CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

OTHER REVIEW(S)

Xeomin PMR/PMC Development Template: PMR # 1

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

PMR/PMC Description: Juvenile rat toxicology study to evaluate effects of Xeomin on growth, reproductive development, and neurological and neurobehavioral development.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	7/21/2010 (submitted)
	Study/Clinical trial Completion Date:	9/30/2010
	Final Report Submission Date:	11/30/2010
	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 product is ready for approval for use in adults and pediatric studies have 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."

A juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of Xeomin on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of Xeomin on growth, reproductive development, and neurological and neurobehavioral development.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of Xeomin (incobotulinumtoxinA) on growth, reproductive development, and neurological and neurobehavioral development.

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.*

Sally Yasuda 7/30/10

(signature line for BLAs)

Xeomin PMR/PMC Development Template: PMR # 2

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

PMR/PMC Description: A prenatal and postnatal development (including maternal function) study to evaluate the effects of Xeomin on developmental endpoints not evaluated in other reproductive and developmental studies.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	7/21/2010 (submitted)
	Study/Clinical trial Completion Date:	5/31/2010 (completed)
	Final Report Submission Date:	11/30/2010
	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 product is ready for approval for use in adults and a prenatal and postnatal development study 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."

A prenatal and postnatal development (including maternal function) study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on stages of development and endpoints not evaluated in an embryo-fetal development study, in accordance with guidance set forth in ICH S5(R2): *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility* (2005).

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.

2. A prenatal and postnatal development (including maternal function) study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on stages of development and endpoints not evaluated in an embryo-fetal development study, in accordance with guidance set forth in ICH S5(R2): *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility* (2005).

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.*

Sally Yasuda 7/30/10

(signature line for BLAs)

Xeomin PMR/PMC Development Template: PMR #3

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

PMR/PMC Description: Pediatric long-term safety study for treatment of upper and lower limb spasticity

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	07/31/2012
Study/Clinical trial Completion Date:	03/31/2018
Final Report Submission Date:	12/31/2018
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 appropriate for a PMR instead of pre-approval because Xeomin will be approved and marketed for other indications.

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."

Long-term safety data are necessary at effective or commonly used doses in spasticity in pediatrics. The safety data are required to evaluate the risk distant spread of toxin effects, and effects on blood glucose and alkaline phosphatase at these doses. Adverse events of concern have been identified in the post-marketing period for other botulinum toxin products when used for treatment of spasticity. Xeomin is approved for use in spasticity in adults in Canada and in Europe, and the "Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology" recommends that "Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children " (***Neurology*® 2008;70:1691–1698).**

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.

Submit safety data assessing distant spread of toxin effects after multiple administrations of Xeomin (incobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years). Approximately one half of the patients must be treated for upper and the other half treated for lower limb extremity spasticity. Patients can be enrolled in either an upper or lower limb safety trial, but not both, and should not receive concomitant botulinum toxin injections for another reason. These safety data could come from open-label extensions of the clinical trials you have committed to perform (see below), from separate longer-term open-label safety trials, or from a long-term controlled safety and efficacy trial. The doses evaluated must be at least as high as those shown effective in these studies, or those commonly used to treat spasticity. (b) (4)

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.*

Sally Yamada 7/30/10

(signature line for BLAs)

Xeomin PMR/PMC Development Template: PMR #4

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

PMR/PMC Description: Adult long-term safety study for treatment of upper and lower limb spasticity

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	12/31/2011
Study/Clinical trial Completion Date:	09/30/2016
Final Report Submission Date:	06/30/2017
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 appropriate for a PMR instead of pre-approval because Xeomin will be approved and marketed for other indications.

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."

Long-term safety data are necessary at effective or commonly used doses in spasticity in adults. The safety data are required to evaluate the risk distant spread of toxin effects, and effects on blood glucose and alkaline phosphatase at these doses. Adverse events of concern have been identified in the post-marketing period for other botulinum toxin products when used for treatment of spasticity. Xeomin is approved for use in spasticity in adults in Canada and in Europe, and the "Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology" recommends that "Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children " (***Neurology*® 2008;70:1691–1698).**

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.

Submit safety data assessing distant spread of toxin effects after multiple administrations of Xeomin (incobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 adult patients. Approximately one half of the patients must be treated for upper and the other half treated for lower limb extremity spasticity. Patients can be enrolled in either an upper or lower limb safety study, but not both, and should not receive concomitant botulinum toxin injections for another reason. These safety data could come from open-label extensions of the clinical trials you have committed to perform (see below), from separate longer-term open-label safety trials, or from a long-term controlled safety and efficacy trial. The doses evaluated must be at least as high as those shown effective in these studies, or those commonly used to treat spasticity. (b) (4)

(b) (4)

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.*

Ashley Garcia 7/30/10
(signature line for BLA)

Xeomin PMR/PMC Development Template: PMC #5

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

PMR/PMC Description: Clinical trial of Xeomin in botulinum toxin-naïve children with lower extremity spasticity

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	01/31/2012
	Study/Clinical trial Completion Date:	07/31/2016
	Final Report Submission Date:	03/31/2017
	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 study is appropriate for a PMC because the drug will be approved for other indications, (b) (4)

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."

Adequate clinical studies have not yet been conducted to determine the efficacy and appropriate dose of Xeomin for the treatment of lower limb spasticity in pediatrics. The risk is the potential for spread of toxin at doses that may exceed those required for efficacy. Efficacy data are needed in pediatrics for use of Xeomin in treatment of lower limb spasticity as other botulinum toxin products are being used off label in this manner. The "Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology" recommends that "Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children " (***Neurology*® 2008;70:1691–1698).**

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.

Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive children age 2-17 years with lower extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

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.*

Kelly Yasuda 7/30/10
(signature line for BLAs)

Xeomin PMR/PMC Development Template: PMC #6

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

PMR/PMC Description: Clinical trial of Xeomin in botulinum toxin-naïve children with upper extremity spasticity

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	01/31/2012
Study/Clinical trial Completion Date:	07/31/2016
Final Report Submission Date:	03/31/2017
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 study is appropriate for a PMC because the drug will be approved for other indications, (b) (4)

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."

Adequate clinical studies have not yet been conducted to determine the efficacy and appropriate dose of Xeomin for the treatment of upper limb spasticity in pediatrics. The risk is the potential for spread of toxin at doses that may exceed those required for efficacy. Efficacy data are needed in pediatrics for use of Xeomin in treatment of upper limb spasticity as other botulinum toxin products are being used off label in this manner. The "Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology" recommends that "Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children " (***Neurology*® 2008;70:1691–1698).**

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.

> Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive children age 2-17 years with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

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.*

Sally Yasuda

(signature line for ~~BLAs~~)

Xeomin PMR/PMC Development Template: PMC #7

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

PMR/PMC Description: Clinical trial of Xeomin in botulinum toxin-naïve adults with lower extremity spasticity

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	06/30/2011
	Study/Clinical trial Completion Date:	12/31/2014
	Final Report Submission Date:	09/30/2015
	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 study is appropriate for a PMC because the drug will be approved for other indications, (b) (4)

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."

Adequate clinical studies have not yet been conducted to determine the efficacy and appropriate dose of Xeomin for the treatment of lower limb spasticity in adults. The risk is the potential for spread of toxin at doses that may exceed those required for efficacy. Efficacy data are needed in adults for use of Xeomin in treatment of lower limb spasticity as other botulinum toxin products are being used off label in this manner. The "Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology" recommends that "Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children " (***Neurology*® 2008;70:1691–1698).**

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.

Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive adults with lower extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

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.*

Sally Yamben 7/30/10

(signature line for BLAs)

Xeomin PMR/PMC Development Template: PMC #8

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

PMR/PMC Description: Clinical trial of Xeomin in botulinum toxin-naïve adults with upper extremity spasticity

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	03/31/2011
	Study/Clinical trial Completion Date:	09/30/2014
	Final Report Submission Date:	06/30/2015
	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 study is appropriate for a PMC because the drug will be approved for other indications, (b) (4)

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."

Adequate clinical studies have not yet been conducted to determine the efficacy and appropriate dose of Xeomin for the treatment of upper limb spasticity in adults. The risk is the potential for spread of toxin at doses that may exceed those required for efficacy. Efficacy data are needed in adults for use of Xeomin in treatment of upper limb spasticity as other botulinum toxin products are being used in this manner. The "Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology" recommends that "Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children " (***Neurology*® 2008;70:1691–1698).**

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.

Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naïve adults with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

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.*

Sally Yamada 7/30/10

(signature line for BLAs)

Xeomin PMR/PMC Development Template: PMC #9

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

PMR/PMC Description: Clinical trial of Xeomin in botulinum toxin-naïve adults blepharospasm

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	07/31/2011
	Study/Clinical trial Completion Date:	01/31/2016
	Final Report Submission Date:	10/31/2016
	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 study is appropriate for a PMC because the drug will be approved for other indications, (b) (4)

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."

Adequate clinical studies have not yet been conducted to determine the efficacy and appropriate dose of Xeomin for the treatment of blepharospasm in botulinum toxin-naive adults. The risk is the potential for spread of toxin at doses that may exceed those required for efficacy. Efficacy data are needed in adults for use of Xeomin in treatment of blepharospasm in toxin naïve adults, as it will be approved for patients previously treated with botulinum toxin, the only population for whom it has been studied for the treatment of blepharospasm.

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.

Randomized, double-blind, adequate and well controlled, parallel group, clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive adults with blepharospasm. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

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.*

Sally Yamada 7/30/10

(signature line for BLAs)

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

Date:	July 21, 2010
To:	Russell Katz, MD., Director Division of Neurology Products
Through:	Carlos Mena-Grillasca, Team Leader 7/21/10 Denise Toyer, PharmD, Deputy Director 7/21/2010 Division of Medication Error Prevention and Analysis
From:	Walter Fava, R.Ph., Safety Evaluator 7-21-10 Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Xeomin (IncobotulinumtoxinA) for Injection 50 units per vial and 100 units per vial
Application Type/Number:	BLA: 125360
Applicant:	Merz Pharmaceuticals, LLC
OSE RCM #:	2009-1705-1

1 INTRODUCTION

This review responds to a request from the Division of Neurology Products for a review of the revised Xeomin labels and labeling submitted on July 15, 2010, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Licensee. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2009-1705 dated June 11, 2010.

2 MATERIAL REVIEWED

The Licensee provided revised label and labeling on July 15, 2010. We also evaluated the recommendations pertaining to the previous revision in OSE review #2010-1705.

3 DISCUSSION

Review of the revised documents show that the Licensee implemented DMEPA's recommendations under OSE review #2010-1705. The Licensee's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

4 CONCLUSIONS AND RECOMMENDATIONS

The revised label and labeling submitted by the Licensee adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact Laurie Kelley, OSE Project Manager, at 301-796-5068.

5 REFERENCES

OSE Review #2010-1705, Label and Labeling Review for Xeomin (IncobotulinumtoxinA) for Injection. Fava, W: June 11, 2010

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

Date:	July 12, 2010
To:	Russell Katz, MD, Director **Division of Neurology Products (DNP)**
Through:	Claudia Karwoski, Pharm D., Director **Division of Risk Management (DRISK)** 7/12/10
	LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Melissa Hulett, MSBA, BSN, RN Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide),
Drug Name(s):	XEOMIN (incobotulinumtoxinA)
Application Type/Number:	BLA 125360
Applicant/sponsor:	Merz Pharmaceuticals
OSE RCM #:	2009-1464

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Xeomin (incobotulinumtoxinA). DRISK's review of the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) was sent to DNP under separate cover dated June 2, 2010.

Merz Pharmaceuticals submitted BLA 125360 for Xeomin (incobotulinumtoxinA) on July 6, 2009, with the proposed indications for the treatment of cervical dystonia (spasmodic torticollis), benign essential blepharospasm, (b) (4) (b) (4) the current submission is being reviewed for the proposed indications of cervical dystonia (spasmodic torticollis) and blepharospasm. The action date of April 30, 2010 has been extended to July 30, 2010.

Please let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Xeomin (incobotulinumtoxinA) Prescribing Information (PI) submitted September 1, 2009 and revised by the Review Division throughout the current review cycle and received by DRISK on July 6, 2010.
- Draft Xeomin (incobotulinumtoxinA) Medication Guide (MG) submitted on September 1, 2009 and revised by the review division throughout the review cycle and received by DRISK on July 2, 2010.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- 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)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

13 pages withheld immediately following this page as B4 (Draft Labeling)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 28, 2010

TO: Tamy Kim, Regulatory Health Project Manager
Anne Constantino, M. D., Medical Officer
Kenneth Bergmann, M.D., Medical Officer
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125360/0 &125360/1

APPLICANT: Merz Pharmaceutical GmbH.

DRUG: Xeomin (botulinum neurotoxin type A)

NME: Yes, Original BLA

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of patients with cervical dystonia and blepharospasm

CONSULTATION REQUEST DATE: September 1, 2009

DIVISION ACTION GOAL DATE: March 7, 2010/Extended to July 30/2010

PDUFA DATE: May 2, 2010/Extended to July 30/2010

I. BACKGROUND:

The Sponsor, Merz Pharmaceutical GmbH submitted a New Drug Application for the marketing approval of Botulinum Neurotoxin Type A (BoNT/A) for the use in patients with cervical dystonia and blepharospasm.

The results of the following two pivotal studies were submitted in support of the application:

- Protocol MRZ 60201-0408 entitled: "A Prospective, Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial with a Double-Blind, Parallel-Group Extension Period to Investigate the Efficacy and Safety of Different Doses of NT 201 in the Treatment of Cervical Dystonia"; and

- Protocol MRZ 60201-0433 entitled: " A Prospective, Double-Blind, Placebo-Controlled, Randomized, Multi-Center trial with an Open-Label Extension Period to Investigate the Efficacy and Safety of NT201 in the Treatment of Blepharospam";

Additionally, the sponsor submitted results of the following study in support of the application as this study provides safety information on exposure to higher doses of drug, although note that the sponsor is not seeking the spasticity indication currently:

- Protocol MRZ 60201-0410 entitled: "A prospective, Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial with an Open-Label Extension Period to Investigate the Efficacy and Safety of NT 201 in the Treatment of Post-Stroke Spasticity of the upper Limb'.

Study Protocol MRZ- 0408 was a prospective phase 3 clinical trial with a randomized, double-blind, placebo- controlled, parallel group trial multicenter design. Eligible male and female patients over 18 years of age were randomized to one of 3 treatment groups in a balanced ratio 1:1:1 as follows: one group received the NT201 dose of (240U) with matching placebo; one group received the NT201 dose of (120U) with matching placebo; and one group received only placebo.

The primary objective of study Protocol MRZ 0408 was to investigate the efficacy of different doses of NT 210 compared to placebo in patients with cervical dystonia (CD). The main treatment period was up to 20 weeks single injection treatment followed by an extension period of 48 week and safety assessments up to 20 weeks versus placebo.

Study Protocol MRZ – 0433 was a prospective phase 3 clinical trial with a randomized, parallel-group, double-blind, placebo-controlled, multicenter design. Eligible patients were assigned to NT201 group or the placebo group in an approximate ratio of 2:1. Subjects received up to (50U) of NT 201 per eye. The open label period consisted of a treatment section (up to 48 weeks) with a maximum of 5 injection sessions. The duration of the Main period was approximately 20 weeks.

The primary objective of the Main period was to investigate the efficacy and safety of a single injection session of NT 201 compared with placebo in subjects with blepharospasm (BEB) who were previously treated with injections of BOTOX and showed a consistent and satisfactory therapeutic response to BOTOX treatment. The objective of the Open-Label Period Extension was to investigate the safety and efficacy of repeated injections of NT 201 in subjects with BEB over a one-year period.

Study Protocol MRZ 60201-0410 was a prospective, double-blind, placebo-controlled, randomized, multicenter trial with an open extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the upper limb. Eligible patients were assigned to NT201 (IM of 170-400 U; calculated volume of 3.4-8.0 mL [number of injections not to exceed 5 during Open-Label Extension (OLEX) period and a single injection of 170 U for the Main Period]. The Main Period of the trial consisted of a one week screening period and 12 to 20 weeks double-blind period. The open-label extension period consisted of 48 weeks and a safety observation period of 20 additional weeks.

The primary objective of the Main Period was to investigate the efficacy of NT210 versus Placebo in the treatment of spastic wrist flexors in patients with post-stroke spasticity. The primary objective of the OLEX Period was to investigate the efficacy and safety of individually dosed repeated injections of NT 201 over one year in patients with post-stroke spasticity of the upper limb.

The review division requested inspections of four clinical investigators (Protocols MRZ-0408 and MRZ-0433) as data from the two protocols are considered essential to the approval decision. These sites were targeted for inspection due to enrollment of a relatively large number of subjects. This application is an original BLA and therefore was linked to a sponsor inspection. The sponsor, Merz Pharmaceutical GmbH was also inspected to support the application. Study protocol MRZ 60201-0410 was covered during the sponsor inspection as to detect any adverse events at higher doses.

II. RESULTS (by protocol/site):

Name of CI, site # and location	**Protocol and # of subjects**	**Inspection Dates**	**Final Classification**
Paul Cullis, M.D St. John's Hospital and Medical Center 22201 Moross Rd. Ste 380 Detroit, MI 48236	Protocol 60201-0408 Number of subjects listed 14	9/14-24/09	NAI
Alberto Vasquez, M.D. Suncoast Neurosciences Associates Inc. 601 7th St. South St Petersburg, FL	Protocol 60201-0408 Number of subjects listed 27	11/10-16/09	NAI

Name of CI, site # and location	**Protocol and # of subjects**	**Inspection Dates**	**Final Classification**
Stephen Gollomp, M.D. Lankenau Hospital 100 Lancaster Avenue Lankenau Medical Bldg. East Wynnewood, PA 190096-3425	Protocol 60201-0433 Number of subjects listed 17	10/26-28/09	NAI
Joohi Jiminez-Sahed, M.D. Joseph Jankovic, M.D. Parkinson's Disease Ctr. 6550 Fannin, Suite 1801 Houston, Tx 77030	Protocol 60201-0433 Number of subjects listed 26	10/7-9/09	NAI
Merz Pharmaceuticals GmbH Eckenheimer-Landstrasse 100 60318 Frankfurt am Main Germany	Protocol 60291-0410 Number of subjects listed 16	11/9-12/09	NAI

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol MRZ-0408- Cevical Dystonia

1. **Paul Cullis, M.D.**
   Detroit, MI 48236

   a. What Was Inspected: At this site, a total of 15 subjects were screened, and fourteen (14) subjects were randomized and completed the study. Ten (10) subjects received NT201 and four subjects received placebo. There were no deaths reported at this site and one SAE was appropriately reported. Review of Informed Consent Documents, for all records reviewed, verified that subjects signed prior to enrollment.

   A review of the medical records/source documents was conducted. The medical records for 15 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, IRB records, use of concomitant medications, and source documents were compared to case report forms and to data listings, including primary efficacy endpoints and adverse events.

b. General observations/commentary: The medical records reviewed disclosed no adverse findings and no evidence of under reporting of adverse events. No significant violations were noted and a From FDA 483 was not issued.

c. Assessment of Data Integrity: The data generated from Dr. Cullis's site are considered reliable and appear acceptable in support of the application.

2. **Alberto Vasquez, M.D.**
   St. Petersburg, Florida

a. What Was Inspected: At this site, a total of 18 subjects were screened, seven (7) subjects were reported as a screen failure and eleven (11) subjects were randomized and completed the study. There were no deaths or adverse events reported. Review of Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 11 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, inclusion/exclusion criteria, and source documents were compared to data listings for primary efficacy endpoints and adverse events.

b. General Observations/Commentary: Our investigation found no evidence of under reporting of adverse events. No significant violations were noted and a Form FDA 483 was not issued.

The medical records/source document reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data, In general, the records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity
The data from Dr. Vasquez's site are considered reliable and appear acceptable in support of the pending application.

Protocol MRZ-0433-Blepharospasm

3. **Stephen M. Gollomp, M.D.**
   Wynnewood, PA 19096

a. What Was Inspected: At this site, a total of 25 subjects were screened, 19 subjects were reported as screen failures, 6 subjects were randomized into the study and 5 subjects completed the main period study and the open label extension period of the study. Review of Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for six subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria use of concomitant medications, and source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events.

b. General Observations/Commentary: Our investigation found no evidence of under reporting of adverse events. No significant violations were noted and a Form FDA 483 was not issued.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity: The data from Dr. Gollomp's site are considered reliable and appear acceptable in support of the pending application.

4. **Joseph Jancovic, M.D.**
   Houston, TX 77030

   a. **What was Inspected:** At this site, a total of 46 subjects were screened and 7 subjects were randomized and completed the study. Review of Informed Consent Documents, for all subjects reviewed, verified that all subjects signed consent forms prior to enrollment.

      The medical records/source data for 7 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB files, prior and current medications, inclusion/exclusion criteria, the use of concomitant medications, and source documents were compared to case report forms and to data listings for primary efficacy endpoint and adverse events.

   b. **General Observations/Commentary:** The medical records reviewed disclosed no adverse findings that would negatively on the reliability of the data. In general, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

   c. **Assessment of Data Integrity:** The data from Dr. Jancovic's are considered reliable and appear acceptable in support of the pending application.

5. **Merz Pharmaceuticals GmbH.**
   Frankfurt am Main, Germany

   a. **What was Inspected:** The sponsor (Merz) inspection was conducted because NT201 Botulinum Neurotoxin Type A (Zeonim) is an original BLA. The inspection covered the Spasticity (b) (4) that used higher doses of NT 201 in order to detect/uncover any adverse events. The field investigator reviewed the firm's various operating procedures (SOPs) in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program, including the monitoring SOPs.

   The inspection audited Protocol MRZ 60201-0410, entitled "A prospective, double-blind, placebo-controlled, randomized, multicenter trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the upper limb" and focused on two clinical investigators: Dr. Czlonkowska and Dr. Stelmasiak.

   b. **General Observations/Commentary:**

   Anna Czlonkowska, M.D. Poland

   At this site, a total of seven subjects were enrolled. Two subjects at this site received greater than 350 units of the test article. Three subjects received less than 350 units of test article and three subjects received placebo. During the open label period (OLEX), there were five subjects that received greater than 350 units of test article. Our investigation found no adverse findings and no under reporting of adverse events.

   Zbigniew Stelmasiak, M.D. Poland

   At this site, a total of 12 subjects were enrolled. During the main period five subjects received greater than 350 units of test article and one subject received less than 350 unites of test article. Six subjects received placebo. During the OLEX period, eleven subjects received greater than 350units of test article. One subject did not enter the open label phase of the study. Our investigation found no evidence of under reporting of adverse events. No significant violations were noted and a Form FDA 483 was not issued.

   The medical documents and other study related sponsor documents reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data.

   c. **Assessment of Data Integrity:** In general, the records and documents reviewed were found to be in order and verifiable. The data generated appear to be acceptable in support of this application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four domestic clinical investigators were inspected in support of this application. The inspections of Drs. Cullis, Vasquez, Gollomp and Jancovic revealed no significant problems that would adversely impact data acceptability. In addition, the sponsor inspection also did not reveal any significant problems and found no evidence of under reporting of adverse events. Overall, the data submitted from these sites are acceptable in support of the pending application.

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

Date:	June 11, 2010
To:	Russell Katz, MD., Director Division of Neurology Products
Thru:	Carlos M. Mena-Grillasca, R.Ph., Team Leader CMena 6/11/2010 Denise Toyer, Pharm D., Deputy Director Carol Holquist for 6-11-2010 Carol Holquist, R.Ph., Director Carol Holquist 6-11-2010 Division of Medication Error Prevention and Analysis (DMEPA)
From:	Walter Fava, R.Ph., MSEd., Safety Evaluator Walter Fava 6-11-10 Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Xeomin (IncobotulinumtoxinA) for Injection 50 units per vial and 100 units per vial
Application Type/Number:	BLA: 125360
Applicant:	Merz Pharmaceuticals, LLC
OSE RCM #:	2009-1705

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Xeomin (BLA 125360) submitted on January 13, 2010 and March 1, 2010.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling submitted on January 8, 2010. (see Appendices A through K for images).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved upon to provide more optimal presentation for increased understanding and readability. We have provided recommendation to address these areas in sections 3.1 and 3.2 below. If you have further questions or need clarifications, please contact, Laurie Kelley, OSE Project Manager, at 301-796-5068.

3.1 COMMENTS TO THE DIVISION

A. PACKAGE INSERT LABELING

1. ***General Comments***

   a. Revise the abbreviation, 'U' to read 'Units' throughout the package insert. The abbreviation, 'U' is designated as an error-prone abbreviation[1] , as the letter 'u' has been mistaken for the numbers '0' or '4' and has resulted in 10 fold overdoses or greater. In June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations in prescribing. As part of this campaign, FDA agreed not to approve such dangerous abbreviations in their labeling because these abbreviations are carried on to the prescribing practice.

   b. Revise the presentation of all numerical dosing references to include the units of measure. For example, in the Highlights of Prescribing Information under Dosage and Administration, Cervical Dystonia, revise the statement, '...120 (b) (4) U per treatment session', to read '...120 units (b) (4) per treatment session.'

   c. Revise the presentation of the strength/potency throughout the package insert to read, '50 units' or '100 units' as applicable in all tables and text.

2. ***Dosage and Administration Section (2.3)***

   a. Delete the statement, (b) (4) and provide the instructions for reconstitution in this section.

   b. Revise the statement in section 2.3.1, (b) (4) to read, 'Diluent Volumes for Reconstitution of Xeomin are indicated in Table (b) .'

[1] Institute of Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations (2007). Available at http://www.ismp.org/Tools/errorproneabbreviations.pdf.

c. Revise the heading of Table (b) to read, 'Diluent Volumes for Reconstitution of Xeomin'.

d. Revise heading of first column in Table (b) to read 'Volume of Preservative-free 0.9% Sodium Chloride.'

e. Remove trailing zeroes from the volumes listed in first column of Table 2. The use of trailing zeros is error-prone[1] and can result in ten-fold overdoses if the decimal is not seen. In June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone dose designations such as trailing zeros in prescribing. As part of this campaign, FDA agreed not to approve error prone dose designations in labeling because they are carried on to the prescribing practice.

f. Remove the statement (b) (4)

3. ***Handling Section (16.3)***

a. Relocate the second paragraph that reads "An appropriate amount of 0.9% saline solution..." to the Dosage and Administration section (2.3.1) and add the statement 'See Section 2.3 Dosage and Administration for reconstitution instructions.'

b. Revise section 16.3 How Supplied/Storage and Handling to include 'Special Instructions for Disposal' which currently appear on the side panel of the carton.

c. Revise 'Special Instructions for Disposal' to explain how practitioners should autoclave spillage or remove the word spillage from the instructions.

3.2 COMMENTS TO THE LICENSEE

A. CONTAINER LABEL (50 units/vial and 100 units/vial)

1. Revise the presentation of the established name, (b) (4) to read, 'IncobotulinumtoxinA'.
2. Ensure the established name is printed in letters that are of a point size and typeface that is as least as prominent as the point size and typeface used in designating the trade name pursuant to 21 CFR 610.62(b) .
3. Include the dosage form statement following the established and proprietary name statements to read 'for injection'.
4. Relocate the strength/potency statement to appear immediately following the presentation of the tradename/established name presentation.
5. Revise the strength/potency statement, (b) (4) to read, '50 units per vial' and '100 units per vial' respectively.
6. Increase the prominence and readability of the strength/potency statement. As currently presented, the small font size makes it difficult to read.
7. Delete the graphic on the principal display panel to allow room for the prominent presentation of important information.

[1] Institute of Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations (2007). Available at http://www.ismp.org/Tools/errorproneabbreviations.pdf.

8. Increase the differentiation of the two product strengths (e.g. different colors). As currently presented, the 50 units per vial strength is not sufficiently differentiated from the 100 units per vial, which may lead to product strength selection errors.
9. Include the U.S. License number of the product on the label.
10. If space permits, include the statement: 'Single Use Vial. Discard Unused Portion'. Inclusion of this statement may minimize the risk of reuse.
11. If space permits, relocate the route of administration statement to the principal display panel and increase its prominence.

B. CARTON LABELING

1. See comments A1 through A11 and apply to carton labeling.
2. Include the statement, 'Dispense enclosed medication guide to every patient' on the principal display panel.
3. Ensure that enough Medication Guides are included in the multiple vial packaging configurations to be dispensed to each patient.
4. Revise the information on the side panel, (b) (4) to read, 'See Package Insert for Disposal Instructions'.
5. Revise the statement, (b) (4), to read, 'Usual dose: See Package Insert.'

7 pages withheld immediately following this page as B4 (draft labeling)

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

Date:	June 11, 2010
To:	Russell Katz, MD., Director Division of Neurology Products
Thru:	Carlos M. Mena-Grillasca, R.Ph., Team Leader Cmena 6/11/2010 Denise Toyer, Pharm D., Deputy Director Carol Holquist for 6-11-2010 Carol Holquist, R.Ph., Director Carol Holquist 6-11-2010 Division of Medication Error Prevention and Analysis (DMEPA)
From:	Walter Fava, R.Ph., MSEd., Safety Evaluator Walter Fava 6-11-10 Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Xeomin (IncobotulinumtoxinA) for Injection 50 units per vial and 100 units per vial
Application Type/Number:	BLA: 125360
Applicant:	Merz Pharmaceuticals, LLC
OSE RCM #:	2009-1705

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2 METHODS AND MATERIALS

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Our evaluation noted areas where information on the container labels and carton labeling can be improved upon to provide more optimal presentation for increased understanding and readability. We have provided recommendation to address these areas in sections 3.1 and 3.2 below. If you have further questions or need clarifications, please contact, Laurie Kelley, OSE Project Manager, at 301-796-5068.

3.1 COMMENTS TO THE DIVISION

A. PACKAGE INSERT LABELING

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   b. Revise the presentation of all numerical dosing references to include the units of measure. For example, in the Highlights of Prescribing Information under Dosage and Administration, Cervical Dystonia, revise the statement, '...120 (b) (4) U per treatment session', to read '...120 units (b) (4) per treatment session.'

   c. Revise the presentation of the strength/potency throughout the package insert to read, '50 units' or '100 units' as applicable in all tables and text.

2. ***Dosage and Administration Section (2.3)***

   a. Delete the statement, (b) (4) ' and provide the instructions for reconstitution in this section.

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c. Revise the heading of Table (b) to read, 'Diluent Volumes for Reconstitution of Xeomin'.

d. Revise heading of first column in Table (b) to read 'Volume of Preservative-free 0.9% Sodium Chloride.'

e. Remove trailing zeroes from the volumes listed in first column of Table 2. The use of trailing zeros is error-prone[1] and can result in ten-fold overdoses if the decimal is not seen. In June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone dose designations such as trailing zeros in prescribing. As part of this campaign, FDA agreed not to approve error prone dose designations in labeling because they are carried on to the prescribing practice.

f. Remove the statement, [redacted] (b) (4)

3. ***Handling Section (16.3)***

a. Relocate the second paragraph that reads "An appropriate amount of 0.9% saline solution…" to the Dosage and Administration section (2.3.1) and add the statement 'See Section 2.3 Dosage and Administration for reconstitution instructions.'

b. Revise section 16.3 How Supplied/Storage and Handling to include 'Special Instructions for Disposal' which currently appear on the side panel of the carton.

c. Revise 'Special Instructions for Disposal' to explain how practitioners should autoclave spillage or remove the word spillage from the instructions.

Skin Comments

3.2 COMMENTS TO THE LICENSEE

A. CONTAINER LABEL (50 units/vial and 100 units/vial)

1. Revise the presentation of the established name, [redacted] (b) (4) to read, 'IncobotulinumtoxinA'.
2. Ensure the established name is printed in letters that are of a point size and typeface that is as least as prominent as the point size and typeface used in designating the trade name pursuant to 21 CFR 610.62(b) .
3. Include the dosage form statement following the established and proprietary name statements to read 'for injection'.
4. Relocate the strength/potency statement to appear immediately following the presentation of the tradename/established name presentation.
5. Revise the strength/potency statement, [redacted] (b) (4) to read, '50 units per vial' and '100 units per vial' respectively.
6. Increase the prominence and readability of the strength/potency statement. As currently presented, the small font size makes it difficult to read.
7. Delete the graphic on the principal display panel to allow room for the prominent presentation of important information.

Xeomin Label Comments

[1] Institute of Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations (2007). Available at http://www.ismp.org/Tools/errorproneabbreviations.pdf.

8. Increase the differentiation of the two product strengths (e.g. different colors). As currently presented, the 50 units per vial strength is not sufficiently differentiated from the 100 units per vial, which may lead to product strength selection errors.
9. Include the U.S. License number of the product on the label.
10. If space permits, include the statement: 'Single Use Vial. Discard Unused Portion'. Inclusion of this statement may minimize the risk of reuse.
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B. CARTON LABELING

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2. Include the statement, 'Dispense enclosed medication guide to every patient' on the principal display panel. .
3. Ensure that enough Medication Guides are included in the multiple vial packaging configurations to be dispensed to each patient.
4. Revise the information on the side panel [redacted] (b) (4) to read, 'See Package Insert for Disposal Instructions'.
5. Revise the statement [redacted] (b) (4), to read, 'Usual dose: See Package Insert.'

7 pages withheld immediately following this page as B4 (Draft Labeling)

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

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number:	STN 125360/0
Name of Drug:	XEOMIN® (b) (4)
Sponsor:	Merz Pharmaceuiticals GmbH
Material Reviewed:	XEOMIN® (b) (4) Carton and Container Labels
OBP Receipt Date:	February 3, 2009
Original Review Date:	September 21, 2009

EXECUTIVE SUMMARY

The carton and container labels for XEOMIN® (b) (4) were reviewed and found to comply with most of 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 200.100 and United States Pharmacopeia, 12/1/09-10/1/10, USP 32/NF27. Labeling deficiencies were identified and will be communicated to the sponsor for mitigation. Please see comments in the conclusions section.

Background

STN 125360/0 for purified Botulinum Neurotoxin Type A is an original Biologic License Application (BLA) is a peripherally-acting muscle relaxant indicated for cervical dystonia (spasmodic torticollis), and benign essential blepharospasm. The product is supplied as sterile lyophilized in single use vials. The product is available in the following strengths: 50 Units and 100 Units.

Labels Reviewed:

XEOMIN® (b) (4) Container Labels
Vial label-50 Units and 100 Units
XEOMIN® (b) (4) Carton Labels
Single vial- Commercial and Physician Sample
(b) (4)
XEOMIN® (b) (4) Package Insert Label

Submission

Vial Labels

(b) (4)

I. Container

A. 21 CFR 610.60 Container Label

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

a. The proper name of the product [redacted] (b) (4) – is displayed along with the proprietary name XEOMIN®. incobotulinunmtoxinA is the USAN name assigned and should be listed as the proper name. This does not conform to the regulation.

b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. "Manufactured for Merz Pharmaceuticals GmbH, Germany" is listed without a designation for the US License no. This does not conform to the regulation.

c. The lot number or other lot identification – The batch number is located on the container label. This conforms to the regulation. Recommend revising "Batch" to lot number.

d. The expiration date – The expiration date is displayed on the container label. This conforms to the regulation.

e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial. This regulation does not apply.

f. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the label. This conforms to the regulation.

g. 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 – This conforms to the regulation.

2. 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. – The container is enclosed in a package (carton). This section does not apply.

3. 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. – This conforms to the regulation.

4. 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. – This container bears a label.

5. 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. – This conforms to the regulation per CMC visual inspection.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. The NDC number does not conform to 21 CFR 207.35 as a 3-2 or 4-1 Product-Package Code configuration. The NDC configuration appears as, "NDC XXXX-XXXX-XX" This does not conform to the regulation.

C. 21 CFR 201.5 Drugs; adequate directions for use – A reference to the prescribing information is stated as "Read the package leaflet before use." This conforms to the regulation.

D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the trade name and proper name. This conforms to the regulation.

E. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is not a specified biologic and is not regulated 21 CFR 201.10. Placement and prominence will be regulated by 21 CFR 610.62. This regulation does not apply.

F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements ("Rx Only") are prominent and do not overlap. This conforms to the regulation.

G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is listed on the label. This conforms to 21 CFR 610.60.

H. 21 CFR 201.25 Bar code label requirements – Biologicals are exempt from this requirement. This regulation does not apply. There is no bar code on the container label.

I. 21 CFR 201.50 Statement of identity – The proper name, (b) (4) is stated on the label with the trade mark name XEOMIN. The proper name does not conform to the regulation. This does not conform to the regulation.

J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents is not declared on the label. The containers are marked (b) (4) This does not conform to the regulation.

K. 21 CFR 201.55 Statement of dosage – The statement, "Read the package leaflet before use." is listed on the label. This conforms to the regulation.

L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only" and other pertinent information. This does not conform to the regulation. Manufacturer information is not correct.

Carton Label

(b) (4)

6 pages withheld immediately following this page as B4 (Draft Labeling)

II. Carton

A. 21 CFR 610.61 Carton/Package Label –

a. The proper name of the product (b) (4) – is displayed along with the proprietary name XEOMIN®. incobtulinumtoxinA is the USAN name assigned and should be listed as the proper name. This does not conform to the regulation.

b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. "Manufactured for Merz Pharmaceuticals GmbH, Germany" is listed without a designation for the US License no. This does not conform to the regulation.

c. The lot number or other lot identification – The batch number is located on the container label. This conforms to the regulation. Recommend revising "Batch" to "lot number".

d. The expiration date – The expiration date is listed below the lot/batch number on the top panel of the carton. This conforms to the regulation.

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" –The statement "No Preservative" is not displayed on the carton. This does not conform to the regulation.

f. The number of containers, if more than one – (b) (4) Single vial ((b) (4) (b) (4) (b) (4) . This conforms to the regulation. Quantity statements are currently on the back panel, recommend moving quantity statement to primary panel with greater prominence to prevent dispensing errors.

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 – The amount of product is

expressed as [redacted] (b) (4); per container. This does not conform to the regulation.

h. The recommended storage temperature – The statement "Store at room temperature, in a refrigerator, or freezer (-20°C to +25°C; -4°F to +77°F) is displayed on the side panel of the carton. This conforms to the regulation. Recommend revising statement for clarity.

i. The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product –This conforms to the regulation. This conforms to the regulation.

j. The recommended individual dose if the enclosed container(s) is a multiple-dose container –This conforms to the regulation.

k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement "For intramuscular use only" is located on the side panel of the carton. This conforms to the regulation. Recommend relocating route of administration to the primary panel.

l. Known sensitizing substances, or reference to enclosed circular containing appropriate information –"1.0 mg human albumin" and "Free from Complexing Proteins" are listed on back the panel. This conforms to the regulation.

m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.

n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, the list of all inactive ingredients must be in alphabetical order. - Inactive ingredients are listed on the back panel of the carton, however the ingredients are not is alphabetical order. This does not conform to the regulations.

o. The adjuvant, if present –None present. This conforms to the regulation.

p. The source of the product when a factor in safe administration –This conforms to the regulation.

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. – Clostridium Botulinum is not listed. This does not conform to the regulation.

(b) (4)

s. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is not located on the carton. This conforms to the regulation.

t. If a Medication Guide is required under part 208 of this 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 – This does not conform to the regulation.

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)]* – This product is not a "specified" biological product. The placement and prominence of the Proper and Tradename does not meet the regulation. This does not conform to the regulation.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown –This regulation does not apply.

D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or 'Marketed by _____". The qualifying phrases may be abbreviated. –no distributor is listed. This regulation does not apply.

E. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.

F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This conforms to the regulation.

G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the front panel of the carton. The NDC number does not conform to 21 CFR 207.35 as a 4-2 Product-Package Code configuration. This does not conform to the regulation.

H. 21 CFR 201.5 Drugs; adequate directions for use – The label states "Read the package leaflet before use." This conforms to the regulation.

I. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the trademark and proper name. This conforms to the regulation.

J. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is not exempt from 610.62. This regulation does not apply.

K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements ("Rx Only") are prominent and do not overlap. This conforms to the regulation.

L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the batch number on the carton label. This conforms to 21 CFR 610.60 and 21 CFR 201.17.

M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.

N. 21 CFR 201.50 Statement of identity – The proper name, (b) (4) is stated on the label with the trade mark name XEOMIN. The proper name does not conform to the regulation. This does not conform to the regulation.

O. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents is not declared on the label. The containers are marked (b) (4) This does not conform to the regulation.

P. 21 CFR 201.55 Statement of dosage –The statement [redacted] (b) (4) is listed on the label. This does not conform to the regulation. Recommend the statement, "Usual dosage: See Package Insert."

Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only" and other pertinent information. This does not conform to the regulation.

Conclusions

The following deficiencies and recommendations were noted in the review of the Xeomin® container and carton labels.

1. Carton label
   a. Please add the statement, "No Preservative" to comply with 21 CFR 610.61(e).

   b. Per USPC Official 12/1/09-10/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of the inactive ingredients in alphabetical order in the following format:
      inactive ingredient (amount)

   c. The number of containers, if more than one are listed on the carton per 21 CFR 610.61(f), please consider moving the quantity statements (number of containers) to the bottom of the primary panel.

   d. Please add a statement indicating the microorganism origin used as a source for the product per 610.61(q).

2. Carton and Container
   a. Please revise the statement '[redacted] (b) (4)' to "Usual dosage: See Package Insert." to comply with 21 CFR 201.5, adequate directions for use.

   b. The recommended storage temperature is listed in the following format, [redacted] (b) (4). consider revising to following consistent format "Store at room temperature, in a refrigerator, or freezer at -20° to 25°C (-4° to 77°F).

   c. Please revise the NDC configuration to a 3-2 or 4-1 Product- Package code format per 21 CFR 201.2 and 21 CFR 207.35(b)(3).

d. Please revise the proper name from [redacted] (b) (4) to the assigned USAN name, "incobotulinumtoxinA" to comply with 21 CFR 610.60 and 610.61.

e. Per 601.2, this product does not meet the criteria as a specified category biologic and is not exempt from 610.62. Please revise position, placement and prominence of the proper name and trade name to comply with 610.62 (a-c). *See recommended format

f. Please revise the dosage form from [redacted] (b) (4) to "For Injection" to comply with the United States Pharmacopeia 12/1/09-10/1/10, USP 32/NF27, General Chapter, Injection <1>, Nomenclature and Definitions. * See recommended format below.

g. Please revise the presentation of strength from [redacted] (b) (4) to "XX Units" per the United States Pharmacopeia, 12/1/09-10/1/10, USP 32/NF27, General Chapter, Injection <1>, "STRENGTH AND TOTAL VOLUME FOR SINGLE-AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS" and 21 CFR 201.55 (g).
* See recommended format below

h. Revise the statement, [redacted] (b) (4) to two separate statements, "Single-Use Vial" and "For Intravenous Infusion only after dilution".

* Recommended format:

IncobotulinumA
XEOMIN®
For Injection

XX units/ vial

For Intramuscular Use
Single-use vial; Discard unused portion

i. Please revise the manufacturer information per 21 CFR 600.3(t) and include the U.S. License Number per 21 CFR 610.60(a)(2) and 21 CFR 610.61(b). Recommended format:

Manufactured by:
Merz Pharmaceuticals GmbH,
Street Address
Germany
US Lic. No. XXXX

2. Patient Package Insert

a. Please revise the presentation of strength from [redacted] (b) (4) to "XX Units" per the United States Pharmacopeia, 12/1/09-10/1/10, USP 32/NF27, General Chapter, Injection <1>, "STRENGTH AND TOTAL VOLUME FOR SINGLE-AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS" and 21 CFR 201.55 (g).

b. Please revise the display "U" to "Units" to comply with the Institute for Safe Medication Practices "List of Error Prone Abbreviations, Symbols and Dose Designations."

c. Please revise the "DESCRIPTION" section to include the identity of the microorganism used in manufacture per 21 CFR 201.57(c)(12)(C) and 21 CFR 610.61(q).

d. Please add the route of administration to the "DESCRIPTION" section per 21 CFR 201.57(c)(12)(B).

e. Please revise the "How Supplied" section to include package configurations and corresponding NDC numbers for each strength that will be marketed. Unmarketed configurations should not be listed in the label. Consider the following format:

Package	Xeomin 50 Units	Xeomin 100 Units
single vial pack	NDC	NDC
[redacted] (b) (4)		

f. Please revise temperature designations to the recommended format X to X°C (Y to Y°F).

g. Please revise the statemen[redacted] (b) (4) statement to "May be stored in a refrigerator at 2-8°C (36-46°F) for up to 24 hours."

6/22/10

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

6/23/10

Ennan Guan, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP

6-27-10

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125360	NDA Supplement #:S- BLA STN # 125360/0 (b) (4) 125360/1 (cervical dystonia); (b) (4) (blepharospasm)	Efficacy Supplement Type SE-
Proprietary Name: Xeomin Established/Proper Name: Botulinum neurotoxin type A Dosage Form: lyophilized powder for Injection Strengths: 50 LD (50) units, lyophilized powder for Injection & 100 LD (50) units, lyophilized powder for Injection		
Applicant: Merz Agent for Applicant (if applicable): James Kenimer (CEO, Biologics Consulting Group, Inc.)		
Date of Application: 7/1/09 Date of Receipt: 7/2/09 Date clock started after UN:		
PDUFA Goal Date: 1/1/10 (b) (4) Priority review)	Action Goal Date (if different): 1/1/10	
Filing Date: 8/31/09 Date of Filing Meeting: 8/5/09		
Chemical Classification: (1, 2, 3 etc.) (original NDAs only) BLA		
Proposed Indication(s): (b) (4) 125360 (b) (4) Cervical Dystonia 125360 (b); Blepharospasm 125360 (b)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: *Refer to Appendix A for further information.*	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	X Standard – for cervical dystonia & blepharospasm X Priority – (b) (4) ☐ Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review X Orphan Designation for cervical dystonia indication	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]	

☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): (b) (4); Cervical dystonia is IND 12,821; Blepharospasm is IND 100,163	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☐ YES X NO – I asked RMS_BLA coordinator to correct cervical dystonia date.
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☐ YES X NO – Working with RMS-BLA coordinator to get these entered.
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☐ YES X NO – Working with RMS-BLA coordinator to get these entered.
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES X NO X YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES ☐ NO
User Fee Status **Comments:**	X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***	☐ YES ☐ NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments:**	☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? *(NDAs/NDA efficacy supplements only)* *Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not required.* **Comments:**	☐ YES # years requested: ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use *(NDAs only)*: Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? *If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/ERB.*	☒ Not applicable ☐ YES ☐ NO

505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	X Not applicable
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. 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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. 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))?	☐ YES ☐ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**: Patent Information 3542a and patent certification not included since this is a biologic. Filed copy certification does not apply since this is a biologic. The sponsor is requesting a waiver on all pediatric studies for all age groups in blepharospasm and cervical dystonia. (b) (4)	X YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	X YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	X YES ☐ NO ☐ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	X YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	X YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☐ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	X YES ☐ NO

Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..." **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (*applies to paper submissions only*) *If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.*	☐ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments:**	X YES ☐ NO
Pediatrics	
PREA *Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments:**	☐ Not Applicable X YES (Waiver is included for cervical dystonia and blepharospasm). (b) (4) ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? *If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).* **Comments:**	☐ YES ☐ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use X MedGuide – this is mentioned but I do not see it. X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? *If no, request in 74-day letter.* **Comments:**	X YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? *If no, request in 74-day letter.* **Comments:**	X YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	X YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	☐ Not Applicable X YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	☐ Not Applicable X YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☐ Not Applicable X YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not Applicable** X Outer carton label X Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) X Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	X YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	X YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	X YES Date(s): 10/12/04; 4/22/05 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	X YES Date(s): 12/12/08 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☐ YES Date(s): ☐ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8/5/09

NDA/BLA #: 125360

PROPRIETARY/ESTABLISHED NAMES: Xeomin

APPLICANT: Merz Pharma

BACKGROUND:
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Tamy Kim	Y
	CPMS/TL:	Eric Bastings/Dave Podskalny	
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Suhail Kasim (b) (4) Anne Constantino	
	TL:		
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:		
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☐ YES ☐ NO

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** **If no, for an original NME or BLA application, include the reason. For example:** o **this drug/biologic is not the first in its class** o **the clinical study design was acceptable** o **the application did not raise significant safety or efficacy issues** o **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**	☐ YES Date if known: X NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☐ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☐ YES ☐ NO ☐ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)**	☐ YES ☐ NO ☐ YES ☐ NO

FACILITY (BLAs only) **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority:

GRMP Timeline Milestones:

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☐ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.