

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125360

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

A#: 125360 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: DNP PDUFA Goal Date: _____ Stamp Date: 7/2/2009
4/30/2010

Proprietary Name: Xeomin
Established/Generic Name: _____ (b) (4)
Dosage Form: Injection
Applicant/Sponsor: Merz Pharmaceuticals GmbH

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) none
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Cervical Dystonia

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

.nis page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Benign Essential Blepharospasm**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

 Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Action C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Chi, Bo

From: CDER-TB-EER
Sent: Wednesday, May 19, 2010 4:28 PM
To: Chi, Bo; Hughes, Patricia
Cc: Pohlhaus, Timothy; CDER-TB-EER
Subject: Final TB-EER response for STN 125360/0, drug substance and drug product

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for Merz Pharmaceuticals, LLC's STN 125360/0. Please see below for individual facility compliance statuses. There are no pending or ongoing compliance actions to prevent approval of this BLA.

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 3218
Silver Spring, MD 20993
Phone - (301) 796-5224

From: Chi, Bo
Sent: Thursday, May 13, 2010 5:34 PM
To: CDER-TB-EER
Cc: Hughes, Patricia
Subject: FW: TB-EER for 125360/0, drug substance and drug product

Hi, please provide TB-EER for the following sites for Merz's new BLA STN125360/0. The PDUFA date is August 1, 2010. All the memos are due on June 1 according to GRMP. Thanks.

Bo

1. Drug substance and drug product manufacturing site:
Merz Group Services GmbH
Site Dessau
Am Pharmapark 15A
D-06861 Dessau-Rosslau
Germany
FEI 3006896175

Inspected November 5-13, 2009 by CDER-DMPQ and classified VAI. The inspection was conducted in support of STN 125360/0 (Xeomin, botulinum neurotoxin type A, NT201) and covered drug substance and drug product manufacturing.

2. Analytical testing site of drug substance and ELISA testing site for drug product:
Merz Pharmaceutircals GmbH
Hermannswerder Haus 15
D-14473 Potsdam
Germany
FEI 3007501745

Inspected February 2-4, 2010 by IOG and classified NAI. Control testing responsibilities for Xeomin

were covered.

3. Microbiological testing of drug substance and and general analytical and stability testing site for drug product:

(b) (4)
[Redacted]

Inspected (b) (4) by CDER-DMPQ and classified VAI. The inspection was conducted in support of STN 125360/0 (Xeomin, botulinum neurotoxin type A, NT201) and covered packaging, testing laboratory, warehouse, media and buffer preparation, and visual inspection.

4. LD50 assay testing of drug substance and drug product:

(b) (4)
[Redacted]

Inspected (b) (4) by CDER-DMPQ and classified VAI. Control testing responsibilities for Xeomin were covered and are acceptable.

5. Stability testing of drug substance:

(b) (4)
[Redacted]

Because this site is not conducting testing on the commercial product, no evaluation is necessary.

6. Master and working cell bank preparation:

(b) (4)
[Redacted]

Evaluation of this site is not necessary. The recipient of materials produced at this site is responsible for ensuring material quality.

7. Product release:

Merz Pharmaceuticals LLC
4215 Tudor Lane
Greensboro, NC 27410
FEI 1012187.

Evaluation of this site is not necessary for approval of this BLA.

**FDA TELECONFERENCE:
MERZ NT-201 FOR BLEPHAROSPASM AND CERVICAL DYSTONIA
MEETING MINUTES**

MEETING DATE: 30 APRIL 2010

TIME: 2:00PM EDT

TELECONFERENCE PARTICIPANTS:

MERZ:

[REDACTED]

Dr. T. Wagner	Vice President Technical Operations
Dr. M. Pfeil	Director API Manufacturing NT101
U. Held	Director Drug Product Manufacturing NT201
Dr. E. Post	Production Technical Services / Microbiology
Dr. P. Stach	Section Head Quality Operations (b)(4) Dessau
Dr. F. Weiler	Section Head Quality Control Dessau
Dr. T. Stibora	Quality Operations Dessau
M. Watzl	Manager Global Drug Regulatory Affairs
Dr. B. Hardas	Vice President & Head, US Research & Development
David Lin, Ph.D.	BCG, CMC Sr. Consultant
Kelly Reich	BCG, Project Manager

FDA:

[REDACTED]

Ellis Unger, MD	Office Deputy Director
Dave Podskalny, MD	Medical Officer, DNP
Kenneth Bergman, MD	Medical Officer, Internal Medicine, DNP
Raymond Brown	Consumer Safety Officer, Office of Compliance
Patricia Hughes	Lead Consumer Safety Officer, Office of Compliance
Bo Chi	Microbiologist
Vandna Kishore, RPh	Project Manager

1. Agenda:

- **CMC Request dated 4/23**
 - **Timing for response**
 - **Clarification of question 8b as this was not understood by Merz as a commitment**

- **CMC Request dated 3/22, due 5/15**
 - **Timing for response for items 3 and 4**
 - **Regarding responses to questions 1 and 2: Merz to provide an update on the plan and the work already done in terms of container closure integrity**

testing and revalidation of the crimping machine and to discuss the timing of submission of validation data

2. Discussion:

- **CMC Request dated 4/23**
 - **Timing for response**

Regarding CMC Request dated 4/23 Merz will provide a response by 5/14.

- **Clarification of question 8b as this was not understood by Merz as a commitment**

Text of 8b: Please provide an update on the completion of these following commitments: Submit microbiological data supporting a (b) (4) for bioburden samples stored at 2-8°C.

(b) (4)

(b) (4) Does FDA want to

see validation data from bioburden samples?

FDA said there was inconsistency in BLA regarding recovery results. Samples immediately assayed for bioburden versus those stored at 2-8. Generally we do not ask for supporting data for less than (b) (4) at 2-8C but we are asking because of discrepancy in recoverability of organisms.

Merz explained discrepancy observed in BLA was on sample material that is not usually withdrawn for analysis and was analyzed by a former contractor located (b) (4) away which created a problem during transportation of material. Merz is no longer using that contract lab and now uses (b) (4) whose QC building is (b) (4) from building where sample material is withdrawn.

FDA: FDA understands the problem so requested that Merz summarize briefly in the response.

- **CMC Request dated 3/22, due 5/15**
 - **Timing for response for items 3 and 4**

Merz intends to submit response by 5/15.

- **Regarding responses to questions 1 and 2: Merz to provide an update on the plan and the work already done in terms of container closure integrity**

testing and revalidation of the crimping machine and to discuss the timing of submission of validation data

Merz committed to container closure integrity testing based on a validated method. FDA had concerns regarding insufficient sensitivity of the original method used. Merz needs to re-validate crimping machine first to comply with FDA concern. Merz began searching for a capable CRO in February and had difficulty identifying a CRO who was familiar with the test. Currently working with CRO in (b) (4) but development of the method is taking longer than originally expected.

Merz found only 1 article with information on the test but found the article slightly unclear so reproducing the results of the article has been a challenge. Merz has observed a shift in sensitivity due to the diameters of microtubes. In addition, reproducibility needs to be increased.

FDA asked if Merz was tied to this lab. The test FDA has requested is a relatively routine test and Merz should not have a problem finding a CRO to conduct a microbial ingress test. There is quite a bit of literature on the microbial ingress test.

Merz explained that the timing might not be predictable at the moment as it depends on the results of the next experiments. Merz asked whether the data on this method could be provided to FDA post-approval?

FDA wants a date when the method can be provided. FDA requires this test from all manufacturers of sterile product that is packaged using a vial or syringe. FDA is currently encouraging for example a dye ingress test which correlates to the microbial ingress test on stability to ensure the integrity of the container closure system.

Merz has a validated method for dye-ingress test. But to conduct that tests with microbes and different pressures is a challenge.

FDA is willing to accept the method as a post-marketing commitment but will need some idea of the submission timeframe.

Merz will explain the difficulties in developing a sensitive and reproducible test method along with a proposed date for this post-marketing commitment with the May 15th response.

FDA wants Merz to include the proposed month and year and how the method will be submitted. FDA recommended a CBE-30 or CBE-0 supplement.

Merz asked FDA for their advice regarding a US CRO capable of performing the requested test.

FDA will provide published references and recommended that Merz seek advice from consultants that can provide more information.

Discussion with Raymond Brown regarding PAI issues:

Letter from 4/28 included issues with validation of methods. Mid-next week Merz will provide summary of issues raised to update status. Merz plans to do endotoxin and bioburden testing but need to implement changes to the validation protocols. Merz will send validation protocols to FDA at the end of next week.

Due to uniqueness of product, Merz manufactures (b) (4) per year. Therefore, Merz has planned (b) (4) (b) (4)



BLA 125360/0

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merz Pharmaceuticals GmbH
c/o Biologics Consulting Group, Inc.
1317 King Street
Alexandria, Virginia 22314

APR 05 2010

ATTENTION: James G. Kenimer, PhD
CEO, Biologics Consulting Group, Inc.

Dear Dr. Kenimer:

Please refer to your Biologics License Application (BLA) dated July 2, 2009, received July 2, 2009, submitted under section 351 of the Public Health Service Act, for Clostridium Botulinum Neurotoxin Type A, for Injection 50 units and 100 units.

We also refer to your January 8, 2010, correspondence, received January 8, 2010, requesting review of your proposed proprietary name, Xeomin. We have completed our review of the proposed proprietary name, Xeomin and have concluded that it is acceptable.

The proposed proprietary name, Xeomin, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your January 8, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact Vandna Kishore, the Office of New Drugs (OND) Regulatory Project Manager, at (301) 796-4193.

Sincerely,

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

3/25 - sent to team

Kishore, Vandna N

From: Fava, Walter
Sent: Thursday, March 25, 2010 12:28 PM
Kishore, Vandna N
Cc: Mena-Grillasca, Carlos; Kelley, Laurie; Fava, Walter
Subject: Proprietary name review for BLA 125360 Xeomin

Good Afternoon Vandna,

This email is to notify you that the Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed proprietary name, Xeomin (incobotulinumtoxinA), is acceptable from a look-alike and sound-alike perspective. In addition, our evaluation did not identify any other factors that render the name unacceptable at this time. Our decision is based upon the information submitted by the Applicant, DDMAC's promotional evaluation, DNP's initial comments, and DMEPA's safety evaluation.

Although we did identify orthographic similarity between the proprietary names Yasmin and Xeomin, our analysis determined that differentiating product characteristics such as dosage form (tablet vs injectable), route of administration (oral vs intramuscular), frequency of administration (once a day vs every 3 months), strength (3 mg/30 mcg vs 50 units or 100 units), and units of measure (milligrams vs units), will minimize the potential for confusion that may contribute to medication errors. We would appreciate the review division's feedback regarding this look-alike name pair.

Please share this information with the Xeomin review team. If the review team believes the name is unacceptable based upon other factors (e.g. clinical, chemistry), please forward the concern and provide rationale.

Given the OSE PDUFA timelines associated with this proprietary name review, we ask that you respond to the request within 7 days of the receipt of this communication so that we can finalize our review. We are willing to meet with the division to discuss, if needed.

Thanks,
Walter

CDR Walter L. Fava, R.Ph.
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Bldg. 22 Room 4410
301-796-2264
FAX: 301-796-9835



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL [125360/0 & 125360/1]

EXTENSION USER FEE GOAL DATE

Merz Pharmaceuticals
Attention: James Kenimer, Ph.D.
President & CEO, Biologics Consulting Group, Inc.
1317 King Street
Alexandria, VA 22314

FEB 23 2010

Dear Dr. Kenimer:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Xeomin® (NT 201, Clostridium botulinum Neurotoxin Type A).

We received your February 5, 2010 amendment to this application on February 5, 2010 and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to provide time for a full review of the amendment.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Vandna Kishore, at (301) 796-4193.

Sincerely,

Russell Katz, M.D. **FEB 23 2010**
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Kishore, Vandna N

From: Lewis, David B
Sent: Thursday, February 04, 2010 2:24 PM
To: Kishore, Vandna N
Subject: FW: What is the status of (b) (4) (a botulinum toxin Type A material from Merz)?
Attachments: (b) (4) incobotulinumtoxinA 12.30.09.doc

The name incobotulinumtoxinA was adopted in December of 2009. Attached is the USAN adoption statement. I g

David Lewis

From: Stephanie Shubat [mailto:Stephanie.Shubat@ama-assn.org]
Sent: Thursday, February 04, 2010 2:22 PM
To: Lewis, David B
Cc: Gail Karet
Subject: RE: What is the status of (b) (4) (a botulinum toxin Type A material from Merz)?

David, (b) (4) was adopted in December 2009. Attached is a copy of the statement and letter.

Stephanie

From: Lewis, David B [mailto:David.Lewis@fda.hhs.gov]
Sent: Thursday, February 04, 2010 12:33 PM
To: Stephanie Shubat; Gail Karet
Subject: What is the status of (b) (4) (a botulinum toxin Type A material from Merz)?

Has either of the names been adopted?

Thanks,

David Lewis

Kishore, Vandna N

From: Kerin Ablashi [kablashi@bcg-usa.com]
Sent: Monday, February 01, 2010 11:34 AM
To: Kishore, Vandna N
Cc: kreich@bcg-usa.com
Subject: RE: Xeomin USAN name update
Attachments: emfinfo.txt

*Kim Rains -
OBP Labeling re: Merz*

Dear Vandna,

Merz has received electronic notification from the USAN, but still doesn't have official notification. Merz has amended their PI & REMS and will redo the 356h with the USAN in the "Established name" section.

Should we send these along now or wait until the hardcopy letter has been received? Will these updates be sufficient or will additional documentation be sent? If so, what else will be needed?

Thank you very much for all of your help.

Best wishes,

-Kerin

*David Lewis - sent 2/1/10
L. D. Lewis -
FDA rep for
USAN*

From: Kishore, Vandna N [mailto:Vandna.Kishore@fda.hhs.gov]
Sent: Wednesday, January 27, 2010 8:31 AM
To: kablashi@bcg-usa.com
Cc: kreich@bcg-usa.com
Subject: RE: Xeomin USAN name update

Hi Kerin,

Don't worry, I'm new to the BLA world myself. From what I gather, an Amendment to the Xeomin BLA is exactly what would take place once you hear from USAN. You can actually submit the letter you receive from them.

Also, you need to amend the pending BLA including labels/labeling (PI, Medguide if it exists, carton/container labels, etc). You should also update your REMS. We would also expect to see a revised 356h since that is the legal document and the name has changed.

Hope this helps,

Vandna

From: Kerin Ablashi [mailto:kablashi@bcg-usa.com]
Sent: Tuesday, January 26, 2010 12:20 PM
To: Kishore, Vandna N
Cc: kreich@bcg-usa.com
Subject: RE: Xeomin USAN name update

Dear Vandna,

Merz said that the week of 11 Jan, Merz Pharmaceuticals GmbH (Germany) heard from Merz USA in Greensboro, NC that they adopted "**incobotulinumtoxinA**" in December and that they will receive the official paperwork soon. To our knowledge the official letter has not yet been received by Merz in Greensboro or in Germany.

Please forgive me, I am new to this part of the process, so I have a few questions. When notifying the FDA about the USAN decision, should we submit an Amendment to the Xeomin BLA (125,360) containing the revised PI and REMS? Does the Amendment need to include additional documents? If so, please specify which documents you would like to be included so that we may give you everything you need.

Thank you very much for your assistance.

-Kerim

From: Kishore, Vandna N [mailto:Vandna.Kishore@fda.hhs.gov]
Sent: Wednesday, January 20, 2010 1:57 PM
To: kreich@bcg-usa.com
Cc: kablashi@bcg-usa.com
Subject: RE: Xeomin USAN name update

Hi Kerin,

I wanted to follow up on the status of the USAN established name submission status. Have you heard further after the last email below?

Please provide an update after following up on this issue.

Kindly,
Vandna

From: Kelly Reich [mailto:kreich@bcg-usa.com]
Sent: Thursday, November 19, 2009 3:35 PM
To: Kim, Tamy
Cc: Kishore, Vandna N
Subject: RE: Xeomin

Dear Tamy,

1. **Tradename proposal** – In early October Merz was seeking an independent analysis of the name Xeomin. The name review application document is near completion with the exception of the analysis documents mentioned. Once Merz receive these documents, they do not anticipate needing more than a week to get them submitted to the BLA. So in summary they have not submitted their tradename proposal to FDA yet.
2. **USAN name** – the USAN Council confirmed receipt of the Merz name submission October 8, 2009. Merz has not received any correspondence from the USAN Council since that letter.

(b) (4)

2/1/2010

(b) (4)

Please let me know if you need any additional information.

Kind regards,
Kelly

~~~~~  
*Kelly H. Reich, M.S.*

Associate  
Biologics Consulting Group, Inc.  
1317 King Street  
Alexandria, VA 22314  
USA  
P (703) 739-5695  
F (703) 548-7457  
[kreich@bcg-usa.com](mailto:kreich@bcg-usa.com)

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**From:** Kim, Tamy [<mailto:Tamy.Kim@fda.hhs.gov>]  
**Sent:** Thursday, November 19, 2009 2:52 PM  
**To:** [kreich@bcg-usa.com](mailto:kreich@bcg-usa.com)  
**Cc:** Kishore, Vandna N  
**Subject:** Xeomin

Hi Kelly,

Can you let me know what the status of the following items are?:

1. Tradename proposal
2. USAN name

(b) (4)

Thanks,  
Tamy

**Tamy Kim, PharmD**  
*Senior Regulatory Project Manager*  
*Division of Neurology Products*  
*Food and Drug Administration*  
*Phone: 301-796-1125*  
*Email: [tamy.kim@fda.hhs.gov](mailto:tamy.kim@fda.hhs.gov)*

**Kishore, Vandna N**

*sent  
to team  
1/22/10*

**From:** Kelley, Laurie  
**Sent:** Friday, January 22, 2010 10:50 AM  
**To:** Kishore, Vandna N  
**Cc:** Fava, Walter; Mena-Grillasca, Carlos  
**Subject:** Proprietary Name Submission BLA 125360

*Amendment #16*

Hello Vandna,

OSE has received a submission for a proposed proprietary name: Xeomin

Submission Date: 01/08/2010  
Stamp Date: 01/08/2010  
Proposed Proprietary Name: Xeomin  
Established Name: [REDACTED] (b) (4)  
Application Type/Number: 125360  
Mid-Review Date: 02/22/2010  
OSE PDUFA Date: 05/02/2010  
DMEPA Safety Evaluator: Walter Fava  
DMEPA Team Leader: Carlos Mena-Grillasca

DDMAC does not have any promotional issues with this name. We realize it is early in your application review cycle, but OSE would like to hear any preliminary concerns your review team may have with the proposed proprietary name at this time. Also, please keep us informed of any emerging issues that may affect our name review as you review the application. As our timeframes are short, **please send us any preliminary comments within 7 days.**

*Done*

Thanks...Laurie

*No issues - told Laurie  
w/ DNDP*

Laurie Kelley, PA-C  
Safety Regulatory Project Manager  
CDER, Office of Surveillance and Epidemiology  
10903 New Hampshire Ave.  
Bldg. 22, Rm 4435  
Silver Spring, MD 20993  
Phone: 301-796-5068  
Email: laurie.kelley@fda.hhs.gov

**Kishore, Vandna N**

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**From:** Kim, Tamy  
**Sent:** Friday, January 08, 2010 3:07 PM  
**To:** Kelley, Laurie; Kishore, Vandna N  
**Subject:** RE: request for proprietary name for NT 201 (Xeomin) (BLA 125360)

FYI, Vandna. When the submission comes in, you'll want to forward this to Laurie so the tradename review starts ASAP.



Thanks,  
Tamy

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**From:** Kerin Ablashi [mailto:kablashi@bcg-usa.com]  
**Sent:** Friday, January 08, 2010 12:06 PM  
**To:** Kim, Tamy; Kelley, Laurie  
**Cc:** kreich@bcg-usa.com  
**Subject:** request for proprietary name for NT 201 (Xeomin) (BLA 125360)

Dear Tamy and Laurie,

As you may know, Kelly Reich will be starting her maternity leave tomorrow. While she is out, I will be managing Merz LLC's BLA 125360.

Please note that the request for proprietary name review for Merz's NT 201 (Xeomin) product was submitted today via the Gateway, as amendment 0016 to BLA 125360.

Please let me know if you have any questions.

Best wishes,

-Kerin

*Kerin L. Ablashi*  
Consultant  
Biologics Consultant Group, Inc.  
[kablashi@bcg-usa.com](mailto:kablashi@bcg-usa.com)  
Phone/fax: 240-683-0007

December 30, 2009

(b) (4)

Re: NT 201

Bhushan Hardas, MD, MBA  
Vice President, US Research & Development  
Merz Pharmaceuticals LLC  
4215 Tudor Lane  
Greensboro, NC 27410

Dear Dr. Hardas,

I am pleased to inform you that the USAN Council has adopted the name ***incobotulinumtoxinA*** as the USAN for NT 201.

Please review the USAN information on the enclosed adoption statement for accuracy, initial, and return the statement to me within 60 days of the date listed above. After March 1, 2010, the information on ***incobotulinumtoxinA*** will be scheduled for posting on the USAN Web site ([www.ama-assn.org/go/usan](http://www.ama-assn.org/go/usan)). At the same time, the information on ***incobotulinumtoxinA*** will be submitted to the United States Pharmacopeial Convention, Inc., for publication in the *USP Dictionary of USAN and International Drug Names*.

You may mail, fax, or e-mail any changes regarding the publication of ***incobotulinumtoxinA*** to me any time before March 1, 2010.

Sincerely,

Stephanie C. Shubat, M.S.  
Director, USAN  
USAN Council Secretary

enclosure: N09/129

December 30, 2009

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (b) (4)

incobotulinumtoxinA

PRONUNCIATION

in" koe bot u line' um tox in A

THERAPEUTIC CLAIM

Treatment of (b) (4) cervical dystonia,  
benign essential blepharospasm (b) (4)  
(b) (4)

CHEMICAL NAMES

- 1.) Botulinum Toxin A
- 2.) highly purified Botulinum neurotoxin type A (free from complexing proteins)

STRUCTURAL FORMULA

(b) (4)



(page 2 adoption of incobotulinumtoxinA cont.),

The processed protein consists of a light chain (b) (4) and a heavy chain (b) (4), linked by a disulphide bridge between the (b) (4) of the precursor protein (b) (4) of the heavy chain).

MOLECULAR FORMULA

Light Chain:

Heavy Chain:

(b) (4)

MOLECULAR WEIGHT

150 kD

TRADEMARK

Xeomin®;

(b) (4)

MANUFACTURER

Merz Pharmaceuticals GmbH

CODE DESIGNATION

NT 201

CAS REGISTRY NUMBER

93384-43-1

scs



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**Memorandum of Meeting**

**Date:** December 1, 2009; 3pm-4pm

**To:** File BLA 125360/0 cervical dystonia  
125360/1 blepharospasms

**Re:** Mid cycle Meeting 12/1/09

---

**Sponsor:** Merz Pharma. Action Date 4/30/10

**Product:** Xeomin (NT201) Botulinum Neurotoxin Type A in the treatment of  
cervical dystonia and blepharospasms

---

**Notes taken by:** C. Michaloski, RPM, covering for V. Kishore (covering for T. Kim)  
*C. Michaloski 2/23/10*

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**Summary Minutes:**

**The meeting content was the summary of issues from individual reviewers.**

**The issues are as follows.**

**Mid cycle Summary of Issues**

- 1. BMT Drug Product Micro Review**
  - Need more information on the container closure integrity test
  - Need more information on the sterile filter validation study
  - Shipping of the drug product has not been validated
  
- 2. Summary Chemistry**

- DP contaminated with impurities that generate a second cleavage fragment of SNAP-25. CMC information request regarding DP contamination has been sent to Merz
- Additional information request to be sent:
  - 1) Provide general safety test results
  - 2) Provide stability data on DP (b) (4) human serum albumin
- Inspectional issues need to be addressed
- The General Safety test must be implemented as a release test for drug product.

Both #1 and #2 have sent information requests to Sponsor.

3. **DMPQ issues: Please see attached- First 3 slides are inspection issues; last 2 slides are the review issues**
4. **CMC Presentation Attached (last 3 slides are the summary slides)**
5. **Also the following CMC questions were sent to the sponsor.**

CMC microbiology information request for BLA STN125360/0:

Drug Product

1. The microbial challenge test (container closure integrity test) used (b) (4) glass vials (Appendix 3.2.P.2-5). According to information provided at the pre-license inspection, Xeomin drug product uses (b) (4) vials. Please clarify if the vials for Xeomin were used in the microbial challenge test for container closure integrity. In addition, please provide the sensitivity (leak size) of the microbial challenge test.
2. It was discovered during the pre-license inspection that the crimping machine was qualified using a non-validated dye ingress test. Please validate a dye ingress test with adequate sensitivity and re-qualify the crimping machine. Information and summary data of the dye ingress test validation and crimping machine qualification should be provided.
3. In your responses (10/27/2009 amendment) to FDA question #8, you provided information on the methylene blue test you will use for your stability samples. Please evaluate the adequacy of the challenge (applying vacuum to vials with negative pressure for 10 minutes) by providing sensitivity of the methylene blue test. In addition, if the dye ingress test used for stability samples is different from the test used to re-qualify the crimping machine, summary validation data for the dye ingress test used for stability samples should be provided.

4. An in-process bioburden limit (b) (4) is necessary to ensure that bioburden in the bulk solution prior to any filtration steps is under control. Please set up an in-process bioburden limit (b) (4). The sucrose (b) (4) prior to be used in DP formulation to ensure microbiological quality of the DP.

5. With regard to the microbial retention validation studies of the (b) (4), please clarify that the worst-case process conditions (e.g., pressure, product-membrane contact time, volume processed, temperature) were used in the scale-down simulation study. If the worst-case process conditions were not used in the validation studies, please revalidate the microbial retention study to include the worse-case process conditions.

6. Please provide summary data for sterilization (b) (4) validation of the (b) (4). In addition, provide the auditing frequency of sterilization dose and bioburden on the (b) (4), (b) (4)

7. With regard to the provided shipping validation study protocol (Merz-VP-061), (b) (4)

In addition, please clarify if a growth promotion study will be conducted on media-filled-vials used in container closure integrity tests after the shipments. Please update the BLA on shipping validation summary data.

8. Provide information and summary data for the qualification of the bioburden test for the formulated bulk drug substance (b) (4)

**Attached slides**

**CMC**

**DMPQ**

## **Kishore, Vandna N**

---

**From:** Kim, Tamy  
**Sent:** Thursday, November 19, 2009 2:26 PM  
**To:** Kelley, Laurie  
**Cc:** Kishore, Vandna N  
**Subject:** Xeomin Tradename Review

Hi Laurie,

Just checking on whether you have been corresponding with the sponsor about getting in their proposed Tradenames for review. Before you know it, the PDUFA date will be here, so I wanted to check the progress on this.

Please note, that while I'm on detail (starting 11/23/09), Vandna Kishore will be covering this project.

Thanks,  
Tamy

**Tamy Kim, PharmD**  
*Senior Regulatory Project Manager*  
*Division of Neurology Products*  
*Food and Drug Administration*  
*Phone: 301-796-1125*  
*Email: [tamy.kim@fda.hhs.gov](mailto:tamy.kim@fda.hhs.gov)*

## Kishore, Vandna N

---

**From:** Kim, Tamy  
**Sent:** Thursday, November 19, 2009 2:32 PM  
**To:** Podskalny, Gerald  
**Cc:** Bergmann, Kenneth; Constantino, Anne; Kishore, Vandna N  
**Subject:** Xeomin FW: Xeomin Tradename Review

FYI, Dave and team. Before I go on detail, there are some things that I wanted to point out to you.

1. The sponsor has not yet proposed a formal tradename for review for OSE, so I just reminded Laurie to follow-up on this since OSE now has responsibility for this.

2. Also, the sponsor applied for a USAN name and I am not sure if USAN approved the established name yet. I'll check with them before I go.

3. Xeomin is a part of a pilot project for PeRC and they are suppose to set up an initial meeting with the reviewers to go over PeRC materials and then set up the PeRC meeting. They have the PeRC materials, but haven't set up any meeting yet. Ken is following up with them on this.

4. The GRMP calculator is in the eRoom with due dates and dates that the labeling/PMRs/REMS comments need to go to the sponsor (some of these dates are also in the mtg notices):

[http://eroom.fda.gov/eRoom/CDER9/DivisionofNeurologicalProducts/0\\_4109](http://eroom.fda.gov/eRoom/CDER9/DivisionofNeurologicalProducts/0_4109).

Thanks,  
Tamy

---

**From:** Kim, Tamy  
**Sent:** Thursday, November 19, 2009 2:26 PM  
**To:** Kelley, Laurie  
**.c:** Kishore, Vandna N  
**Subject:** Xeomin Tradename Review

Hi Laurie,

Just checking on whether you have been corresponding with the sponsor about getting in their proposed Tradenames for review. Before you know it, the PDUFA date will be here, so I wanted to check the progress on this.

Please note, that while I'm on detail (starting 11/23/09), Vandna Kishore will be covering this project.

Thanks,  
Tamy

**Tamy Kim, PharmD**  
*Senior Regulatory Project Manager*  
*Division of Neurology Products*  
*Food and Drug Administration*  
*Phone: 301-796-1125*  
*Email: tamy.kim@fda.hhs.gov*

**Kishore, Vandna N**

---

**From:** Kelly Reich [kreich@bcg-usa.com]  
**Sent:** Thursday, November 19, 2009 3:35 PM  
**To:** Kim, Tamy  
**Cc:** Kishore, Vandna N  
**Subject:** RE: Xeomin  
**Attachments:** emfinfo.txt

Dear Tamy,

1. **Tradename proposal** – In early October Merz was seeking an independent analysis of the name Xeomin. The name review application document is near completion with the exception of the analysis documents mentioned. Once Merz receive these documents, they do not anticipate needing more than a week to get them submitted to the BLA. So in summary they have not submitted their tradename proposal to FDA yet.
2. **USAN name** – the USAN Council confirmed receipt of the Merz name submission October 8, 2009. Merz has not received any correspondence from the USAN Council since that letter.

(b) (4)

Please let me know if you need any additional information.

Kind regards,  
Kelly

~~~~~  
Kelly H. Reich, M.S.

Associate
Biologics Consulting Group, Inc.
1317 King Street
Alexandria, VA 22314
USA
P (703) 739-5695
F (703) 548-7457
kreich@bcg-usa.com

From: Kim, Tamy [mailto:Tamy.Kim@fda.hhs.gov]
Sent: Thursday, November 19, 2009 2:52 PM
To: kreich@bcg-usa.com
Cc: Kishore, Vandna N
Subject: Xeomin

Hi Kelly,

Can you let me know what the status of the following items are?:

11/20/2009

1. Tradename proposal

2. USAN name

(b) (4)

Thanks,
Tamy

Tamy Kim, PharmD

Senior Regulatory Project Manager

Division of Neurology Products

Food and Drug Administration

Phone: 301-796-1125

Email: tamy.kim@fda.hhs.gov

(b) (4)

From: Kelly Reich [mailto:kreich@bcg-usa.com]
Sent: Thursday, November 19, 2009 3:35 PM
To: Kim, Tamy
Cc: Kishore, Vandna N
Subject: RE: Xeomin

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(b) (4)

Please let me know if you need any additional information.

Kind regards,
Kelly

Kelly H. Reich, M.S.
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Alexandria, VA 22314

11/20/2009

USA
P (703) 739-5695
F (703) 548-7457
kreich@bcg-usa.com

From: Kim, Tamy [<mailto:Tamy.Kim@fda.hhs.gov>]
Sent: Thursday, November 19, 2009 2:52 PM
To: kreich@bcg-usa.com
Cc: Kishore, Vandna N
Subject: Xeomin

Hi Kelly,

Can you let me know what the status of the following items are?:

1. Tradename proposal
2. USAN name
 (b) (4)

Thanks,
Tamy

Tamy Kim, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Food and Drug Administration
Phone: 301-796-1125
Email: tamy.kim@fda.hhs.gov



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125360/0
BL 125360/1

FILING ISSUES
September 14, 2009

Merz Pharmaceuticals GmbH
In care of: James G. Kenimer, PhD
CEO Biologics Consulting Group, Inc.
1317 King Street
Alexandria, VA 22314

Dear Dr. Kenimer:

Please refer to your biologics license application (BLA), dated July 1, 2009, received July 2, 2009, submitted under section 351 of the Public Health Service Act, for Xeomin (botulinum neurotoxin type A). Also refer to our filing letter dated August 31, 2009. While conducting our filing review we identified the following potential review issues:

1. Some studies (including MRZ-60201-0003) appear to have been scanned and cannot be searched for key words. Please ensure that the text of all final study reports are searchable.
2. The analysis datasets for the Cervical Dystonia clinical trials 60201-0408/1, 60201-0408/2 and Blepharospasm trials 60201-0433/1, 60201-0433/2 lack sufficient information that relates the data tables to the total dose of Xeomin subjects received at individual visits, adverse event and to demographic information.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

We also request that you submit the following information:

1. Revised analysis datasets for pivotal clinical trials for the Blepharospasm and Cervical Dystonia indications in a format that will facilitate independent analysis by the Division's clinical reviewers. Please see the attached request for revised SAS Transport Files (shell tables) for efficacy and safety analysis data sets for studies supporting both the

Blepharospasm (60201-0433/1 and 2) and Cervical Dystonia (60201-0408/1 and 2) applications.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Tamy Kim, PharmD, Senior Regulatory Project Manager, at (301) 796-1125.

Sincerely,



/Russell Katz/
Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

BLA 125360/1 Xeomin

Trial MRZ 60201- 0433 (Blepharospasm) dataset request

To the Sponsor:

This is a request for datasets to be provided in a particular structure that will make review efficient and timely. Please create the files, and the variables in them, using the names supplied in the tables below.

The requested dataset files that describe demographics for the double blind and open label portions of the trial (named **DMDB.xpt** and **DMOLEX.xpt**, respectively) are typical SDTM format with one row per subject. The datasets that describe adverse events for the double blind and open label portions of the trial (named **AEDB.xpt** and **AEOLEX.xpt**, respectively) are typical SDTM format with one row per AE. Most of the key variable names in these tables will also appear familiar to users of SDTM.

The other requested datasets provide a particular structure for the outcome variables of interest in the double blind and open label portion of the trial. Note that it is one line per subject with all visits for that subject occupying the same row. In the open label datasets, depending upon how many additional Xeomin treatments the subject received in that extension period, not all cells will be filled.

Provide days, dates, units, etc in a format that may be used for calculation in SAS. The same format should be used in all the requested tables. For each of the 13 requested files, provide a definition table indicating from which of your eCTD datasets each variable's data was taken including the source filename and source variable name. Provide this in .xml format.

A. In a file named **DMDB.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of this trial. In this file, there should be just 1 row for each subject.

STUDYID	602 0433/1
USUBJID	A unique identifier for each patient in this trial. The identifier should be the same for each patient in both the double blind and open label portions of the trial. We ask that it be used in all datasets we request (at this time and in future requests).
SITE	Site number
INVNAME	Principal investigator's last name
AGE	Age in years
GENDER	Gender (M or F)
ARM	NT201 or PCB
ITTPOP	Patient is in ITT Population (Y/N)
NAIVE	Received other BoNT within 1 year of enrollment in 4033 (Y/N)

B. In a file named **DMOLEX.xpt**, create a dataset which includes the following variables for all patients in the open label extension portion of this trial. In this file, there should be just 1 row for each subject.

STUDYID	602 0433/2
USUBJID	A unique identifier for each patient in this trial. The identifier should be the same for each patient in both the double blind and open label portions of the trial. We ask that it be used in all datasets we request (at this time and in future requests).
SITE	Site number
INVNAME	Principal investigator's last name
AGE	Age in years
GENDER	Gender (M or F)

C. In a file named **AEDB.xpt**, create a dataset which includes the following variables for all patients in only the double blind portion of the trial: The table should appear that for a given patient (USUBJID) each AE has a unique sequence number (AESEQ); one AE per row.

STUDYID	602 0433/1
USUBJID	Unique patient identifier
AESEQ	Number each AE consecutively for each patient
ARM	NT201 or PCB
AETERM	Verbatim description of AE
AEDECOD	Preferred Term
AEBODSYS	SOC
AESEV	AE severity (mild/moderate/severe)
AEOUT	Resolved (Y/N)
DISCONT	Patient discontinued from trial (Y/N) due to AE
LATENCY	Number of days after injection that AE began
DURATION	Duration of AE (in days)
AESER	AE seriousness criteria

D. Create a file named AEOLEX.xpt which includes the following variables for all patients in only the open label blind portion of the trial. The table should appear that for a given patient (USUBJID) each AE has a unique sequence number (AESEQ); one AE per row.

STUDYID	602 0433/2
USUBJID	Unique patient identifier
AESEQ	Number each AE consecutively for each patient
AETERM	Verbatim description of AE
AEDECOD	Preferred Term
AEBODSYS	SOC
AESEV	AE severity (mild/moderate/severe)
AEOUT	Resolved (Y/N)
DISCONT	Patient discontinued from trial (Y/N)
LASTINJ	Date of the open label injection after which AE began
RTEYE	Units of NT201 injected around RIGHT eye at this injection session
LEFTEYE	Units of NT201 injected around LEFT eye at this injection session
BOTHEYES	Units of NT201 injected around BOTH eyes at this injection session
LATENCY	Number of days after injection that AE began
DURATION	Duration of AE in days
AESER	AE seriousness criteria

E. In a file named **DBJRSSEV.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602 0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTPOP	Patient is in ITT Population (Y/N)
RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
JRSS2	JRS Severity score at baseline (Visit 2)
DATEV3	Date of Visit 3
JRSS3	JRS Severity score at Visit 3
DATEV4	Date of Visit 4
JRSS4	JRS Severity score at Visit 4
DATEV5	Date of Visit 5
JRSS5	JRS Severity score at Visit 5
JRSSDIFF	JRS Severity change from baseline to Visit 5
V2V5INT	Number of days between Visit 2 injection and Visit 5

F. In a file named **DBJRSFRQ.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602 0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTPOP	Patient is in ITT Population (Y/N)
RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
JRSF2	JRS Frequency Score at baseline (Visit 2)
DATEV3	Date of Visit 3
JRSF3	JRS Frequency Score at Visit 3
DATEV4	Date of Visit 4
JRSF4	JRS Frequency Score at Visit 4
DATEV5	Date of Visit 5
JRSF5	JRS Frequency Score at Visit 5
JRSFDIFF	JRS Frequency change from baseline to Visit 5
V2VSINT	Number of days between Visit 2 injection and Visit 5

G. In a file named **DBJRSBDI.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602 0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTOP	Patient is in ITT Population (Y/N)
RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
BDI2	BDI baseline score at Visit 2
DATEV3	Date of Visit 3
BDI3	BDI score at Visit 3
DATEV4	Date of Visit 4
BDI4	BDI score at Visit 4
DATEV5	Date of Visit 5
BDI5	BDI score at Visit 5
BDIDIFF	BDI change from baseline to Visit 5
V2V5INT	Number of days between Visit 2 injection and Visit 5

H. In a file named **DBJRSCGI.xpt**, create a dataset which includes the following variables for all patients in the double blind portion of the trial:

STUDYID	602 0433/1
USUBJID	Unique patient identifier
SITE	Site number
INVNAME	Principal investigator's last name
ARM	NT201 or PCB
ITTPOP	Patient is in ITT Population (Y/N)
RTEYE	Number of units of NT201 injected around RIGHT eye
LEFTEYE	Number of units of NT201 injected around LEFT eye
BOTHEYES	Number of units of NT201 injected around BOTH eyes
DATEBL	Date of baseline visit (Visit 2)
DATEV3	Date of Visit 3
PNEED3	Patient feels need for injection at Visit 3 (Y/N)
INEED3	Investigator feels need for injection at Visit 3 (Y/N)
V2V3INT	Number of days between Visit 2 injection and Visit 3
DATEV4	Date of Visit 4
PNEED4	Patient feels need for injection at Visit 4 (Y/N)
INEED4	Investigator feels need for injection at Visit 4 (Y/N)
V2V4INT	Number of days between Visit 2 injection and Visit 4
V2INJINT	Number of days between Visit 2 and follow-up injection, if performed
DATEV5	Date of Visit 5
PNEED5	Patient feels need for injection at Visit 5
INEED5	Investigator feels need for injection at Visit 5
V2V5INT	Number of days between Visit 2 injection and Visit 5
PEGR5	PEGR at Visit 5
IGAE5	Investigator global assessment of efficacy (1-4) at Visit 5
IGAT5	Investigator global assessment of tolerability (1-4) at Visit 5

I. In a file named **OLBONT.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602 0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
RTEYE1	Number of units of NT201 injected around RIGHT eye 1st open label injection
LEFTEYE1	Number of units of NT201 injected around LEFT eye 1st open label injection
BOTHEYE1	Number of units of NT201 injected around BOTH eyes 1st open label injection
V6V7INT	Days from 1st open label injection session until Control Visit (Visit7)
V6V8INT	Days from 1st open label injection session until Visit 8
V8DATEOL	Date of 2nd open label injection session (Visit 8)
RTEYE2	Number of units of NT201 injected around RIGHT eye 2nd open label injection session
LEFTEYE2	Number of units of NT201 injected around LEFT eye 2nd open label injection session
BOTHEYE2	Number of units of NT201 injected around BOTH eyes 2nd open label injection session
V8V9INT	Days from 2nd open label injection session until Control Visit (Visit 9)
V8V10INT	Days from 2nd open label injection session until Visit 10
V10DATE	Date of 3rd open label injection session (Visit 10)
RTEYE3	Number of units of NT201 injected around RIGHT eye 3rd open label injection session
LEFTEYE3	Number of units of NT201 injected around LEFT eye 3rd open label injection session
BOTHEYE3	Number of units of NT201 injected around BOTH eyes 3rd open label injection session
V10V11INT	Days from 3rd open label injection session until Control Visit (Visit 11)
V10V12NT	Days from 3rd open label injection session until Visit 12
V12DATE	Date of 4th open label injection session (Visit 12)
RTEYE4	Number of units of NT201 injected around RIGHT eye 4th open label injection session

LEFTEYE4	Number of units of NT201 injected around LEFT eye 4th open label injection session
BOTHEYE4	Number of units of NT201 injected around BOTH eyes 4th open label injection session
V12V13NT	Days from 4th open label injection session until Control Visit (Visit 13)
V12V14NT	Days from 4th open label injection session until Visit 14
V14DATE	Date of 5th open label injection session (Visit 14)
RTEYE5	Number of units of NT201 injected around RIGHT eye 5th open label injection session
LEFTEYE5	Number of units of NT201 injected around LEFT eye 5th open label injection session
BOTHEYE5	Number of units of NT201 injected around BOTH eyes 5th open label injection session
V14V15NT	Days from 5th open label injection session until Control Visit (Visit 15)
V16DATE	Date of termination visit (Visit 16)
V14V16NT	Days from 5th open label injection session until Termination Visit (Visit 16)
V6V16NT	Days from 1st open label injection session until Termination Visit (Visit 16)

J. In a file named **OLJRSSEV.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602 0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
JRSS1	JRS Severity score at 1st open label injection session
V7DATEOL	Date of 1st open label injection session Control Visit (Visit7)
JRSS1C	JRS Severity score at 1st open label injection session Control Visit
V8DATEOL	Date of 2nd open label injection session (Visit 8)
JRSS2	JRS Severity score at 2nd open label injection session
V9DATEOL	Date of 2nd open label injection session Control Visit (Visit 9)
JRSS2C	JRS Severity score at 2nd open label injection session Control Visit
V10DATE	Date of 3rd open label injection session (Visit 10)
JRSS3	JRS Severity score at 3rd open label injection session
V11DATE	Date of 3rd open label injection session Control Visit (Visit 11)
JRSS3C	JRS Severity score at 3rd open label injection session Control Visit
V12DATE	Date of 4th open label injection session (Visit 12)
JRSS4	JRS Severity score at 4th open label injection session
V13DATE	Date of 4th open label injection session Control Visit (Visit 13)
JRSS4C	JRS Severity score at 4th open label injection session Control Visit
V14DATE	Date of 5th open label injection session (Visit 14)
JRSS5	JRS Severity score at 5th open label injection session
V15DATE	Date of 5th open label injection session Control Visit (Visit 15)
JRSS5C	JRS Severity score at 5th open label injection session Control Visit
TERMDATE	Date of termination visit (Visit 16)
JRSS6	JRS Severity score at termination visit

K. In a file named **OLJRSFRQ.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602 0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
JRSF1	JRS Frequency Score at 1st open label injection session
V7DATEOL	Date of 1st open label injection session Control Visit (Visit7)
JRSF1C	JRS Frequency Score at 1st open label injection session Control Visit
V8DATEOL	Date of 2nd open label injection session (Visit 8)
JRSF2	JRS Frequency Score at 2nd open label injection session
V9DATEOL	Date of 2nd open label injection session Control Visit (Visit 9)
JRSF2C	JRS Frequency Score at 2nd open label injection session Control Visit
V10DATE	Date of 3rd open label injection session (Visit 10)
JRSF3	JRS Frequency Score at 3rd open label injection session
V11DATE	Date of 3rd open label injection session Control Visit (Visit 11)
JRSF3C	JRS Frequency Score at 3rd open label injection session Control Visit
V12DATE	Date of 4th open label injection session (Visit 12)
JRSF4	JRS Frequency Score at 4th open label injection session
V13DATE	Date of 4th open label injection session Control Visit (Visit 13)
JRSF4C	JRS Frequency Score at 4th open label injection session Control Visit
V14DATE	Date of 5th open label injection session (Visit 14)
JRSF5	JRS Frequency Score at 5th open label injection session
V15DATE	Date of 5th open label injection session Control Visit (Visit 15)
JRSF5C	JRS Frequency Score at 5th open label injection session Control Visit
TERMDATE	Date of termination visit (Visit 16)
JRSF6	JRS Frequency Score at termination visit

L. In a file named **OLBDL.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602 0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
V6DATEOL	Date of 1st open label injection session (Visit 6)
BDI1	BDI score at 1st open label injection session
V7DATEOL	Date of 1st open label injection session Control Visit (Visit 7)
BDI1C	BDI score at 1st open label injection session Control Visit
V8DATEOL	Date of 2nd open label injection session (Visit 8)
BDI2	BDI score at 2nd open label injection session
V9DATEOL	Date of 2nd open label injection session Control Visit (Visit 9)
BDI2C	BDI score at 2nd open label injection session Control Visit
V10DATE	Date of 3rd open label injection session (Visit 10)
BDI3	BDI score at 3rd open label injection session
V11DATE	Date of 3rd open label injection session Control Visit (Visit 11)
BDI3C	BDI score at 3rd open label injection session Control Visit
V12DATE	Date of 4th open label injection session (Visit 12)
BDI4	BDI score at 4th open label injection session
V13DATE	Date of 4th open label injection session Control Visit (Visit 13)
BDI4C	BDI score at 4th open label injection session Control Visit
V14DATE	Date of 5th open label injection session (Visit 14)
BDI5	BDI score at 5th open label injection session
V15DATE	Date of 5th open label injection session Control Visit (Visit 15)
BDI5C	BDI score at 5th open label injection session Control Visit
TERMDATE	Date of termination visit (Visit 16)
BDI6	BDI score at termination visit

M. In a file named **OLCGI.xpt**, create a dataset which includes the following variables for all patients in only the open label portion of the trial:

STUDYID	602 0433/2
USUBJID	Unique patient identifier
INJNUM	Number of NT201 injections patient received in open label period
PEGROL2	PEGR at 2nd open label injection session
PEGROL3	PEGR at 3rd open label injection session
PEGROL4	PEGR at 4th open label injection session
PEGROL5	PEGR at 5th open label injection session
PEGROLT	PEGR at termination visit
IGAEOL2	Investigator global assessment of efficacy (1-4) at 2nd open label injection session
IGAEOL3	Investigator global assessment of efficacy (1-4) at 3rd open label injection session
IGAEOL4	Investigator global assessment of efficacy (1-4) at 4th open label injection session
IGAEOL5	Investigator global assessment of efficacy (1-4) at 5th open label injection session
IGATOL2	Investigator global assessment of tolerability (1-4) at 2nd open label injection session
IGATOL3	Investigator global assessment of tolerability (1-4) at 3rd open label injection session
IGATOL4	Investigator global assessment of tolerability (1-4) at 4th open label injection session
IGATOL5	Investigator global assessment of tolerability (1-4) at 5th open label injection session



DEPARTMENT OF HEALTH AND HUMAN SERVICES

**Food and Drug Administration
Silver Spring MD 20993**

Our STN: BL 125360/0
BL 125360/1

FILING COMMUNICATION
August 31, 2009

Merz Pharmaceuticals GmbH
In care of: James G. Kenimer, PhD
CEO Biologics Consulting Group, Inc.
1317 King Street
Alexandria, VA 22314

Dear Dr. Kenimer:

This letter is in regard to your biologics license application (BLA), dated July 1, 2009, received July 2, 2009, submitted under section 351 of the Public Health Service Act, for Xeomin (botulinum neurotoxin type A).

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today for the blepharospasm and cervical dystonia indications. The review classification for this application and these indications is Standard. Therefore, the user fee goal date is May 2, 2010. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

[REDACTED] (b) (4)
[REDACTED]. We have changed STN 125360/0 to be assigned to the cervical dystonia indication and STN 125360/1 to the blepharospasm indication for administrative purposes. [REDACTED] (b) (4)
[REDACTED].

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before September 14, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If

major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 23, 2010.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients (birth to 16 years). Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Tamy Kim, PharmD, Senior Regulatory Project Manager, at (301) 796-1125.

Sincerely,



/Russell Katz/
Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125360	NDA Supplement # BLA STN # /0 cervical dystonia /1 blepharospasm	If NDA, Efficacy Supplement Type:
Proprietary Name: Xeomin Established/Proper Name: incobotulinumtoxinA Dosage Form: injection		Applicant: Merz Pharmaceuticals GmbH Agent for Applicant (if applicable): Biologics Consulting Group
RPM: Kishore		Division: Neurology Products
<p>NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>8/1/2010</u> 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		X None
<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>Application Characteristics ²</p> <p>Review priority: X Standard <input type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch</p> <p><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch</p> <p><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)</p> <p><input type="checkbox"/> Restricted distribution (21 CFR 314.520)</p> <p>Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR</p> <p><input type="checkbox"/> Submitted in response to a PMC</p> <p><input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>		
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input checked="" type="checkbox"/> Yes, dates 072910</p>	
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>	
<p>Public communications (<i>approvals only</i>)</p>		
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p>X Yes <input type="checkbox"/> No</p>	
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p>X Yes <input type="checkbox"/> No</p>	
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input checked="" type="checkbox"/> None HHS Press Release</p> <p><input type="checkbox"/> FDA Talk Paper</p> <p><input type="checkbox"/> CDER Q&As</p> <p><input type="checkbox"/> Other</p>	

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each **paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP on 07/30/10
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	072910
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	070109
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 6/18/10

Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	072910
<ul style="list-style-type: none"> Original applicant-proposed labeling 	070109
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	071410
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	Cond. Acceptable Ltr: 4/5/2010 Review: 4-5-2010
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input type="checkbox"/> DMEPA 6-11-2010 <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	Reg. Filing Rev. 8-??-2009 draft OBP Filing Rev.: 8/5/2009 Clin. Filing Rev.: 8/31/2009 P/T Filing Rev.: 8/5/2009
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes X No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>030710</u> If PeRC review not necessary, explain: _____ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included 7-2-2009
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Filing Communication: 8/31/09 Filing Issues Letter: 9/14/2009 PDUFA Ext. Letter: 2/23/2010 Teleconference: 4-30-2010
❖ Internal memoranda, telecons, etc.	Mid-cycle Mtg: 12/1/09 5-19-2010 5-20-2010
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	X No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	X N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 073010
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 072510
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 072810
PMR/PMC Development Templates (9))	<input type="checkbox"/> None 073010
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	072910
• Clinical review(s) (<i>indicate date for each review</i>)	June 2010 Constantino Cervical Dystonia 6-21-2010-Safety Review 7-2-2010 7-14-2010
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	072910 final <input type="checkbox"/> None 6-12-2010 6-18-2010
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Letter: 11/25/2009 Letters: 2/1/2010 (2) Letter: 2/24/2010 Letter: 3/31/2010 Summary: 6-28-2010
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 060710
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 060710
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	See Primary Review 070110
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	See Primary Review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Signed but undated:
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 072910
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	X None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 072810
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 072810
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 072810
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	X None requested

Product Quality <input type="checkbox"/> None	
Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 071610
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7-30-2010 (DRAFT)
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed June 7, 2010 June 11, 2010 June 11, 2010
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: 07/29, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.