation to RT can be drawn based on the analysis by Frisell (2016), which did not control for potential confounding factors. The data sources cited in PBER suggest no increased cancer risk from use of RT; however, the findings are inconclusive due to the lack of analyses by time since initial exposure or cumulative duration of treatment and indications that rheumatoid arthritis (RA) clinical trial participants were at lower cancer risk than other RA patients.

2. **QUESTION:** Evaluate external data sources used as comparative data by Genentech. Specifically, evaluate the strengths and weaknesses of using these data sources to assess the malignancy risk observed in the ocrelizumab MS controlled trials.

ANSWER: Using the MS and RA data sources for safety data is useful; however, the statistical analyses that were done were inadequate to account for the latency period for cancers to develop and also did not examine potential confounding factors. Using the Surveillance, Epidemiology, and End Results (SEER) database is not useful because of potential differences in cancer risk, confounding factors, and cancer screening rates between MS patients and the general population.

3. **QUESTION:** Evaluate the Sponsor's proposal for their postmarketing assessment of malignancy risk with ocrelizumab. Please consider this independently as well as in the context of a potential long-term observational study that would not be limited to malignancies.

ANSWER: The proposed PMR is inadequate for determining the risk of malignancies and other long-term adverse effects, but it can be revised to be more informative.

Recommendations

- Revise the MS and RA safety analysis to account for the latency period for cancers to develop, examine potential confounding factors, and estimate risk measures such as hazard ratios for each individual study and a separate pooled risk measure for the MS and RA clinical studies.
- DEPI recommends alternative language for the PMR to examine malignancies and other long-term effects of OCR.

(b) (4)

1 INTRODUCTION

The purpose of this review is to answer three questions posed by Division of Neurology Products (DNP) to Division of Epidemiology (DEPI) regarding the Sponsor's analyses of a malignancy signal for ocrelizumab (OCR) that appeared during clinical trials for multiple sclerosis (MS). Breast cancer and all malignancies combined were increased among OCR-treated patients compared with either placebo or interferon-treated participants in MS trials. The review also proposes potential post-marketing requirement (PMR) language to further assess the safety signal. OCR is a biologic drug submitted for FDA priority approval that is intended to treat relapsing multiple sclerosis (MS) and primary progressive MS. OCR is a recombinant, humanized monoclonal antibody that targets CD20-expressing B-cells (B lymphocytes). The drug aims to modulate the immune system by reducing the number and function of B-cells, which are involved in the pathophysiology of MS.

Rituximab (RT), an older monoclonal antibody, also targets the C20 antigen on B-cells. One difference between OCR and RT is that RT is a chimeric molecule containing both human and mouse DNA whereas OCR is a monoclonal antibody manufactured to more closely resemble human proteins. DNP asked DEPI to review a safety report on RT that was submitted by the Sponsor as part of the biologic licensing application for OCR because the malignant adverse event experience of RT may be relevant to OCR.

2 DOCUMENTS THAT WERE REVIEWED

The following documents were reviewed for this consult, all of which were submitted by Genentech as part of the Biologic Licensing Application (BLA) for OCR.

- Sponsor's Clinical Overview^a
- Sponsor's Summary of Clinical Safety^a
- Sponsor's Integrated Summary of Safety Information for Ocrevus® (ocrelizumab)^a
- David Wormser and Nicole Mairon: Long-term Surveillance of Ocrelizumab-treated Patients with Multiple Sclerosis^a
- Thomas Frisell: Breast cancer among RA [rheumatoid arthritis] patients using Mabthera [rituximab] in ARTIS [Swedish RA registry], 2016^a
- Periodic Benefit-Risk Evaluation Report/ Periodic Safety Update Report 1058003 for Rituximab, 2015^a

^a Clinical Overview can be found in this folder: <\\CDSESUB1\evsprod\BLA761053\0001\m2\25-clin-over> .

Summary of Clinical Safety can be found here: <\\CDSESUB1\evsprod\BLA761053\0001\m2\27-clin-sum> .

Integrated Safety Summary can be found here: <\\CDSESUB1\evsprod\BLA761053\0001\m5\53-clin-stud-rep\535-rep-efic-safety-stud\ms\5353-rep-analys-data-more-one-stud\iss> .

Long-term Surveillance of Ocrelizumab-treated Patients with Multiple Sclerosis can be found here:

<\\CDSESUB1\evsprod\BLA761053\0001\m1\us> .

Frisell (2016) can be found here: <\\CDSESUB1\evsprod\BLA761053\0001\m5\54-lit-ref> .

Periodic Benefit-Risk Evaluation Report/ Periodic Safety Update Report 1058003 for Rituximab can be found here: <\\CDSESUB1\evsprod\BLA761053\0001\m5\54-lit-ref> .

3 REVIEW RESULTS

3.1 DNP QUESTION 1 AND RELATED ANALYSIS/FINDINGS

QUESTION: Evaluate the two sources cited by Genentech (PBER [Periodic Benefit-Risk Evaluation Report], Frisell, ARTIS [Anti-Rheumatic Therapies in Sweden] assessment) which they claim found no additional risk of malignancy with Rituxan (rituximab).

Frisell: Using data from ARTIS, a Swedish registry of rheumatoid arthritis (RA) that includes almost 80% of RA patients in Sweden, Frisell (2016) did an analysis of breast cancer incidence rates among 2,447 female RA patients treated with rituximab (RT) compared with 40,182 female RA patients who were described as bionative (having no previous exposure to biological drug products). The breast cancer incidence rates were 1.85 per 1,000 person-years (95% CI for rate: 1.05-3.03)^b among the RT group and 2.46 (95% CI for rate: 2.23-2.70) among the bionative group. The crude Hazard Ratio (HR) comparing RT-treated with bionative patients was 0.77 (95% CI: 0.45-1.32) and an age-adjusted HR was 0.82 (0.48-1.41). No analyses were presented by length of follow-up, daily dose, or cumulative dose. Other than age, adjustments were not made for potential confounding factors.

Periodic Benefit-Risk Evaluation Report (PBER) for RT among patients with autoimmune disease and other (non-oncology) indications: Among patients treated with RT, malignancy data from clinical trials, epidemiologic studies, and disease registries were reviewed among patients with RA, Granulomatosis with polyangiitis (GPA), and Microscopic polyangiitis (MPA). No increased risk was observed in the RT-treated RA patients compared with placebo controls: 0.74 malignant events vs. 0.81 events per 100 person-years (N=3,595 participants). Also, no meaningful increase in malignancies with RT treatment was observed compared with the US national database on cancer incidence (Surveillance, Epidemiology, and End Results (SEER) or compared with published data on adults with RA. Furthermore, no differences in cancer incidence rates were observed between patients treated with RT compared with those treated with either tumor necrosis factor inhibitors or non-biologic disease modifying anti-rheumatic drugs. Research literature indicates that tumor necrosis factor inhibitors increase the risk of non-melanoma skin cancers.

A small clinical trial of RT in treatment of GPA/MPA observed 11 malignancies in the RT group vs. 7 in the cyclophosphamide/azathioprine control group, resulting in an 18-month standardized cancer incidence rate of 2.06 in RT-treated patients vs. 2.0 in controls. Cyclophosphamide is considered to be a carcinogen.

The report stated that RA patients had an increased risk of overall malignancy, regardless of treatment, compared with the US general population (Standardized Incidence Ratio (SIR)=1.20), together with an increased risk of lymphoma (SIR=2.60), lung cancer (SIR=1.66), and non-melanoma skin cancer (SIR=1.83). The estimated SIR for colorectal cancer was 0.80.¹

^b DEPI reviewer calculated the 95% confidence intervals for the breast cancer incidence rates by using Miettinen's Mid-P exact tests by using OpenEpi software.

Confidence intervals were not provided. The report said that the literature search did not identify any publications on the risk of malignancy among RA patients treated with RT.

The analysis concluded that RT is not implicated as a carcinogen.

3.2 DNP QUESTION 2 AND RELATED ANALYSIS/FINDINGS

QUESTION: Evaluate external data sources used as comparative data by Genentech. Specifically, evaluate the strengths and weaknesses of using these data sources to assess the malignancy risk observed in the ocrelizumab MS controlled trials

Increased cancer incidence rates were observed among OCR-treated patients compared with placebo controls and interferon-treated controls in the MS randomized controlled clinical trials. This was seen for all malignancies combined, malignancies excluding non-melanoma skin cancer, and breast cancer (Genentech Integrated Safety Summary, Table 105, page 283).

The Sponsor performed three key analyses to explore the increased incidence of cancer among OCR-treated patients relative to comparators in clinical trials.

- Aggregating data from 4 clinical trials of OCR for treatment of relapsing MS or primary progressive MS.
- Aggregating data from 9 clinical trials of OCR for rheumatoid arthritis (RA). (Genentech Summary of Clinical Safety 2016, page 14).
- Comparing findings from clinical trials with external data sources, including the Surveillance, Epidemiology, and End Results (SEER) database that estimates US cancer incidence and mortality rates.

The Sponsor did not provide hazard ratios or incidence rate ratios for malignancies, although it had the necessary data and did provide hazard ratios for infections. Incidence rates and standardized incidence rates (standardized by age group, stratified by gender) were provided.

MS clinical trials. Regarding the MS clinical trials, the Sponsor stated: “Malignancy was reported in a total of 19 (0.9%) ocrelizumab-treated patients in the MS program and 4 (0.4% patients) patients in the comparator groups (pooled placebo and interferon beta-1a) of the RMS [relapsing MS] and PPMS [primary progressive MS] studies. The incidence rate (IR) of first malignancy (number of first malignancy events per 100PY [person-years] exposure, limited to time to first event) was 0.425 per 100PY for patients treated with ocrelizumab compared with a pooled crude IR from the comparator arms of 0.195 per 100PY. The only cluster which could be identified was female breast cancer, where all cases occurred in ocrelizumab-treated patients (7 patients, 6 during the controlled treatment periods; IR 0.261 per 100PY); however these had no specific type of clinical or histological pattern. All other malignancies were individual cases.” (Genentech Clinical Overview, page 102)

Malignancy incidence rates were not presented by time since first exposure or cumulative duration of treatment. Analyses were not done to determine whether potential confounding

factors such as smoking, alcohol, and body mass index were balanced between the randomized groups.

RA clinical trials. OCR was administered in combination with a disease-modifying non-biologic drug (such as methotrexate) in all of the RA clinical trials. Of 2,926 patients, a total of 94 OCR-exposed patients in 9 RA clinical trials developed malignancies. Of these 94 patients, 26 had basal cell carcinoma and 7 had forms of breast cancer (5 were coded as breast cancer, 2 were coded as intraductal proliferative breast lesions, and 1 was coded as inflammatory carcinoma of the breast). The other common types of cancers were prostate cancer (N=6), malignant melanoma (N=6), and squamous cell carcinoma of the skin (N=6).

The all-malignancy incidence rates per 100 person-years were as follows:

OCR 400 mg=	0.90 (95% CI: 0.41-1.70)
OCR 1000 mg =	1.32 (95% CI: 0.68-2.31)
Placebo=	1.11 (95% CI: 0.53-2.04)

No analyses were presented by time since first exposure or by cumulative duration of treatment. Data were not presented to indicate balance between OCR and placebo groups for characteristics affecting cancer risk.

Clinical trials for other indications. Safety data for 3 clinical trials of OCR for systemic lupus erythematosus (SLE), lupus nephritis (LN), or non-Hodgkin's lymphoma (NHL) were not included in the main analysis, but were briefly summarized in the Integrated Safety Summary. The 3 excluded clinical trials had 48 NHL patients, 33 SLE patients, and 381 LN patients. In the LN trial, the cancer incidence rates were similar between the OCR-treated and placebo patients: 4.7 to 4.8%. The Sponsor's rationale for excluding the findings from SLE, LN, and NHL was "because of the considerable differences in the general health of these patients, concomitant medications (e.g., treatment with pulse steroids and high-dose steroid tapering) and study design." (Genentech Summary of Clinical Safety, 2016, page 14).

Comparison with SEER. With respect to the comparisons with the SEER database, the Sponsor explained that standardized incidence rates were calculated for OCR-treated patients and compared with the general US population for calendar year 2000. Data were stratified by gender. Results for both 5-year age adjustments and 10-year age adjustments were reported. Aside from age, no analyses were done to address potential confounding factors or race, region, and calendar year. The Sponsor also presented some analyses in which MS patients were assumed to have a 9% lower cancer risk and adjusted the SEER data accordingly to make the groups more comparable.

The Sponsor stated: "When comparing against the SEERs database, standardized incidence rates in the ocrelizumab group were similar (OCR 0.262 per 100PY [95% CI: 0.132, 1.584] and SEERs 0.242 per 100PY [95% CI: 0.241, 0.242])."

3.3 DNP QUESTION 3 AND RELATED ANALYSIS/FINDINGS

QUESTION: Evaluate the Sponsor's proposal for their post marketing assessment of malignancy risk with ocrelizumab. Please consider this independently as well as in the context of

a potential long-term observational study that would not be limited to malignancies.

(b)(4)

4 DISCUSSION

4.1 DNP QUESTION 1

QUESTION: Evaluate the two sources cited by Genentech (PBER, Frisell, ARTIS assessment) which they claim found no additional risk of malignancy with Rituximab.

Frisell: The analysis by Frisell suggests no significant differences between the Swedish female RT-treated RA group and the female bionative RA group. However, no conclusions about breast cancer risk in relation to RT can be drawn from Frisell's analysis. Because the RA patients were not drawn from a randomized controlled clinical trial, adjustment for potential confounding factors was essential, but not done. There likely were differences between RA patients treated with RT and those not treated with biologics in terms of disease severity and possibly in factors affecting cancer incidence and detection, which could have resulted in biased risk estimates. Furthermore, Frisell did not present data by time since initial exposure or by dosage, which is critical for analyses of cancer risk.

One potential specific source of bias in the analysis is that women with disabling illnesses are less likely to receive screening mammograms, cervical cancer screening, and colonoscopies.² This could result in lower cancer incidence rates among patients with more severe disease. One Canadian study observed that MS patients diagnosed with cancer had larger tumor sizes, which suggests that they are receiving lower rates of screening.³

PBER: The PBER analyses suggest that RA patients treated with RT do not have increased risk of malignancy when compared with placebo controls, published data on RA patients, and the US national population. The lack of differences with the US national population is surprising because other research has indicated that RA is associated with increases in the risk of lung

cancer, lymphoproliferative malignancies, and non-melanoma skin cancer. It is possible that volunteers for clinical trials differ from the general population in ways that affect cancer incidence.

Data were not presented by time since initial exposure, which is necessary when analyzing cancer risk. Dose-response analyses also were not presented.

One factor that complicates interpretation of this analysis is that RT has been compared with drugs that increase cancer risk, including cyclophosphamide and tumor necrosis factor inhibitors. If RT has similar cancer incidence rates to those drugs, then RT may in fact contribute to increasing cancer risk.

4.2 DNP QUESTION 2

QUESTION: Evaluate external data sources used as comparative data by Genentech. Specifically, evaluate the strengths and weaknesses of using these data sources to assess the malignancy risk observed in the ocrelizumab MS controlled trials.

The Sponsor provided insufficient analyses of malignancy incidence rates. Data were not presented by time since first exposure to OCR or placebo/comparator drug, which is important because tumors take years to develop. Dose-response analyses by cumulative doses also were not provided. Furthermore, smoking, race, region, and frequency of mammogram or other cancer screening were not examined. This is particularly important because these pooled analyses do not stratify by study (these are not meta-analyses) so that confounding is still a concern even though the data are from randomized controlled clinical trials. The fact that neither hazard ratios nor incidence rate ratios were provided for malignancies, although the Sponsor had sufficient data to do these calculations and had done so for infections, made evaluating comparisons difficult.

Comparing study incidence rates to SEER rates is likely to provide, at best, limited information on OCR-specific risks. MS patients appear to be at lower risk of malignancy than the general population regardless of treatment, even lower than the 9% adjustment included by the Sponsors. Kingwell et al. observed standardized incidence ratios (SIRs) of 0.88 (95% CI: 0.78–0.99) among female MS patients and 0.80 (95% CI: 0.67–0.96) among male MS patients for all malignancies (excluding non-melanoma skin cancers) relative to the Canadian population.³ Even lower SIRs were observed for colorectal cancer: 0.57 (95% CI: 0.34–0.90) among females and 0.54 (95% CI: 0.23–0.99) among male MS patients. One possible explanation for Kingwell et al.'s findings is that there may be lower rates of cancer screening among MS patients with more severe disease compared with the general population.^{2, 3} As a result, a comparison of observed rates to national population rates of cancer is unlikely to provide information on OCR-specific risks.

Another consideration is that the malignancy rates among participants in RA clinical trials were lower than the general population of RA patients. This suggests that volunteers for clinical trials may be at lower risk for malignancies, which could be due to lower smoking rates and lower exposure to other factors increasing cancer risk. This complicates comparisons with disease-specific patient registries.

4.3 DNP QUESTION 3

QUESTION: Evaluate the Sponsor's proposal for their postmarketing assessment of malignancy risk with ocrelizumab. Please consider this independently as well as in the context of a potential long-term observational study that would not be limited to malignancies.

The Sponsor's proposal has the following limitations.



5 CONCLUSIONS

- **ANSWER TO QUESTION 1:** No conclusions on breast cancer risk in relation to RT can be drawn based on the analysis by Frisell (2016), which did not control for potential confounding factors. The data sources cited in PBER suggest no increased cancer risk from use of RT; however, the findings are inconclusive due to the lack of analyses by time since initial exposure or cumulative duration of treatment and indications that RA clinical trial participants were at lower cancer risk than other RA patients.

- **ANSWER TO QUESTION 2:** Using the MS and RA data sources for safety data is useful; however, the statistical analyses were inadequate to account for the latency period for cancers to develop and also did not examine potential confounding factors. Using SEER is not useful because of potential differences in cancer risk, confounding factors, and cancer screening rates between MS patients and the general population.
- **ANSWER TO QUESTION 3:** The proposed PMR is inadequate for determining the risk of malignancies and other long-term adverse effects, but it can be revised to be more informative.
- The Sponsor should revise its analyses of malignancies to present data on time since initial exposure, explore potential dose-response relationships, and discuss the balance of potential confounding factors in the clinical trials that were pooled.
- The PMR should be revised (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6 RECOMMENDATIONS

DEPI recommends the following to the Sponsor:

- Revise the MS and RA safety analysis to account for the latency period for cancers to develop and dose-response, examine potential confounding factors, and estimate risk measures such as hazard ratios for each individual study and a pooled risk measure separately for the MS and RA clinical studies.

DEPI recommends the following PMR language:

[REDACTED] (b) (4)

7 REFERENCES

- ¹ Smitten AL, Simon TA, Hochberg MC, Suissa S. [A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis.](#) Arthritis Res Ther. 2008;10(2):R45. doi: 10.1186/ar2404. Epub 2008 Apr 23.
- ² Dobos K, Healy B, Houtchens M. [Access to Preventive Health Care in Severely Disabled Women with Multiple Sclerosis.](#) Int J MS Care. 2015 Jul-Aug;17(4):200-5. doi: 10.7224/1537-2073.2013-046.
- ³ Kingwell E, Bajdik C, Phillips N, Zhu F, Oger J, Hashimoto S, Tremlett H. [Cancer risk in multiple sclerosis: findings from British Columbia, Canada.](#) Brain. 2012 Oct;135(Pt 10):2973-9. doi: 10.1093/brain/aws148. Epub 2012 Jun 21.
- ⁴ Gibney GT, Messina JL, Fedorenko IV, Sondak VK, Smalley KS. [Paradoxical oncogenesis--the long-term effects of BRAF inhibition in melanoma.](#) Nat Rev Clin Oncol. 2013 Jul;10(7):390-9. doi: 10.1038/nrclinonc.2013.83. Epub 2013 May 28.

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/s/

ELISA R BRAVER
07/18/2016

LOCKWOOD G TAYLOR
07/18/2016

SIMONE P PINHEIRO
07/18/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
10903 New Hampshire Ave.
Silver Spring, MD 20903**

Memorandum to File

Date: 6/25/2016

From: Bindu Kanapuru, M.D.
Medical Officer, Division of Hematology Products

Through: Nicole Gormley, M.D.
Acting Clinical Team Leader
Division of Hematology Products

Edward Kaminskas, M.D.
Deputy Division Director, Division of Hematology Products

To: Nahleen Lopez, RPM
Division of Neurology Products (DNP)

Reference: BLA 761053 Ocrelizumab
Genentech

Consult question regarding ocrelizumab

The Division of Neurology Products (DNP) seeks guidance from the Division of Hematology Products (DHP) regarding the malignancy risk with ocrelizumab.

According to the Sponsor, given the evidence of B-cell involvement in the pathophysiology of MS, they undertook the ocrelizumab development program, which selectively targets CD20 expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells or plasma. Ocrelizumab selectively depletes CD20-expressing B cells by mechanisms such as antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis ([Kappos et al. 2011](#)), the capacity for B-cell reconstitution and pre-existing humoral immunity are preserved ([DiLillo et al. 2008](#)).

On 4/28/16, Genentech submitted a BLA for ocrelizumab to the Division of Neurology Products. Ocrelizumab is an anti-CD20 recombinant humanized monoclonal antibody intended for the treatment of relapsing and primary progressive forms of multiple sclerosis (MS).

Two pivotal trials included studies WA21092 and WA21093, which were identically designed, randomized, active comparator (IFN-B-1a) trials. An additional trial in primary progressive MS was study WA25046 (placebo comparator). Genentech also included data from their abandoned rheumatoid arthritis development program (9 trials, 2926 patients) and limited data from abandoned NHL, SLE, and LN development programs.

In the MS clinical trial data, a higher rate of malignancy was observed among patients receiving ocrelizumab, compared to IFN-B-1a or placebo. The majority of cancers were isolated types, but there was a cluster of breast cancer cases. In controlled trials, there were 7 patients receiving ocrelizumab who were diagnosed with breast cancer, compared with no cases in the comparator groups (which included IFN or placebo).

DNP Questions:

- 1. In describing the malignancy risk in the controlled trials, is it appropriate to consider all diagnosed cancers, regardless of cell type, or should the assessment focus only on the cluster of breast cancer cases?**

In describing the malignancy risk, it is appropriate to consider all diagnosed cancers. However, since the review identified an increased number of breast cancer cases, it is also appropriate to focus assessment on malignancy risk from breast cancer alone.

The alemtuzumab (Lemtrada ®) prescribing information (PI) describes malignancy risk from controlled trials in multiple sclerosis (MS) population and lists increased malignancy risk from individual cancers in Warnings and Precautions: thyroid, melanomas and lymphoproliferative disorders.

From the alemtuzumab PI; “LEMTRADA may increase the risk of thyroid cancer. In controlled clinical studies, 3 of 919 (0.3%) LEMTRADA-treated patients developed thyroid cancer, compared to none in the interferon beta-1a-treated group”.

- 2. Considering the low number of events and limited follow up cited by Genentech, do you view the imbalance in breast cancer diagnoses (6 vs. 0) in these controlled trials as concerning?**

Yes. The imbalance of breast cancer cases in the ocrelizumab group and combined placebo and interferon group at this stage of follow-up is concerning. Longer follow-up is recommended to further characterize this finding. Please see response to Question 1. Please also see consult responses by DOP1 with respect to breast cancer cases.

- 3. Do you find Genentech’s comparison to outside databases reassuring, despite the observed imbalance from within the controlled trials?**

No. As stated by the Sponsor, the comparisons to outside database are limited by the low number of malignancies reported in the ocrelizumab MS program and the short follow up.

DHP review identified one article in PubMed database evaluating impact of disease-modifying treatments and cancer risk in 7,418 MS patients gathered from nine French MS center ([Lebrun C 2008](#)). The review concluded that MS patients have a decreased overall risk of cancer; however an increased risk for breast cancer was noted in women with MS treated with immunosuppressive therapy (IS).

We defer to OSE's assessment for a final decision with regard to the validity of these databases, as well as the role of the comparison of data within controlled trials to these outside databases.

4. If you agree with Genentech that no conclusion on malignancy can be made, do you think it is appropriate to further evaluate this signal in the post marketing period as proposed?

Please see response to Question 3. We agree that (b) (4) as proposed by the Sponsor is necessary to make a definitive conclusion about ocrelizumab and malignancy risk in patients with MS. However, the results from the controlled trials of imbalance in breast cancer diagnoses (6 vs. 0) should be included in the proposed labeling for ocrelizumab. This recommendation is consistent with alemtuzumab PI and the approach used by DHP for other products.

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BINDU N KANAPURU
07/02/2016

NICOLE J GORMLEY
07/05/2016

**Medical Officer Review of Consult
Division of Oncology Products-1**

BLA #	761053
Drug(s)	Ocrelizumab
BLA Sponsor	Genentech
Consulting Division	Division of Neurology Products, Nahleen Lopez, RPM
Primary Reviewer	Gwynn Ison, MD
Team Leader	Laleh Amiri, MD
Consult Due Date	7/8/16

Background:

According to the Sponsor, given the evidence of B-cell involvement in the pathophysiology of MS, they undertook the ocrelizumab development program (described by this clinical overview), which selectively targets CD20 expressing B cells. CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells or plasma. Ocrelizumab selectively depletes CD20-expressing B cells by mechanisms such as antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediate cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis ([Kappos et al. 2011](#)), the capacity for B-cell reconstitution and pre-existing humoral immunity are preserved ([Martin and Chan 2006](#); [DiLillo et al. 2008](#)).

The precise mechanisms through which ocrelizumab is thought to exert its therapeutic clinical effects in MS are not fully elucidated, but involve immunomodulation through reduction in the number and function of B cells. These changes are thought to be responsible for the consequent improvement in the disease course of MS ([Avivi et al. 2013](#)).

On 4/28/16, Genentech submitted a BLA for ocrelizumab to the Division of Neurology Products. Ocrelizumab is an anti-CD20 recombinant humanized monoclonal antibody to be used for the treatment of relapsing and primary progressive forms of multiple sclerosis (MS). Two pivotal trials included studies WA21092 and WA21093, which were identically designed, randomized, active comparator (IFN-B-1a) trials. An additional trial in primary progressive MS was study WA25046 (placebo comparator). Data from 9 additional trials in other indications (including 2926 patients) were also part of the database. One study, WA21493, was a Phase II placebo controlled dose finding study of ocrelizumab vs. placebo in patients with RRMS.

In the clinical trial data, a higher rate of malignancy was observed among patients receiving ocrelizumab, compared to IFN-B-1a or placebo. The majority of cancers were isolated types, but there was a cluster of breast cancer cases. In controlled trials, there were 7 patients receiving ocrelizumab who were diagnosed with breast cancer, compared with no cases in the comparator groups (which included IFN or placebo).

Questions for DOP1:

1. In describing the malignancy risk in the controlled trials, is it appropriate to consider all diagnosed cancers, regardless of cell type, or should the assessment focus only on the cluster of breast cases?

DOP1 response:

In attempting to determine malignancy risk potentially related to ocrelizumab, it is important to consider all cancers diagnosed and identified in the BLA database. This should include all documented cases of malignancy in any patient who received ocrelizumab, regardless of whether the drug was received on a controlled trial or not, and regardless of whether the treatment was received during the randomized or open-label portion of the trial. Based upon the limited assessment performed (including reading summaries and narratives provided by the Sponsor), it appears that the Sponsor's report of 19 cases of malignancy in ocrelizumab treated patients may be accurate, but an exhaustive review of the datasets should be performed to confirm this. See response to Question 2, with regard to the breast cancer cases.

2. Considering the low number of events and limited follow up cited by Genentech, do you view the imbalance in breast cancer diagnoses (6 vs. 0) in these controlled trials as concerning?

DOP1 response: Based upon our review of the narratives submitted, there appear to be 7 cases of breast cancer diagnosed in patients who received ocrelizumab (not 6, as noted by the Sponsor). The study and ID numbers for these patients are as follows:

- 1) WA21092-206629-1920773
- 2) WA21092-234347-2926392
- 3) WA25046-208039-47403
- 4) WA25046-208185-10201
- 5) WA25046-208661-21006
- 6) WA25046-20878-32301
- 7) WA21493-140954-1052

There do not appear to have been any breast cancer cases diagnosed in the placebo or comparator (IFN) arms of the trials conducted. The narratives for each of the above cases were reviewed and assessed for details, including age of the patient at cancer diagnosis, number of days on therapy with ocrelizumab, presence of family history of breast or other cancers, and pertinent pathological tumor characteristics and stage at diagnosis. Unfortunately, details of stage and subtype (ER/PR status, HER2 status) were not provided for most of the breast cancer cases described. It was interesting that some of the patients continued on therapy with ocrelizumab, despite cancer diagnosis, where as some of the patients had therapy

discontinued by the investigator, since the cancer was thought (by the investigator) to possibly be related to therapy with ocrelizumab, in those cases. Although it is difficult to make any conclusions about whether there is cause for concern, with respect to the imbalance in cases diagnosed in ocrelizumab treated patients, a potential safety signal should not be ruled out, at this time. See also response to Question 4.

3. Do you find Genentech's comparison to outside databases reassuring, despite the observed imbalance from within the controlled trials?

DOP1 response: No, but we defer to OSE's assessment of this aspect of the Sponsor's account, with regard to the validity of these databases, as well as the role of the comparison of data within controlled trials to these outside databases.

4. If you agree with Genentech that no conclusion on malignancy can be made, do you think it is appropriate to further evaluate this signal in the post-marketing period as proposed?

DOP1 response: We do not agree that no conclusion on malignancy can be made. The signal identified within the trials in the ocrelizumab does warrant further evaluation, and should include collection of information on newly diagnosed malignancies, in general. Specific guidance should be given to the Sponsor on the information collected going forward, but should include, at a minimum, the pathological cancer diagnosis, stage at diagnosis, time on therapy with ocrelizumab at the time of cancer diagnosis, and action taken with ocrelizumab therapy at that point (continue vs. discontinue). For breast cancer cases, specifically, details collected should include stage at diagnosis and hormonal status of the tumor (to include ER/PR status and HER2 status).

Although it is difficult to make a conclusion about whether causality can be attributed to ocrelizumab in any of the cancer cases identified, a relationship should not be ruled out, at this time. We think that there is precedent for including the information about potential malignancy risk in the product labeling. For example, other products such as olaparib (Lynparza) and alemtuzumab (Lemtrada) include information on cases of malignancy in the label and have malignancy risk as a section in Warnings and Precautions. The Lemtrada label also contains a box warning describing the risk of malignancy. Using these examples, it is warranted to have further discussions with the Sponsor regarding the need to include this information in the label.

Breast cancer cases table:

#	Study	Patient ID/ Age/ sex	Underlying disease	Cancer diagnosed	Treatment arm and dose	Days on study drug (Sponsor derived)	Time from last dose study drug to cancer in days (Sponsor derived)	Narrative info- study day of event, outcome if available
1	WA21092	206629- 1920773/ 54 y/o white female Czech	MS	Invasive ductal carcinoma (breast)	Ocre 600	840	57	Event diagnosed Study day 393, G4 AE- study drug stopped as result of dx. Withdrawn from study D 421.
2	WA21092	234347- 1926392 29 y/o female US	MS	Invasive ductal carcinoma (breast)	Ocre 600	502	463	Event diagnosed study day 463, but narrative states she was only on drug for 84 days- d/c due to UTI.
3	WA25046	208039- 47403 54 y/o female France	MS	Invasive ductal carcinoma (breast)	Ocre 600	968	47	Last infusion Ocre D856. D882 mammo performed. Subsequent biopsy revealed invasive ductal carcinoma. Underwent surgery with mastectomy and ALND. No other info given.
4	WA25046	208185- 10201 54 y/o female Germany	MS	Breast cancer	Ocre 600	886	115	Last infusion of ocre was Day 351. Narrative states she had breast biopsy D451 with malignant cells and had R mastectomy D471. Investigator attributed breast cancer to be related to ocrelizumab.
5	WA25046	208661- 21006 47 y/o female Poland	MS	Invasive breast cancer	Ocre 600	832	58	According to the narrative, on study day 737 she had U/S L breast which revealed hypogenic tumor. Study D811 she was diagnosed with invasive breast carcinoma. Ocrelizumab was discontinued. She had radical mastectomy, but diagnosis was deemed unrelated to study drug by investigator.
6	WA25046	208787- 32301 52 y/o female US	MS	Invasive ductal carcinoma- breast	Ocre 600	1273	92	Narrative states that she stopped therapy with ocrelizumab on D 854. On study day 917, patient had a R breast biopsy, which revealed infiltrating ductal carcinoma. She began radiation therapy and tamoxifen on study day 1012. Investigator attributed diagnosis as related to study drug.
7	WA21493	140954- 1052 45 y/o female Bulgaria	MS	Breast cancer	Ocre 1000	1291	258	Narrative states that patient had h/o bilateral breast fibroadenomas treated with partial breast resection in 2005. Began ocrelizumab 2009. On study day 491,

								completed treatment phase. On D748 she developed L breast induration with palpable mass. On D773 had subtotal mastectomy and axillary lymph node dissection. She had Stage III invasive ductal cancer- ER+ PR+, HER2-. On D836 she started unspecified chemotherapy.
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/s/

GWYNN ISON
06/28/2016

LALEH AMIRI KORDESTANI
06/28/2016