APPLICATION NUMBER:

125274

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

NDA/BLA#: 125286 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DDDP PDUFA Goal Date: 1/12/09 Stamp Date: 3/14/2008

Proprietary Name: Reloxin

Established/Generic Name: botulinum toxin type A

Dosage Form: Pellet for reconstitution

Applicant/Sponsor: Ipsen

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(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):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: RELOXIN® is a neurotoxin indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients ≤ 64 years of age.

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.)

ction 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)

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

ıe: 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]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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).

ıeffective 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.

ːtion 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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: _____

'ote: 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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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)

e: 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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.

This 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.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # BLA # 125274/1 (Formerly 125286)	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Dysport Established/Proper Name: abobotulinumtoxinA Dosage Form:		Applicant: Ipsen Biopharm Agent for Applicant (if applicable): Biomeasure
RPM: Tamika White		Division: Division of Dermatology and Dental Products

NDAs: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	4/13/09
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ 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.

Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	12/10/08
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☒ Yes, date 4/9/09
BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☒ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: 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.*	☒ No ☐ Yes If, yes, NDA/BLA #, and date exclusivity expires:
• (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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• 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.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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)*).*	☐ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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). *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action: AP Date: 4/29/09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	4/29/09
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	4/29/09
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	4/28/09
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM OBP 4/14/09 ☐ DMEPA ☐ DRISK ☒ DDMAC 4/16/09; 4/20/09 ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	4/24/09; 4/21/09; 9/22/08
Administrative / Regulatory Documents	
Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	4/21/09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☐ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	4/10/09

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	4/16/09
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	Letters: 1/6/09; 5/22/08; 5/13/08 Faxes/e-mails: 11/15/08; 9/29/08; 9/5/08;
❖ Internal memoranda, telecons, etc.	11/12/08
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 9/17/07
• EOP2 meeting *(indicate date)*	☐ No mtg 1/8/04
• Other (e.g., EOP2a, CMC pilot programs)	Meeting after RTF: 3/4/08 CMC/Facility EOP2: 4/29/04 Teleconference: 4/2/09
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None pending
Division Director Summary Review *(indicate date for each review)*	☐ None 3/24/09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	3/4/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See page 80 of Clinical Review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See page 11 of Clinical Review
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☐ None OSE Review: 3/31/09 OSE Addendum: 4/15/09 REMS Memo: 4/29/09 REMS Documents: 4/29/09
DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Review: 12/1/08; Letter 11/24/08; Letter

[5] Filing reviews should be filed with the discipline reviews.

	11/24/08
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 11/21/08
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/3/08
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 4/17/09
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 2/4/09; Memo 4/16/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 3/18/09
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None 12/17/08 (Reference is made to BLA 125274/0)
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	4/3/09; 12/17/08 (2 Reviews completed for BLA 125274/0) ☐ Not needed
Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Chemistry Review (3/18/09), page 139
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: 6/2-6/10/08 ☒ Acceptable (Reference to 125274/0) ☐ Withhold recommendation Date completed: 4/1/09 ☐ Requested ☒ Accepted ☐ Hold

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125286 Product: Botulinum Toxin Type A Applicant: Ipsen

Final Review Designation (circle one) (Standard) Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date 4/28/08 Committee Recommendation (circle one) (File) RTF

RPM: [signature] 4/21/09
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ✓ Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): Emnan Guan / Michelle Clark-Stuart
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): Jill Merrill
  - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Tapash Ghosh Jang Ik-Lee Kathleen Finksch
- ☐ Memo of Filing Meeting Denise Cook

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed ❑ including list of all establishment sites and their registration numbers ❑ If foreign applicant, US Agent signature.	(Y) N (Y) N (Y) N	
Comprehensive Table of Contents	Y (N)	
Debarment Certification with correct wording (see * below)	(Y) N	
User Fee Cover Sheet	(Y) N	
User Fee payment received	(Y) N	
Financial certification &/or disclosure information	(Y) N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	
Pediatric rule: study, waiver, or deferral	(Y) N	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	(Y) N (Y) N (Y) N (Y) N Y (N) (Y) N (Y) N Y N Y N Y (N) (Y) N	N/A N/A

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y) N	
❑ legible	(Y) N	
❑ English (or translated into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
❑ summary reports reference the location of individual data and	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
records □ protocols for clinical trials present □ all electronic submission components usable (e.g. conforms to published guidance)	Y (N) (Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	N/A
if CMC supplement: □ description and results of studies performed to evaluate the change □ relevant validation protocols □ list of relevant SOPs	Y N Y N Y N	N/A
if clinical supplement: □ changes in labeling clearly highlighted □ data to support all label changes □ all required electronic components, including electronic datasets (e.g. SAS)	Y N Y N Y N	N/A
if electronic submission: □ required paper documents (e.g. forms and certifications) submitted	Y (N)	Electronically signed documents in the eCTD

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? NO

Does this submission relate to an outstanding PMC? NO

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: N/A
- Dates: N/A

Recommendation (circle one): File RTF

RPM Signature: Branch Chief concurrence:

White, Tamika

From: steve.scott@ipsen.com
t: Thursday, April 16, 2009 10:32 AM
White, Tamika; Kim, Tamy
Subject: Fw: Dysport Comments
Importance: High
Attachments: 1-14-1-1-draft-carton-container-labels.pdf; 1-14-1-3-draft-labeling-text-medication-guide.doc; BLA 125274 - 125286.Response to April 10, 2009 Request for Information..pdf; 1-14-1-3-draft-labeling-text.doc; ATT1660288.txt

Dear Tamika and Tamy,

Please confirm receipt of this email. Andrew Slugg has tried to send this but he is experiencing email problems.

Thanks,

Steve

Steven R. Scott
Vice President, Regulatory Affairs
Biomeasure Incorporated
27 Maple Street
Milford, MA 01757
(508) 478-0144

M. , MA 01757
Telephone: 1 508 478-0144
Fax: 1 508 473-3531

----- Forwarded by Steve Scott/BI-Group on 04/16/2009 10:30 AM -----

Andrew Slugg/BI-Group

04/16/2009 10:15 AM

To Andrew Slugg/BI-Group@Beaufour-ipsen
cc steve.scott@ipsen.com, "White, Tamika" <Tamika.White@fda.hhs.gov>, "Kim, Tamy" <Tamy.Kim@fda.hhs.gov>
Subject Re: Dysport CommentsLink

Dear Tamika,

Attached is the email I sent last night ~5pm ET. Note, I have replaced the labeling with the version incorporating the minor revision to section 2 [affecting Cervical Dystonia section only] I sent through this AM a few minutes ago (9:54AM ET).

I understand by your email from this morning (10:08 AM ET) that you did not receive last night's email. Can you please confirm receipt of this email?

Ki. gards,

Andrew

Andrew P Slugg

4/30/2009

Regulatory Affairs
Biomeasure Incorporated
27 Maple Street
Milford, MA 01757
andrew.slugg@ipsen.com
Tel: 1 508 478-0144 x 144
Fax: 1 508 473-3531

Andrew Slugg/BI-Group

04/15/2009 05:09 PM

To "Kim, Tamy" <Tamy.Kim@fda.hhs.gov>

cc steve.scott@ipsen.com, "White, Tamika" <Tamika.White@fda.hhs.gov>

Subject Re: Dysport Comments Link

Dear Tamy and Tamika,

Attached please find Ipsen's response to the Post Marketing Requirements and Commitments, revised labelling integrating both the Cervical Dystonia and Glabellar Lines indications, and comments on the carton and container for the Cervical Dystonia 500U/vial product received in your April 10, 2009 email. As previously agreed, the response has been consolidated into a single document and will be appended by the carton and container labels, draft labeling and draft Medication Guide. The latter two documents are presented in track changes. This will be submitted as an official amendment to both BLAs tomorrow.

Additionally, in the next week, we would like to schedule a teleconference with the appropriate Divisions of the agency to discuss any outstanding issues pertaining to the labeling and/or REMS (to which we will respond by COB tomorrow).

Thank you in advance for your consideration of this request. We look forward to speaking with you soon.

Kind Regards,

Andrew

P.S. Please confirm receipt of this email.

Andrew P Slugg
Regulatory Affairs
Biomeasure Incorporated
27 Maple Street
Milford, MA 01757
andrew.slugg@ipsen.com
Tel: 1 508 478-0144 x 144
Fax: 1 508 473-3531

"Kim, Tamy" <Tamy.Kim@fda.hhs.gov>

04/10/2009 05:10 PM

To andrew.slugg@ipsen.com

cc "White, Tamika" <Tamika.White@fda.hhs.gov>, steve.scott@ipsen.com

Subject Dysport Comments

[ndrew,

Attached are the labeling, Medication Guide, PMRs/PMCs, and DMEPA and OBP comments to the carton and container and labeling.

1. Labeling:
<<Dysport labeling ToSpon.4.10.09_DNP_DDDP.Clean.doc>> <<Dysport labeling ToSpon.4.10.09_DNP_DDDP.doc>>

2. Medication Guide:
<<Dysport MG. ToSpon.4.10.09_DNP_DDDP.Clean.doc>> <<Dysport MG. ToSpon.4.10.09_DNP_DDDP.doc>>
3. PMRs/PMC
<<BLA 125274 Dysport PMR_PMC.ToSpon_4.10.09.doc>>
4. DMEPA and OBP comments to the carton and container and labeling
<<Carton and Container and Labeling DMEPA_OBP comments ToSpon.4.10.09.doc>>
For the labeling and Medication Guide, we accepted changes in certain instances. Therefore, the track-changed copy does not show all of the track changes; however, I provided the track changes that were available, so that you could view some of the changes that were made. Please use the copies denoted as "Clean" to respond to the labeling and medication guide. Comments on your REMS will be forthcoming.

Please respond to these comments by COB, Wednesday, April 15, 2009. Please confirm receipt of this email.

Best regards,
Tamy

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

[attachment "Dysport labeling ToSpon.4.10.09_DNP_DDDP.Clean.doc" deleted by Andrew Slugg/BI-Group] [attachment "Dysport labeling ToSpon.4.10.09_DNP_DDDP.doc" deleted by Andrew Slugg/BI-Group] [attachment "Dysport MG. ToSpon.4.10.09_DNP_DDDP.Clean.doc" deleted by Andrew Slugg/BI-Group] [attachment "Dysport MG. ToSpon.4.10.09_DNP_DDDP.doc" deleted by Andrew Slugg/BI-Group] [attachment "BLA 125274 Dysport PMR_PMC.ToSpon_4.10.09.doc" deleted by Andrew Slugg/BI-Group] [attachment "Carton and Container and Labeling DMEPA_OBP comments ToSpon.4.10.09.doc" deleted by Andrew Slugg/BI-Group]

b(4)

2.1.2.11 CMC Post-Marketing Commitment 8: Regarding a Single Use Dose for Glabellar Lines

8. To develop a 125U single use dosage form for the dermatologic indication. A supplement for approval of this dosage form will be submitted to the Agency by [SPONSOR PROPOSED DATE].

- **IPSEN CMC Post-Marketing Commitment 8**

IPSEN commits to develop a 125U single use dosage form for the dermatologic indication. A supplement for approval of this dosage form will be submitted to the Agency by March 31, 2010.

2.1.3 Additional CMC Comments

2.1.3.1 FDA CMC Comment 1: Stability

The Agency remains concerned about the stability of drug product. Therefore, please amend the BLA as follows:

a) Remove the stability protocol for drug the purpose of extending the drug product dating period beyond 12 months. While you may have stability protocols that extend beyond 12 months, you may not extend the dating

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

Office of Biotechnology Products
Rockville, MD 20852
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125286/0/14

Name of Drug: Reloxin® (botulinum Toxin A)

Sponsor: Ipsen Biopharm Limited

Material Reviewed: Reloxin® (botulinum Toxin Type A) Carton and Container Labels

OBP Receipt Date: February 10, 2009

Amendment Reviewed:

Background:

STN 125286/0 for Botulinum Type A Toxin is an original Biologic License Application (BLA) intended to achieve and maintain improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients. The neurotoxin is supplied as a 300 unit pellet for reconstitution with sterile saline and is injected intramuscularly. The single use vial label contains a unique hologram.

Labels Reviewed:

Reloxin® (botulinum Toxin Type A) Container Label
- Professional Sample Vial Label
- Vial Label

Reloxin® (botulinum Toxin Type A) Carton Label
- Professional Sample Carton Label
- Carton Label

Review

The carton and container labels for Reloxin® (botulinum Toxin Type A) were reviewed and conformed to a majority of the regulations under 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100; and The U.S. Pharmacopeia, USP31/NF36 (12/1/08-4/30/09) except where noted in the conclusions section of this review memo. Please see the comments in the conclusions section.

Professional Sample Vial Label

b(4)

Vial Label

3 pages of draft labeling was removed after this page.

I. Conclusions

A. The proposed carton and vial labeling are acceptable only upon the following changes:

1. Please provide the vial size and indicate how the label is affixed to the vial to permit inspection of the contents per 21CFR 610.60 (e).

2. The route of administration is not provided on the vial labels or on the primary panels of the cartons. Per 21 CFR 201.5 (f) and 21 CFR 610.61 (k), please add the route of administration to the vial labels and to the primary panels of the cartons.

3. The license number does not appear on any labeling with the manufacturer information. Please add the license number with the manufacturing information per 21 CFR 610.60(2) and 21 CFR 610.61(b).

4. b(4)

5. Manufacturer information per the 356h form identifies one manufacturer, Ipsen Biopharm Ltd. Wrexhem, UK; however the carton labels display two manufacturers. Please clarify if Medicis Pharmaceutical Corporation is a second manufacturer or a distributor and use the appropriate regulation to display the information. If it is a second manufacturer, please comply with 21 CFR 610.63 and if is a second distributor, please comply with 21 CFR 610.64.

6. If the product is light sensitive, please add "Protect from Light" and "Do not Freeze" statements to the carton labels and the "How supplied section" of the package insert per 21 CFR 610.61(i).

7. Per USPC Official 12/1/08-4/30/09, USP 31/NF26, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients from the current edition of one of the following reference works (in the following order of precedence): (1) the United States Pharmacopeia or the National Formulary; (2) USAN and the USP Dictionary of Drug Names; (3) CTFA Cosmetic Ingredient Dictionary; (4) Food chemicals codex. The ingredients must also be listed in alphabetical order.

8. Please consider adding the trade name on the side panel above the lot and expiration information and the back panel.

APPEARS THIS WAY ON ORIGINAL

4/14/09

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

Comment/Concurrence:

Susan L. Kushner for Ennan Guan 4/14/09

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

4-14-09

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

32 pages of draft labeling was removed after this page.

White, Tamika

n:	Kim, Tamy
t:	Friday, April 10, 2009 5:10 PM
To:	'andrew.slugg@ipsen.com'
Cc:	White, Tamika; steve.scott@ipsen.com
Subject:	Dysport Comments
Attachments:	Dysport labeling ToSpon.4.10.09_DNP_DDDP.Clean.doc; Dysport labeling ToSpon.4.10.09 _DNP_DDDP.doc; Dysport MG. ToSpon.4.10.09_DNP_DDDP.Clean.doc; Dysport MG. ToSpon.4.10.09_DNP_DDDP.doc; BLA 125274 Dysport PMR_PMC.ToSpon_4.10.09.doc; Carton and Container and Labeling DMEPA_OBP comments ToSpon.4.10.09.doc

Dear Andrew,

Attached are the labeling, Medication Guide, PMRs/PMCs, and DMEPA and OBP comments to the carton and container and labeling.

1. Labeling:

Dysport labeling ToSpon.4.10.0... Dysport labeling ToSpon.4.10.0...

2. Medication Guide:

'sport MG. ..4.10.09_DNP Dysport MG. Spon.4.10.09_DNP.

3. PMRs/PMC

BLA 125274 sport PMR_PMC.To

4. DMEPA and OBP comments to the carton and container and labeling

Carton and ontainer and Label..

For the labeling and Medication Guide, we accepted changes in certain instances. Therefore, the track-changed copy does not show all of the track changes; however, I provided the track changes that were available, so that you could view some of the changes that were made. Please use the copies denoted as "Clean" to respond to the labeling and medication guide. Comments on your REMS will be forthcoming.

Please respond to these comments by COB, Wednesday, April 15, 2009. Please confirm receipt of this email.

Best regards,
Tamy

Tamy Kim, PharmD
Safety Regulatory Project Manager
'sion of Neurology Products
d and Drug Administration
Phone: 301-796-1125
Email: tamy.kim@fda.hhs.gov

BLA 125274 Dysport
Postmarketing Requirements (PMR)/Postmarketing Commitments (PMC)

CMC PMCs
We propose the following post-marketing commitments:

1. Regarding specifications

    a. To establish a drug substance release specification for Clp protease. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSED DATE].

    b. To establish a drug substance release specification for aggregates using a validated sensitive method for quantification. As stated in the September 9, 2008 (Sequence 0013) amendment responding to the Division's April 8, 2008 Information Request, the Applicant will employ the SE-FPLC method. The proposed SE-FPLC analytical method, validation data and specification will be submitted to the Agency by [INSERT DATE].

    c. To provide data demonstrating the specificity of the capture antibody used in the ELISA based identity release test to the Agency by [INSERT DATE].

2. Regarding additional characterization tests

    a. To develop and validate a Western blot assay for release of the drug substance as an identity test and submit this information to the Agency by [Insert date].

3. Regarding potency test
    a. To investigate the development and implementation of a non-animal based potency assay(s) for drug substance and drug product release testing.

4. Regarding drug product identity test

    a. To develop and implement non-animal based identity test for drug product release. The animal based identity test for the first lot of drug product manufactured from every new lot of drug substance should be maintained. A summary report together with any proposed modifications to the process and/or stability protocol will be submitted to the Agency by [INSERT DATE].

5. Regarding reference standard

    a. To develop drug substance and drug product reference standards from the materials made at the IBL facility. Routine use of the new reference standards will be implemented by [INSERT DATE].

b. To provide a protocol that describes extension of reference standard dating period. The protocol will be submitted to the Agency by [INSERT DATE].

6. Regarding the drug product lot release protocol:

   a. To add SE-HPLC results for bulk drug substance to the lot release protocol when the SE-HPLC assay(s) is validated. A supplement for approval of this drug substance release specification will be submitted to the Agency by [SPONSOR PROPOSED DATE].

7. Regarding System Suitability Criteria:

   a. To establish system suitability criteria for the assessment of the cut point in the RIPA and confirmatory RIPA to control for drift in the cut point. The system suitability criteria will be submitted to the Agency by [INSERT DATE].

8. To develop a 125U single use dosage form for the dermatologic indication. A supplement for approval of this dosage form will be submitted to the Agency by [SPONSOR PROPOSED DATE].

Clinical PMRs

1. *Pediatric study:*
   A randomized, double-blind, placebo-controlled, multiple fixed doses, parallel group clinical trial of Dysport in children with lower-limb spasticity associated with cerebral palsy, in botulinum toxin-naïve subjects. The recommended duration of the study is 12 weeks. Safety data must be collected in the controlled trial, to include data on the systemic spread of the toxin. In addition to signs of systemic botulism, you should measure the effects of Dysport on blood glucose and alkaline phosphatase as a marker of bone metabolism. Simultaneous with this study, a juvenile toxicity study should also be conducted.

   After the completion of the controlled phase, a long-term open-label extension study, preferably for 12 months duration, is required to systematically collect safety data including data on the systemic spread of the toxin. At least 100 subjects exposed at clinically relevant doses for at least 12 months is a minimum requirement for assessment of longer-term safety. The safety data must be documented at or above the dose or doses identified as effective in an adequately designed trial, as described above. If an adequately designed and conducted efficacy trial fails to detect a drug effect, one year safety data must still be collected, at doses at least high as the doses typically used in treating children with botulinum toxin products. Pediatric subjects can be eligible for enrollment in the one year safety study even if they have not participated in the controlled efficacy study. Effects of Dysport on growth and maturation should also be examined.

Protocol Submission:	3 months from approval
Clinical Trial Start Date:	1 year after protocol submission
Final Report Submission:	4 years after trial start date

2. *Adult Study:*
   A randomized, double-blind, placebo-controlled, multiple fixed doses, parallel group clinical trial of Dysport in adults with lower-limb spasticity, in botulinum toxin-naïve subjects. The recommended duration of the study is 12 weeks. Safety data must be collected in the controlled trial, to include data on the systemic spread of the toxin.

   After the completion of the controlled phase, a long-term open-label extension study, preferably for 12 months duration, is required to systematically collect safety data including data on the systemic spread of the toxin. At least 100 subjects exposed at clinically relevant doses for at least 12 months is a minimum requirement for assessment of longer-term safety. The safety data must be documented at or above the dose or doses identified as effective in an adequately designed trial, as described above. If an adequately designed and conducted efficacy trial fails to detect a drug effect, one year safety data must still be collected, at doses at least high as the doses typically used in treating adults with lower limb spasticity. Adult subjects can be eligible for enrollment in the one year safety study even if they have not participated in the controlled efficacy study.

Protocol Submission:	3 months from approval
Clinical Trial Start Date:	1 year after protocol submission
Final Report Submission:	4 years after trial start date

Nonclinical PMRs

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

Protocol Submission:	by November 2009
Study Start Date:	by February 2010
Final Report Submission:	by August 2011

4. An embryo-fetal development study in rabbit to identify the unexpected serious risk of adverse effects on embryo-fetal development. The pivotal embryo-fetal development study (Study #AA28028) was inadequate because the high dose was lethal to pregnant dams. However, in a preliminary study (No. 434/363), the same

high dose (20 U/day), administered using the same dosing regimen was tolerated. This apparent discrepancy in the tolerability of DYSPORT will need to be explored prior to selection of doses for a pivotal study.

Protocol Submission:	by August 2009
Study Start Date:	by October 2009
Final Report Submission:	by June 2010

CMC PMR:

5. To establish tighter potency acceptance criteria for the qualification of new reference standards. The acceptance criteria should ensure consistent potency assessment when different reference standards are used. This is critical as potency is reported relative to the potency of the reference standard. Amended criteria will be submitted to the Agency by [SPONSOR PROPOSED DATE].

Additional CMC comments

1. The Agency remains concerned about the stability of drug product. Therefore, please amend the BLA as follows:
   a. Remove the stability protocol for drug the purpose of extending the drug product dating period beyond 12 months. While you may have stability protocols that extend beyond 12 months, you may not extend the dating period beyond 12 months based on the results from those studies without prior approval of the Agency.
   b. Add that you will place the first lot of drug product made from each new batch of drug substance on stability in addition to the lot placed on stability annually to comply with cGMPs.
2. ⌜

b(4)

⌟

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: April 2, 2009

Time: 4:00 p.m. – 4:30 p.m.

Application: BLA 125286 - Reloxin (botulinum toxin type A)

Meeting Chair: Julie Beitz, M.D.

Meeting Recorder: Tamika White

FDA Participants:

Office of Drug Evaluation III
Julie Beitz, M.D., Director
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs (Acting)

Division of Dermatology and Dental Products
Tatiana Oussová, M.D., M.P.H., Deputy Director for Safety
Denise Cook, M.D., Medical Officer
Margo Owens, Project Management Team Leader
Tamika White, Regulatory Project Manager

Office of Surveillance and Epidemiology
Janet Anderson, PharmD., Project Manager

Division of Medication Error Prevention and Analysis
Carol Holquist, R.Ph., Director

Sponsor Participants:

Ipsen Biopharm Ltd.
Gerard Picot, V.P., Global Regulatory Affairs
Steven R. Scott, V.P., North American Regulatory Affairs
Andrew P. Slugg, Director, Regulatory Affairs
Michelle Landolfi, Director, Regulatory Affairs
Phil Weatherhill, Director, Global Pharmacovigilance

Medicis
Ira Lawrence,V.P., Clinical Development
Diane Stroehman, Manager, Regulatory Affairs

Background:
BLA 125286, (botulinum toxin type A) was submitted on March 12, 2008 for the treatment of glabellar lines in adults with the proposed trade name Reloxin.

The purpose of today's teleconference is to discuss the naming issues for the product, trade name, labeling, Risk Evaluation and Mitigation Strategy (REMS) and the timing of actions.

Discussion:

Established Name

FDA acknowledged the ongoing discussion regarding safety issues associated with the same established name for multiple botulinum toxin products. FDA clarified that a decision has been reached and that the established name for this product will be abobotulinumtoxinA.

Tradename

FDA informed the applicant that Reloxin is unacceptable as a tradename for two reasons, promotional and safety. FDA explained that Reloxin was considered unacceptable by the Division of Drug Marketing Advertising and Communications due to the promotional nature of the name. FDA further explained that the tradename was also unacceptable to the Division of Therapeutic Proteins, the Division of Dermatology and Dental Products and the Division of Medication Error and Prevention Analysis for safety reasons. FDA recommended Dysport as the tradename for the dermatologic indication. FDA explained that a single name would result in better name recognition for their product among prescribers and patients. This would be preferable from a safety standpoint, since the risks of the product could be expected to affect any patient population administered the product, namely the potential for distant spread of botulinum toxin after local injection, and the potential for medication errors related to the lack of interchangeability with other licensed botulinum toxin products.

Labeling/REMS

FDA acknowledged that labeling had been discussed with the Division of Neurology Products. FDA proposed to begin labeling negotiations regarding the dermatologic indication. FDA informed the sponsor of the plan to have one package insert that describes both indications and one Medication Guide since most of the information is applicable to both indications. FDA further explained that managing both indications under a single REMS would provide an opportunity to assess the effectiveness of the REMS to mitigate dosing errors in a consolidated manner.

The applicant asked whether the Division of Neurology Products was aware of the plan to have one package insert, Medication Guide and communication plan.

FDA informed the applicant that the Office of Drug Evaluation I and the Division of Neurology Products are aware.

Timing of Action

FDA acknowledged that April 13, 2009 is the goal date for BLA 125286 and April 29, 2009 is the goal date for BLA 125274. FDA informed the sponsor that we are considering delaying the action for BLA 125286 and coordinating an action with DNP for BLA 125274 at the end of the month.

The applicant was agreeable to this path forward

[redacted] b(4)

FDA stated that this would not be an acceptable approach and reiterated that the product is best managed under one tradename, one Medication Guide and one communication plan.

The applicant stated that they are not in a position to comment on the acceptability of Dysport as the single tradename for both products at this time. The applicant indicated that they are ready to begin labeling negotiations as soon as possible and that they would be in touch with the Project Manager to coordinate efforts.

The teleconference was then concluded.

Tamika White

Julie Beitz, M.D.

Hughes, Patricia

From: Stock, Marisa
Sent: Wednesday, April 01, 2009 4:44 PM
To: Hughes, Patricia
Cc: CDER-TB-EER
Subject: RE: BLA 125286

Follow Up Flag: Follow up
Flag Status: Red

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Ipsen Biopharm Ltd., Wrexham, UK was last inspected June 2-10, 2008 and classified NAI. The BTP profile was covered and is acceptable. [redacted] was last inspected [redacted] and classified VAI. The CTL profile was covered and is acceptable. An inspection assignment has been issued for this site. There are no pending or ongoing compliance actions to prevent approval of BLA 125286 at this time. b(4)

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Hughes, Patricia
Sent: Monday, March 30, 2009 9:02 AM
To: CDER-TB-EER
Subject: BLA 125286

Please submit an EER on the following sites in support of BLA 125286:

Drug substance and drug product manufacturing, release and stability testing:
Ipsen Biopharm Ltd.
Wrexham Industrial Estate
Ash Road, Wrexham LL13UF
UK b(4)

The PDUFA date is April 13, 2009

Thank you.

Patricia

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125286

JAN 0 6 2009

Biomeasure, Inc.
U.S. Agent for Ipsen Biopharm Ltd.
Attention: Steven R. Scott, Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757-3650

Dear Mr. Scott:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Reloxin (botulinum type A toxin).

We received your December 3, 2008, amendment to this application on December 8, 2008, 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 April 13, 2009, 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, Tamika White, at (301) 796-0310.

Sincerely,

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Hughes, Patricia

From: Hoyt, Colleen
Sent: Friday, December 12, 2008 2:38 PM
To: Hughes, Patricia
Subject: CORRECTION - FW: Compliance check for BLA 125274

Correction to classification

Colleen

From: Hoyt, Colleen
Sent: Friday, December 12, 2008 2:36 PM
To: Hughes, Patricia; CDER-TB-EER
Subject: RE: Compliance check for BLA 125274

The Manufacturing Assessment and Preapproval Compliance Branch has completed the review and evaluation of the TB-EER below. The June 2008 inspection conducted by Michelle Clark-Stuart on June 2-10, 2008 has been classified NAI by the International Compliance Team. There are no pending or ongoing compliance actions or investigations to prevent approval of STN 125274 at this time.

Colleen F. Hoyt
Compliance Officer/DMPQ Biotech Liaison
U.S. Food and Drug Administration
CDER/OC/DMPQ
o - (301) 796-3251
f - (301) 847-8741
colleen.hoyt@fda.hhs.gov

10903 New Hampshire Avenue
WO51-Room 4308
Silver Spring, MD 20993

From: Hughes, Patricia
Sent: Friday, December 12, 2008 2:14 PM
To: CDER-TB-EER
Subject: Compliance check for BLA 125274

Please conduct an establishment evaluation of Ipsen Biopharm LTD, Wreham Industrial Estate, Ash Road, Wreham, LL13 9UF, UK FEI= 1000346340. The site manufactures drug substance and drug product C. botulinum type A toxin (Dysprot for Injection) in a sterile lyophilized vial. the profile categories should be TPR and SVL. the facility was inspected by Michelle Clark Stuart on June 2-10, 2008. no obervations were issued. the inspection was classified as NAI. The PDUFA date is Dec 28, 2008 and the approval letter is currenlty being drafted.

Thank you.

Patricia

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 1, 2008

TO: Tamika White, Regulatory Project Manager
Denise Cook, M.D., Medical Officer
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA#: 125286

APPLICANT: Ipsen Biopharm Limited

DRUG: Reloxin® (botulinum type A toxin-hemagglutinin complex)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of glabellar lines

CONSULTATION REQUEST DATE: July 9, 2008

DIVISION ACTION GOAL DATE: January 8, 2009

PDUFA DATE: January 12, 2009

I. BACKGROUND:

The protocols inspected include:

Protocol #Y-97-52120-719 entitled "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Reloxin® in the Treatment of Glabellar Lines", and

Protocol #A-2006-01 entitled "A Phase III, Randomized, Placebo-Controlled, Multi-Center, Double-Blind Study of the Safety and Duration of Efficacy of Reloxin® (Botulinum Type A Toxin) in Correction of Moderate to Severe Glabellar Lines (and Including a Sub-Study to Detect Any Treatment Related QT Interval Changes), and

Protocol #Y-97-52120-085 entitled "A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Reloxin® in the Re-Treatment of Glabellar Lines Following Open-Label Treatment".

The conduct of protocol #s A-2006-01 and Y-97-52120-085 was inspected at the site of Joel Schlessinger, M.D., and the conduct of protocol #s A-2006-01 and Y-97-52120-719 was inspected at the site of Fredric Brandt, MD. b(6)

Both sites also demonstrated pronounced efficacy.

The primary objectives of these studies were: (1) for protocol # Y-97-52120-719, to demonstrate the efficacy of a single treatment of Reloxin® (50 units) compared with placebo in the treatment of glabellar lines; (2) for protocol # Y-97-52120-085, to demonstrate the efficacy of repeat treatment with Reloxin® (50 units) in the treatment of glabellar lines; and (3) for protocol # A-2006-01, to establish the safety and efficacy of Reloxin® when used to produce a sustained reduction in glabellar line severity. The efficacy of treatment for these protocols was, in general, determined by both subject and investigator assessments of glabellar line severity at different time points during and after treatment with the study article.

APPEARS THIS WAY
ON ORIGINAL

II. RESULTS (by Site):

Name of CI, or Sponsor/ Location	Protocol #: and # of Subjects:	Inspection Dates	Final Classification
Joel Schlessinger, M.D. Skin Specialists P.C. 2802 Oak View Mall Drive Omaha, NE 68144	Y-97-52120-085/ 6/ 65/ and A-2006-01/ 88/ 36/	21-23 Oct 08	NAI
Fredric Brandt, MD Dermatology Research Institute LLC 4425 Ponce de Leon Blvd., Suite 200 Coral Gables, FL 33146	A-2006-01/ 73/ 25/ and Y-97-52120-719/ 1/ 54/	20-24 Oct 08	VAI
Medicis Pharmaceutical Corporation 7720 North Dobson Road Scottsdale, AZ 85256 Diane Stroehmann, RAC Manager, Regulatory Affairs Medicis Pharmaceutical Corporation Phone: 480-291-5611 Fax: 480-291-8611 E-mail: dstroehmann@medicis.com	#Y-97-52120-719, and #A-2006-01, and #Y-97-52120-085	Oct-Nov 08	Pending (Preliminary classification is NAI.)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Joel Schlessinger, M.D.
   Skin Specialists P.C.
   2802 Oak View Mall Drive
   Omaha, NE 68144

   a. **What was inspected**: 42 subjects were consented for protocol #A-2006-01, 6 were screen failures, and 35 completed the study. 70 subjects were consented for the initial portion and 35 subjects were consented for the extension of protocol Y-97-52120-085. There were five screen failures in the initial study

and no screen failures in the extension study. Nine subjects dropped from the initial study and none from the extension. 56 subjects completed the initial study and 35 completed the extension study. The study records for one-half of the subjects who completed each protocol were reviewed in-depth. Primary efficacy endpoints, adverse events, and drug accountability reporting were reviewed.

b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

c. **Assessment of data integrity**: Data appear acceptable in support of the respective application.

2. Fredric Brandt, MD
Dermatology Research Institute LLC
4425 Ponce de Leon Blvd., Suite 200
Coral Gables, FL 33146

a. **What was inspected**: 54 subjects were consented for protocol Y-97-52120-719 with 53 subjects completing the study, and 30 subjects were consented under protocol A-2006-01 with 24 subjects completing the study. The study records for 23 subjects for protocol Y-97-52120-719 and eight subjects for protocol A-2006-01 were reviewed in-depth. Adverse events, sponsor, monitor, and IRB correspondence, concomitant medications, and drug accountability were reviewed. Source documents were compared with the corresponding case report forms (CRFs) and the data listings accompanying the assignment.

b. **General observations/commentary**: Review of the records for protocol #Y-97-52120-719 revealed that study drug allocated to subjects was not dispensed in sequential order as required by protocol. Subjects receiving study drug in non-sequential order included, but were not limited to, subjects 001, 005, 006, 009, 012, and 020.

c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

3. Medicis Pharmaceutical Corporation
7720 North Dobson Road
Scottsdale, AZ 85256

a. **What was inspected**: Medicis entered into an agreement with Ipsen to retain all study records for studies conducted in support of this BLA [redacted] was responsible for monitoring protocol Y-97-52120-719 and the initial portion of protocol Y-97-52120-085, with Medicis monitoring the final portions of this protocol and all of protocol A-2006-01. The inspection assignment requested that the monitoring records for these

b(4)

protocols be reviewed and that sponsor/monitor responsibilities be reviewed and documented.

b. **General observations/commentary**: Personal communications with the field investigator indicate that no regulatory violations were observed.

c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data generated by the clinical sites of Drs. Schlessinger and Brandt appear acceptable in support of the respective application.

A final classification of the inspection of Medicis is pending receipt and review of the inspection report. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the establishment inspection report (EIR).

Roy Blay Ph.D. 1 DEC 08

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, MD, MPH 12/1/08

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

White, Tamika

From: White, Tamika
nt: Saturday, November 15, 2008 11:30 AM
: steve.scott@ipsen.com
Cc: 'andrew.slugg@ipsen.com'
Subject: CMC Information Request

Attachments: BLA 125286 CMC IR 11_14_08.pdf

As mentioned in the teleconference held on November 12, 2008, we have a request for additional CMC information. We have requested a quick turnaround. Let me know if you have a problem with meeting this date.

If you have any questions, please let me know.

Thanks,

Tamika

3LA 125286 CMC IR 11_14_08.pdf...

Tamika White
Regulatory Health Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5183
903 New Hampshire Avenue
.ver Spring, MD 20993
Phone: (301) 796-0310
Fax: (301) 796-9894/9895

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: November 14, 2008

To: Steven R. Scott, Director Regulatory Affairs	**From:** Tamika White Regulatory Project Manager
Company: Biomeasure, Inc., U.S. Agent for Ipsen Biopharm Limited	Division of Dermatology and Dental Products
Fax number: (508) 473-3531	**Fax number:** (301) 796-9895
Phone number: (508) 478-0144 x142	**Phone number:** (301) 796-0310

Subject: BLA 125286 Reloxin (botulinum type A toxin- hemagglutinin complex)

Total no. of pages including cover: 2

Comments:

Please see the attached request for information.

Thank you.

Document to be mailed: ☐ YES ☒ NO

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FDA Facsimile Memorandum

Date: November 14, 2008
To: Steven R. Scott, Director Regulatory Affairs
From: Tamika White, Regulatory Project Manager
Subject: BLA 125286 Reloxin (botulinum type A toxin-hemagglutinin complex)

This communication is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We are reviewing your application dated March 13, 2008 for Reloxin (botulinum type A toxin-hemagglutinin complex) and have determined that the following information is necessary to take a complete action on your application:

CMC

DP Stability:
The limited real time stability data for the 300 U presentation you provide in the BLA indicate that your drug product [redacted] for potency over time. b(4)

1) Submit updated real time potency stability data for your drug product to support your proposed 12- month shelf life.

2) Provide trending analyses with 95% CI for real time potency stability data

DP potency specification:
Revise the DP potency specification for the 300 U presentation to be consistent with the 500 U presentation.

It is requested that you promptly submit a complete response to the items listed above no later than November 19, 2008.

If you have any questions, contact me at (301) 796-0310.

Thank you.

Tamika White
Regulatory Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg. 22, Room 5183
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (301) 796-0310
Fax: (301) 796-9895

White, Tamika

From: White, Tamika
nt: Monday, September 29, 2008 9:32 AM
: steve.scott@ipsen.com
Cc: 'andrew.slugg@ipsen.com'
Subject: Information Request for Reloxin

Attachments: Clinical and Biostatistics Information Request 9-29-08.pdf

Hello Steve,

Attached is a clinical/biostatistics information request. Let me know if you have any questions.

Tamika

Clinical and Biostatistics Inf...

Tamika White
Regulatory Health Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5183
10903 New Hampshire Avenue
Silver Spring, MD 20993
one: (301) 796-0310
x: (301) 796-9894/9895

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: September 29, 2008

To: Steven R. Scott, Director Regulatory Affairs	**From:** Tamika White, Regulatory Project Manager
Company: Biomeasure, Inc., U.S. Agent for Ipsen Biopharm Limited	Division of Dermatology and Dental Products
Fax number: (508) 473-3531	**Fax number:** (301) 796-9894/9895
Phone number: (508) 478-0144 x142	**Phone number:** (301) 796-0310

Subject: BLA 125286 Reloxin (botulinum type A toxin – hemagglutinin complex)

Total no. of pages including cover: 2

Comments:
Please see the attached request for information.

Document to be mailed: YES ☑NO

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FDA Facsimile Memorandum

Date: September 29, 2008

To: Steven R. Scott, Director Regulatory Affairs

From: Tamika White, Regulatory Project Manager

Subject: BLA 125286 Reloxin (botulinum type A toxin – hemagglutinin complex)

This communication is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We are reviewing your application dated March 13, 2008 for Reloxin (botulinum type A toxin – hemagglutinin complex) and have determined that the following information is necessary to take a complete action on your application:

Clinical/Biostatistics

Submit the electronic datasets (in SAS transport format) and accompanying dataset documentation for Study 718. The format should be comparable to other studies submitted with the BLA.

Include in your submission an analysis of the proportion of responders with a 2+ grade improvement along with a 2+ composite analysis for the primary endpoints of trial 718 for the ITT, MITT, and PP populations.

It is requested that you promptly submit a complete response to the items enumerated above no later than October 6, 2008.

If you have any questions, contact Tamika White, Regulatory Project Manager, at (301) 796-0310.

Thank you.

Tamika White
Regulatory Health Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5183
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-0310
Fax: (301) 796-9894/9895

Kim, Tamy

From: Clark-Stuart, Michelle
Sent: Thursday, September 18, 2008 11:26 AM
To: Kim, Tamy
Cc: Clark-Stuart, Michelle
Subject: FW: Facility check for a BLA

See EER below.
I am awaiting some information from Ipsen that should arrive shortly for my review. Once I review it I will incorporate it into my memo. I will let you know when the review is being sent to you.

Michelle Y. Clark-Stuart, MGA/MIS, MT (ASCP)
FDA/CDER/OC/DMPQ
White Oak Bldg. 51, Room #4222
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone - 301-796-3197
Fax - 9-301-847-8724
e-mail: Michelle.Clark-Stuart@fda.hhs.gov
DMPQ main phone - 301-796-3120

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From: Ferguson, Shirnette D
Sent: Tuesday, September 09, 2008 1:18 PM
To: Clark-Stuart, Michelle; CDER-TB-EER
Subject: RE: Facility check for a BLA

The Manufacturing Assessment and Preapproval Compliance Branch has competed its review and evaluation of the

compliance check below. There are no ongoing or pending compliance actions that would prevent approval of STN 125274/0. Ipsen Biopharm, LTD was last inspected by Team Biologics on 6/2-6/10/2008. There is no final district decision nor has the profiles been updated.

Shirnette Ferguson

From: Clark-Stuart, Michelle
Sent: Friday, September 05, 2008 11:53 AM
To: CDER-TB-EER
Cc: Clark-Stuart, Michelle; Kim, Tamy
Subject: Facility check for a BLA
Importance: High

Hello,

Application - BLA, STN 125274/0 from Ipsen Biophram, Limited at their Wrexham, United Kingdom location.

Product - CNT52120 (Dysport), *Clostridium botulinum* toxin Type A haemagglutinin complex for injection.

Indication -Treatment of cervical dystonia.

Manufacturing Facilities for drug substance (DS):

Ipsen Biophram, Limited
Unit 9 Ash Road, Wrexham Industrial Estate
Wrexham, United Kingdom LL139UF
Manufacture of bulk active substance, storage, stability and release testing.
FEI =1000346340

PDUFA Date: 28 June 2008

Thank you.

Michelle

Michelle Y. Clark-Stuart, MGA/MIS, MT (ASCP)
FDA/CDER/OC/DMPQ
White Oak Bldg. 51, Room #4222
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone - 301-796-3197
Fax - 9-301-847-8724
e-mail: Michelle.Clark-Stuart@fda.hhs.gov
DMPQ main phone - 301-796-3120

****

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White, Tamika

From: White, Tamika
nt: Friday, September 05, 2008 4:15 PM
: steve.scott@ipsen.com
Subject: Information Request for BLA 125286

Attachments: Clinical and Nonclinical Information Request 9-5-08.pdf

Hi Steve,

I have attached an information request for clinical and nonclinical information. Let me know if you have any questions.

Thanks,

Tamika

Clinical and Nonclinical Infor...

Tamika White
Regulatory Health Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5183
10903 New Hampshire Avenue
ver Spring, MD 20993
one: (301) 796-0310
Fax: (301) 796-9894/9895

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: September 5, 2008

To: Steven R. Scott, Director Regulatory Affairs	**From:** Tamika White, Regulatory Project Manager
Company: Biomeasure, Inc., U.S. Agent for Ipsen Biopharm Limited	Division of Dermatology and Dental Products
Fax number: (508) 473-3531	**Fax number:** (301) 796-9894/9895
Phone number: (508) 478-0144 x142	**Phone number:** (301) 796-0310

Subject: BLA 125286 Reloxin (botulinum type A toxin – hemagglutinin complex)

Total no. of pages including cover: 3

Comments:
Please see the attached request for information.

Document to be mailed: YES ☑ NO

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FDA Facsimile Memorandum

Date: September 5, 2008

To: Steven R. Scott, Director Regulatory Affairs

From: Tamika White, Regulatory Project Manager

Subject: BLA 125286 Reloxin (botulinum type A toxin – hemagglutinin complex)

This communication is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We are reviewing your application dated March 13, 2008 for Reloxin (botulinum type A toxin – hemagglutinin complex) and have determined that the following information is necessary to take a complete action on your application:

Clinical

1. Provide a safety assessment of Reloxin for those subjects that received 50 units only of the Ipsen botulinum toxin product to treat glabellar lines from trials 718, 096, 085, A-2006-01, 732 and 720.

2. Provide a safety assessment from the double-blind placebo controlled trials of a single 50 unit dose of Reloxin in trials 718, 719, part C of 085 and A-2006-01. All of the placebo subjects from trial A-2006-01 should be added in this analysis.

   Both of these assessments (1) and (2) should include adverse event tables of any adverse events that occurred in the Reloxin 50 unit dose arms vs. the placebo arms in decreasing order of frequency that occurred at greater than or equal to 1%. There should be tables of most common adverse events and ocular related events.

3. Provide a plan for reducing the unit dose vial when reconstituted to 50 units rather than 300 units. This vial should be a single dose/single patient vial so that only the needed amount of toxin is available for use.

4. Provide a draft Medication Guide specific to the indication for glabellar lines.

Nonclinical

5. Submit the interim report investigating the 13-week recovery at the local nerve terminals after repeat dosing with Dysport. If full recovery of the NMJs has not been demonstrated by week 13, the 26-week recovery data should be submitted by the end of November 2008.

6. Confirm that all drug product used in all nonclinical studies (see list of nonclinical studies below) was stored as a lyophylisate at approximately 4°C until it was prepared daily as an injection solution.

   Nonclinical studies

   Clostridium botulinum toxin type A hemagglutinin complex- Single dose intramuscular toxicity study with 12-week follow-up in the rat (— AA40423)

   Clostridium botulinum toxin type A hemagglutinin complex – Sub-chronic toxicity study (6 intramuscular injections at 4-week intervals) in the rat (— AA40095) b(4)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Embryotoxicity study by the intramuscular route in the rabbit (— AA28028)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Embryotoxicity study by the intramuscular route in the rat (— AA28029)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Preliminary embryotoxicity study by daily intramuscular injection in the pregnant rabbit (— 434/363 RE) b(4)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Preliminary embryotoxicity study by two sequential intramuscular administrations in the pregnant rabbit (— 434/364 RE)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Preliminary study after two intramuscular administrations in the non-pregnant female rabbit (— 434/359 RE)

Botulinum toxin type A hemagglutinin complex (Dysport®)- 14-Day preliminary study intramuscular administration in the non-pregnant female rabbit (— 434/360 RE)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Preliminary embryotoxicity study by daily intramuscular injection in the pregnant rat (— 434/361 RE)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Preliminary embryotoxicity study by sequential intramuscular administrations in the pregnant rat (— 434/362 RE)

Botulinum toxin type A hemagglutinin complex (Dysport®)- Preliminary study after three intramuscular administrations in the non-pregnant female rat (— 434/358 RE) b(4)

Botulinum toxin type A hemagglutinin complex (Dysport®)- 14-Day preliminary study intramuscular administration in the non-pregnant female rabbit (— 434/357 RE)

Clostridium botulinum toxin type A hemagglutinin complex- Single dose intramuscular toxicity study with 12-week follow-up in the rat (AA40423)

Clostridium botulinum toxin type A hemagglutinin complex- Sub-chronic toxicity study (6 intramuscular injections at 4-week intervals) in the rat (AA40095)

Clostridium botulinum toxin type A hemagglutinin complex – fertility toxicity study by the intramuscular route in the rat (Segment I)(AA38304-D)

Clostridium botulinum toxin type A hemagglutinin complex – Pre- and post-natal development study by the intramuscular route in the rat (Segment III)(AA38305-D)

Dysport botulinum type A toxin – Single dose administration in the beagle dog (434/199)

Test to evaluate acute ocular irritation and reversibility in the rabbit (204323)

A comparison of 500 Unit vials of *C. botulinum* type A toxin hemagglutinin complex prepared with bulk active substance 96/002, VPU/2002/006 and WBAS/001 on muscle force development (TA/04-1055)

7. Submit the individual animal data supporting the shrinkage of the injected muscles in the study report "*Clostridium botulinum* toxin type A hemagglutinin complex – Sub-chronic toxicity study (6 intramuscular injections at 4-week intervals) in the rat (AA40095)".

It is requested that you promptly submit a complete response to the items enumerated above no later than September 19, 2008.

If you have any questions, contact Tamika White, Regulatory Project Manager, at (301) 796-0310.

Thank you.

Tamika White
Regulatory Health Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5183
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-0310
Fax: (301) 796-9894/9895

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING ISSUES

Our STN: BL 125286/0

MAY 22 2008

Biomeasure, Inc.
U.S. Agent for Ipsen Biopharm Ltd.
ATTENTION: Steven R. Scott, Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757-3650

Dear Mr. Scott:

Please refer to your biologics license application (BLA), dated March 12, 2008, received March 14, 2008, submitted under section 351 of the Public Health Service Act, for Reloxin (botulinum type A toxin – hemagglutinin complex). Also refer to our filing letter dated May 13, 2008. While conducting our filing review we identified the following potential review issues:

b(4)

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. Provide specific discussion on any toxicities for all products with botulinum toxin, especially in post-marketing, in the 120-day safety update. Include updates and follow-up information for all patients who were included in trials with this product.

2. Identify all specific information intended to address efficacy at the lowest dose and safety at the highest dose proposed for labeled use of the product.

3. Provide your rationale for assuming the applicability of foreign data in the submission to the U.S. population. Include in your assessment racial and ethnic demographics, regional practice of medicine, and analysis of data by region.

4. Provide a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures.

5. Provide the individual animal data supporting the shrinkage of the injected muscles in the study report entitled: *Clostridium botulinum* toxin type A hemagglutinin complex – Sub-chronic toxicity study (6 intramuscular injections at 4-week intervals) in the rat (AA40095). Discuss potential human safety implications and adequacy of labeling to address this concern.

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 Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

Our STN: BL 125286/0

MAY 13 2008

Biomeasure, Inc.
U.S. Agent for Ipsen Biopharm Ltd.
ATTENTION: Steven R. Scott, Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757-3650

Dear Mr. Scott:

This letter is in regard to your biologics license application (BLA), dated March 12, 2008, received March 14, 2008, submitted under section 351 of the Public Health Service Act, for Reloxin (botulinum type A toxin – hemagglutinin complex).

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. The review classification for this application is Standard. Therefore, the user fee goal date is January 14, 2009. 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.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before May 28, 2008.

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 full waiver of pediatric studies for this application for pediatric patients.

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 Margo Owens, Regulatory Project Manager, at (301) 796-2100.

Sincerely,

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 10,673

Medicis Pharmaceutical Corporation
Attention: Don Selvey, Director, Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258

Dear Mr. Selvey:

Please refer to your Investigational New Biologic Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reloxin® (Botulinum Toxin Type A – Hemagglutinin Complex) for the treatment of glabellar lines.

We also refer to the meeting between representatives of your firm and the FDA on September 17, 2007. The purpose of the meeting was to discuss the proposed BLA submission for Reloxin®.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Melinda Bauerlien, M.S., Regulatory Project Manager, at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	September 17, 2007
TIME:	9:30 A.M.
LOCATION:	White Oak/Bldg. 22, Room 1313
APPLICATION:	BB-IND 10,673
DRUG NAME:	Reloxin (Botulinum Toxin Type A – Hemagglutinin Complex)
TYPE OF MEETING:	Pre-BLA

MEETING CHAIR: Stanka Kukich, M.D., Deputy Director, DDDP

MEETING RECORDER: Catherine Carr, M.S., Project Manager, DDDP

FDA ATTENDEES: (Title and Office/Division)

Stanka Kukich, M.D./Deputy Director, Division of Dermatology and Dental Products (DDDP)
Jill Lindstrom, M.D./Clinical Team Leader, Dermatology, DDDP
Paul Brown, Ph.D./Pharmacology Toxicology Team Leader, DDDP
Jill Merrill, Ph.D./Pharmacology Reviewer, DDDP
Catherine Carr, M.S./Regulatory Health Project Manger, DDDP
Lisa Skarupa, R.N./Regulatory Health Project Manger, DDDP
Kathleen Fritsch, Ph.D./Biostatistian, Office of Biostatistics
Zei-Pao Huang, OBPS/RRSS
Susan Kirshner, Biologist, Office of Biotechnology Products

EXTERNAL CONSTITUENT ATTENDEES: Medicis Pharmaceutical Corporation

Joe Cooper/Executive Vice President, Medicis
Mitch Wortzman, Ph.D./Executive Vice President, CSO
Sharron Gargosky, Ph.D./Executive Director, Clinical Research, Medicis
Fred Reno, Ph.D./Toxicologist, Medicis
Stacy Woodard, Ph.D./Manager Biostatistics, Medicis
[redacted] Dermatology Consultant
William Jones/Vice President, Regulatory Affairs, Ipsen
Don Selvey/Director, Regulatory Affairs, Medicis

b(4)

BACKGROUND:

The sponsor submitted a briefing document, dated August 15, 2007, which included background information and questions for discussion.

Draft responses were sent to the sponsor on September 14, 2007. After viewing the Draft Reviewer Comments, the sponsor provided a handout for discussion during the pre-BLA meeting. The handout is included in the minutes as an Attachment.

MEETING OBJECTIVES:

The purpose of the meeting was to seek input from the Agency regarding the suitability of non-clinical and clinical studies in support of the BLA filing.

DISCUSSION POINTS:

General Comment:

Sponsor provided handout of topics to be discussed during the meeting.

Pharmacology/Toxicology

Both the single dose toxicity study and the chronic toxicity study will include specialized staining techniques to evaluate the condition of the nerves. These studies are being conducted in response to the Division's request to evaluate the effects of chronic dosing (as per memorandum to the sponsor, 10-6-06). The sponsor has contracted with [redacted] to undertake the method development to visualize the effects of chronic dosing at the neuromuscular junction. In addition to basic histological techniques, the sponsor is investigating silver stains and immunohistology. b(4)

Question 16:

The following additional toxicology studies will be included with the BLA submission:

Fertility Toxicity Study in the rat (Seg I);
Embryofetal development in the rat and rabbit (Seg II);
Pre- and postnatal development in the rat (Seg III); and
Chronic study (six intramuscular injections at 4-week intervals) in the rat
Single dose intramuscular toxicity study with 12-week follow-up in the rat.

Do these studies satisfy the Agency's expectations for non-clinical toxicology studies of Reloxin?

Response:

The sponsor has previously submitted study reports for embryofetal development in the rat ([redacted] AA28029) and rabbit ([redacted] AA28028). With the exception that rats received 10 U on an intermittent basis only and not both daily and on an intermittent basis (as described in the current pre-BLA meeting briefing document), these studies seem to be the same. Please clarify whether these are the same as previously submitted/reviewed or if they are new studies. b(4)

Meeting Discussion:

Sponsor confirmed that studies were previously submitted.

We anticipate that the chronic rat study will incorporate methods that assess the denervation/re-innervation process. If so then, in theory, the above-mentioned studies satisfy the Agency's

expectations for non-clinical testing for Reloxin. However, a definite answer depends on the Division's review of these studies.

Question 17:

The Agency suggested that the effects of chronic dosing be examined, particularly the "...effects at local affected nerve terminal...[which] may require special techniques in addition to standard histopathology."

Standard histopathology studies with Haematoxylin and Eosin and toluidine blue stains are underway. The Sponsor is also evaluating such visualization techniques as, immunohistology targeting acetylcholinesterase and argyrophilic stains.

Medicis has contracted with _____ to undertake a method development program to be able to visualize and possible effects at the neuromuscular junction in studies performed at their laboratories. b(4)

Considering the scope and complexity of studies to evaluate the effects on the local nerve terminal, is it acceptable to complete the current research on this issue as a post-approval activity, with the proviso that it may not be possible to come to a conclusive determination of the effects of Reloxin at local affected nerve terminals? Does the Agency suggest other approaches to studying the effects at the local nerve terminal post-approval?.

Response:

The effect of chronic dosing at the nerve terminal needs to be evaluated and the sponsor should submit data as it becomes available. The Division anticipates receiving data with the BLA that investigates the extent to which chemical denervation reverses after chronic dosing. The adequacy of the data to support BLA approval will be determined during the review. Any additional data on this issue collected after BLA submission should also be submitted in a timely fashion.

Meeting Discussion:

The sponsor indicated that they are still working on the histology data. However, the majority of the toxicity data will be submitted in the BLA.

Question 18:

Does the Agency foresee any other issues or questions pertaining to the non-clinical studies of Reloxin that might preclude a filing of the BLA submission?

Response:

In theory the studies appear adequate to support the filing of the BLA submission. However, the pre-BLA meeting briefing document mentions the following studies as initiated and completed by Ipsen which the Division has not previously reviewed:

434/199: Dysport botulinum type A toxin – single dose administration in the beagle dog

204323: Test to evaluate acute ocular irritation and reversibility in the rabbit

TA/04-105 A comparison of 500 Unit vials of *C. botulinum* type A toxin hemagglutinin complex prepared with bulk active substance 96/002, VPU/2002/006 and WBAS/001 on muscle force development

Please submit these studies to the Division for review.

Meeting Discussion:

The sponsor indicated that they will submit the 434/199, 20423, and TA/04-105 study reports to the IND and BLA.

Clinical/Biostatistics and CMC

Question 1:

The Sponsor believes that Studies 719, 085, and 50U subset of 06-01 are adequate to support a BLA filing for a 50U fixed dosing to treat glabellar lines. Does the Agency concur?

Question 2:

The Sponsor believes that Study 06-01 is adequate to support a BLA filing for variable dosing to treat glabellar lines. Does the Agency concur?

Response (to Questions 1 and 2):

On the basis of the synopses, Studies 719, 085, and 06-01 appear to support filing. However, until the studies are reviewed, the Agency cannot comment as to whether the studies are adequate to support the safety and efficacy of either dosing regimen. Note that the Agency is likely to consider Study 085 as supportive rather than pivotal due to the randomization problems (see the response to Question #4). It is also not clear whether Study 06-01 would provide adequate safety (particularly long-term safety) for the higher variable dosing regimen.

It is not clear why the sponsor is pursing two dosing regimens for the same indication in the same population. The sponsor is requested to address how the clinician should determine which regimen to select. Additionally, for the variable dosing regimen, the sponsor will need to address in labeling how the clinician is to discriminate between patients with small, medium and large muscle masses.

Meeting Discussion:

The sponsor presented their rationale for the variable dosing regimen. The Agency requested and the sponsor agreed to supply an analysis to correlate muscle mass with baseline

investigator's global assessment. The Agency indicated that the dosing regimen will need to be supported by the clinical data.

Question 3:

Will this meet the Agency's request for a composite 2-grade improvement at Day 30 as the primary efficacy analysis?

Response:

For studies in which the composite 2-grade improvement endpoint was not pre-specified as the primary endpoint, it is acceptable to present the 2-grade improvement endpoint along with the pre-specified primary endpoint. It is acceptable to present the composite 2-grade improvement endpoint in the ISE.

Question 4:

Do you agree that the re-randomization of Study 085 enables it to be a pivotal study to support the BLA filing?

Response:

No, the Agency cannot agree that Study 085 is pivotal. The original randomization problems are a real concern. The problems required unblinding, modification of study objectives, and modification of study population (for example subjects assigned to Reloxin in Cycle B and therefore eligible for Cycle C were 'early relapsers' and entered Cycle B sooner). Although the study modifications with the addition of a randomized Cycle C may have allowed the study to maintain some scientific merit, Study 085 should be considered supportive rather than pivotal.

The sponsor is reminded that during the May 24, 2006 teleconference meeting, the sponsor acknowledged that given the error in randomization, study 085 could no longer be a pivotal efficacy trial.

Question 5:

Are the proposed Data Integration Plan and Integrated Statistical Analysis Plan acceptable?

Response:

Yes.

Question 6:

Do these analyses adequately address the Agency's concerns regarding live and photographic assessments?

Question 7:

Do these analyses adequately address the Agency's concerns regarding the correlation between Investigator and subject assessments?

Question 8:

Does the Agency foresee any other questions or issues pertaining to the efficacy anaysis of the current Reloxin program that may preclude the filing of the BLA submission?

Response (questions 6-8):

Because of the potential for unblinding side effects, the review of photographs in a blinded manner is an important secondary endpoint. It appears that independent reviewers' assessment of photographs by a panel blinded as to treatment assignment and response status was only conducted for one of the pivotal trials (study 719), and no independent reviewers' assessment of photographs was performed in study 06-01. The impact of the absence of this data will be a review issue.

Question 9:

Does the Agency concur that the extent of exposure is adequate to assess the safety of Reloxin IBL when administered in repeated doses for the indicated use?

Response:

The adequacy of the exposure data will be a review issue.

Question 10:

Does the Agency concur with this proposal?

Response:

No. Please include a study report on interim database with BLA, and provide an update in the 120-day safety update.

Meeting Discussion:

The sponsor agreed to provide the full clinical study report and 120-day safety update.

Question 11:

In view of the extensive safety data we are providing, the additional QT_c sub-study, and including the absence of any related cardiac arrhythmias in the clinical studies, does the Agency find the study as performed, presuming statistical validity, adequate to ensure that the Agency's concerns regarding cardiac safety have been met?

Response:

The sub-study and additional data appear adequate for BLA submission, but whether the data will be sufficient to address Agency concerns regarding cardiac safety will be a review issue.

Question 12:

If additional data are needed to address cardiac safety, can this data be submitted as a Phase 4 commitment?

Response:

Yes.

Question 13:

Given the extent of safety data, and the limitations of doing a conceptual integration, does the Agency agree that any additional analyses could be requested during the review process?

Response:

Yes.

Question 14:

Does the Agency have any questions or concerns related to the sample analysis, assay sensitivity and specificity?

Response:

The Agency commends the development of non-animal based screening and confirmatory assays to evaluate patient sera for the presence of antitoxin antibodies. Please include a full discussion of the antitoxin assessment (RIPA/RIPA-C) in the BLA submission including data supporting the validation of the assays (see Mire-Sluis et al. J Immunol Methods, 2004, 289:1 – 16; and Gupta et al. J Immunol Methods, 2007, 321: 1 – 18) and SOPs for the assays. Please be aware that samples testing positive in the screening and confirmatory assays should be evaluated in a neutralizing assay.

Meeting Discussion:

The sponsor requested the submission of the neutralizing assay data and updated study report with the120-day safety update. The sponsor reported that there were about 10 positive patients out of 2368 total. The Agency indicated that the sponsor should submit the RIPA/RIPA-C and the mouse protection assay validation reports with the submission of the BLA. The sponsor requested reconsideration of the Agency's decision. The Agency indicated that they would discuss and add as an addendum to the minutes.

The Agency requested that the sponsor submit SOPs for assays and non-compendial procedures. The sponsor agreed.

Addendum to minutes:

The sponsor may submit the neutralizing assay data and updated study report with the 120-day safety update. However, please clearly identify and flag in your database the patients who were positive in the RIPA/RIPA-C.

Question 15:

Does the Agency foresee any other issues or questions pertaining to the safety of Reloxin that might preclude a filing of the BLA submission?

Question 19:

Are the provision of datasets and corresponding documentation following CDISC SDTM requirements acceptable?

Response:

It is acceptable to submit data in the CDISC SDTM format. However, in addition to the SDTM datasets the sponsor will also need to submit 'analysis-ready' datasets with derived variables suitable for conducting efficacy and safety analyses. The sponsor is encouraged to submit analysis datasets following the general principles specified by the CDISC Analysis Data Model (ADaM) team (see http://www.cdisc.org/models/adam/V2.0/index.html), though adherence to the model is not required. Analysis datasets should include endpoint variables, treatment assignments and distinguish between observed and imputed observations. The submission should include adequate documentation for the datasets including definitions, formulas for derived variables, and decodes for any classification variables, so that all categories are well-defined in the documentation. The datasets should be in SAS transport format.

The sponsor is encouraged to contact esub@cder.fda.gov and submit a sample datasets before the actual submission to ensure the system compatibility. Please visit the following site for the specific guidance: http://www.fda.gov/cder/regulatory/ersr/ectd.htm
Please look for the guidance of the "Study Data Specifications" and follow the instruction for the folder structure also.

Meeting Discussion:

The Agency clarified that the sponsor should submit analysis ready datasets for each individual study. The sponsor agreed.

Question 20:

Medicis proposes to submit only data (in CDISC format) for the studies being integrated in the ISS and ISE (Table 6). Is this proposal acceptable to the Agency?

Response:

It is acceptable for filing to submit the datasets for the 6 studies appropriate for the ISS and ISE. The Agency may request additional datasets during the course of the review if necessary. Studies submitted in SDTM format should also have corresponding analysis-ready datasets.

Question 21:

Medicis proposes to submit the Integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy (ISE) detailed analyses in Module 2 under the Clinical Summary of Safety (CSS) and Clinical Summary of Efficacy (CSE), respectively, with tables, figures, and listings placed in Module 5.

Response:

Although the guidance allows for the case where the narrative portion of the integrated summaries are placed in Module 2 with supportive appendices in Module 5, the guidance also states that this should be used in cases where the integrated summary is 'small'. With 6 studies of varying designs, the ISS and ISE may be too large for this approach. The sponsor is encouraged to include the full ISS and ISE in Module 5 with appropriate summaries in Module 2.

Additional Statistical Comments:

1. The BLA submission should include the following items:
   a. study protocols, protocol amendments, and statistical analysis plans including date of finalization
   b. the randomization lists and the actual treatment allocations (with date of randomization) from the trials
   c. subgroup analyses by race, age, gender, and baseline severity

Additional Administrative Comments:

1. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

2. The sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires 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.

3. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the BLA might identify additional comments or informational requests.

4. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

5. The sponsor is reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

6. We note that SPL should be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. During the initial implementation phase of the PLR (until the end of 2006), FDA advises applicants to make a good faith effort to provide PLR-compliant SPL with their marketing applications or efficacy supplements. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

   Please submit the completed Highlights Data Element Table. To complete the Highlights data elements, please refer to the following two documents at the FDA Data Standards Council website (http://www.fda.gov/oc/datacouncil) under Structured Product Labeling: "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table." The companion document provides information on the appropriate terminology standards. If you need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov.Structured Product Labeling (SPL):

   The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

   Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

ATTACHMENTS/HANDOUTS:

1. Reloxin Pre-BLA Meeting PowerPoint Presentation prepared by Medicis Pharmaceutical Corporation.

17 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Linked Applications	Sponsor Name	Drug Name
IND 10673	IPSEN LTD	Clostridium Botulinum Toxin Type A-Hemagglutinin Complex (Reloxin; Product #52120)

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

/s/

STANKA KUKICH
10/15/2007

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: MAY 2 7 2004

Subject: End of Phase 2 IND Meeting Summary

From: *James H. Reese, Ph.D., DRMP, HFM-589*

Meeting Date and Time: April 29, 2004; 1:30 – 3:00 p.m.

Meeting Requestor/Sponsor: Ipsen, Ltd.

Product: Botulinum Toxin Type A, DYSPORT

Meeting Purpose: To discuss the CMC and Facility issues relative to the proposed Phase 3 studies for treatment of glabellar lines

DISCUSSION:

PRODUCT ISSUES

b(4)

7 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF NEW DRUGS

OFFICE OF DRUG EVALUATION VI

DIVISION OF REVIEW MANAGEMENT AND POLICY

Woodmont Office Complex II, 6th Floor
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FAX TO: Steven Scott / Biomeasure

Facsimile Telephone No. 5084733531 **Voice Telephone No.** _____

FROM: J. Reese

Facsimile Telephone No. _____ **Voice Telephone No.** 3018274358

DATE: 2/9/04 **TIME:** _____

MESSAGE: Meeting Summary

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our Reference: BB-IND 10673

FEB 0 6 2004

Biomeasure Incorporated
For Ipsen Limited
Attention: Steven R. Scott
Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757

Dear Mr. Scott:

Please refer to your **Investigational New Drug Application (IND)** for "Clostridium Botulinum Toxin Type A-Hemagglutinin Complex (Dysport; Product #52120)" and to the meeting held on January 8, 2004, between representatives of Ipsen Limited and this agency. As discussed, a copy of our memorandum of that meeting is attached for your information.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence regarding this IND should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
HFM-99, Room 200N
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

James H. Reese

James H. Reese, Ph.D.
Regulatory Project Manager
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: FEB 0 6 2004

Subject: End of Phase 2 IND Meeting Summary

From: *James H. Reese, Ph.D., DRMP, HFM-589*

Meeting Date and Time: January 8, 2004; 3 – 4:30 p.m.

Meeting Requestor/Sponsor: Ipsen, Ltd.

Product: Botulinum Toxin Type A, DYSPORT

Meeting Purpose: To discuss the Phase 2 study results and the proposed Phase 3 studies for treatment of glabellar lines

INTRODUCTION

Ipsen presented a brief overview of their key points and goals for the meeting.

DISCUSSION:

PRODUCT ISSUES

No CMC issues were discussed at this meeting due to the attendance of a third party – Ipsen's clinical collaborators. Ipsen was advised to contact DMPQ since a new facility is planned. It was agreed that a meeting to discuss CMC issues and facility issues will be arranged in the future.

CLINICAL ISSUES

Question 1:
The sponsor proposes to use the same Phase II efficacy co-primary endpoints and variables outlined below to evaluate the severity of glabellar lines in two Phase III studies to support the following labeling statements:

- *Investigator's Assessment: XX% of patients achieved a severity score of none (0) or mild (1) at maximum frown at Day 30.*

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- *Patient's Global Assessment: XX% of patients assessed moderate or better improvement (+2 or better) in the appearance of their glabellar lines at Day 30.*

The co-primary efficacy variables:

- *The investigator's assessment of glabellar lines at maximum frown on a validated 4-Point Photographic Scale (none [0], mild [1], moderate [2], severe [3] at Day 30, and*

- *The patient's global assessment of change in appearance of glabellar lines at Day 30.*

The co-primary efficacy endpoints:

- *Investigator's assessment of glabellar lines at maximum frown:*
  A responder is defined as a patient who has a rating of 'none' (0) or 'mild' (1)' for glabellar lines at maximum frown at Day 30.

- *Patient's overall assessment of glabellar lines:*
  A responder is defined as a patient who has a score of at least +2 (moderate improvement, about 50%) in the appearance of glabellar lines at Day 30.

The sponsor expects to obtain similar efficacy results from its proposed Phase III trials as obtained in its competed Phase II trial as provided below:

Phase II Co-primary Efficacy Data at Day 30
Table No. 1: ITT Population: Source: Clinical Study Report, Section 14.2, Table 6.1.1A

Dose	Investigator's Assessment at Maximum Frown % Response (95% CI)	Patient's Global Assessment % Response (95% CI)
Placebo	6.4 (1.5 – 11.3)	10.6 (4.4 – 16.8)
20 units	64.8 (55.0 – 74.6)	71.4 (62.1 – 80.7)
50 units	77.4 (68.9 – 85.9)	84.9 (77.6 – 92.2)
75 units	85.3 (78.2 – 92.4)	84.2 (76.9 – 91.5)

Does FDA agree that the co-primary efficacy endpoints discussed above are clinically meaningful and are acceptable to make the stated labeling statements?

FDA agrees that assessments by investigator and by patient are appropriate primary co-endpoints, Day 30 post-treatment is optimal for assessing this endpoint, and a clinically meaningful description of these results could be included in the label.

We recommend that treatment success be defined as "no" or " mild" lines as assessed by investigator and by patient.

FDA recommends utilizing a "static' patient global assessment. A 4-point scale similar to that used for the investigator evaluation may be used. This would require defining the four categories. In addition, the patient's assessment needs to be performed prior to the assessment by the investigator to maintain independence of the patient's assessment.

The investigator assessment should be corroborated by blinded assessors. The 4-Point photographic Scale should be used as reference/ training of investigators and blinded assessors .

We would like additional statistical analyses to confirm validity of the scales utilized in the Phase 2 study and proposed for evaluation of the Phase 3 studies:

Ipsen will provide them.

Ipsen asked whether both the investigator assessment and panel review would be required.

FDA stated that investigator assessment was a co-primary efficacy endpoint with panel review as an important secondary endpoint. The results of the investigator assessment should be consistent with those of the panel review.

Ipsen asked if the patient assessment should occur in reference to the photographic scale.

FDA stated that the patient scale cannot be standardized and could be an ordinal scale of the patient's perception. A visual analog scale may also be acceptable. FDA agreed to considerthe sponsor's thoughts about how to create the patient scale.

Question 2:

The selection of optimal dose is based on a prospectively defined dose selection methodology, which included efficacy, duration of effect assessments and safety. The sponsor followed this prospective dose selection procedure and determined 50 units to be the optimal dose of 52120 to be used for the treatment of glabellar lines in the Phase III clinical program.

Does FDA agree with the dose selection for the proposed Phase III trials?

Based on the activity data provided, the injection of 50 unit doses into five sites as described, seems acceptable for further study.

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Question 3:

The sponsor conducted an exploratory analysis in the Phase II program comparing the results of Independent Photographic Reviewer (IPR) assessments of glabellar line severity of patient's photographs taken at maximum frown at baseline and at day 30 using the validated 4-Point Photographic Scales. These results were compared to the co-primary efficacy endpoint of live investigator's assessment of patient's glabellar lines at maximum frown at baseline and at day 30 using the validated 4-Point Photographic Scales as a guide. The results are presented in Table 2 below:

Table No. 2: Comparability of Number of Responders in each treatment group by Investigator's Live Assessment and IPRs Photographic Assessment (mean scores of the 3 investigators of the IPR) of Glabellar lines at Maximum Frown (MITT Population)

Parameter	Placebo (N=90)	20 units 52120 (N=88)	50 units 52120 (N=91)	75 units 52120 (N=91)	Total (N=360)
Live (n)	3	58	72	80	213
Proportion of success	0.034	0.682	0.791	0.889	0.600
Photo (n)	4	53	70	79	206
Proportion of success	0.047	0.716	0.854	0.929	0.632
p-value*	0.654	0.643	0.285	0.353	0.393

* p-value comparing the proportions of success between live and photo assessment using a Chi-Square test.
Source: Exploratory Analysis Report, Table 1, Appendix 2

The exploratory analysis suggests that the proportions of successes (i.e., clinical responses) with both the live and IPR methods are comparable and the proportions of successes with the IPRs show slightly better results than the live assessment.

However, the experts in the areas of dermatology and facial plastic surgery recommend that a direct, live assessment of the subject's glabellar lines by the treating physician or by another trained individual against the 4-Point Photographic Scales should be utilized instead of evaluation of photographs of the subject's own glabellar lines by a physician, group of physicians or other trained individuals against a reference scale. The live assessment method offers the specific advantage that the observer/physician is able to assess the level of effort that the subject is able to exert while attempting to frown.

The live assessment method may be criticized by those who believe that the treating physician may become unblinded to the nature of the injection administered during treatment (i.e., placebo or study drug) due to assessments made at time points prior to day 30 (i.e., Day 7). However, with respect to maintaining the blind, prior evaluation was performed using the photographs taken on Day 7 by an individual other than the investigator responsible for evaluating study endpoints at Day 30 (primary endpoint) and subsequent follow-ups. Efficacy assessment at Day 7 involved a photographic evaluation in comparison to the

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Photoguide performed by the investigator after the patient completed the study to maintain the blind. Therefore, the blinding of the live assessment process remains intact at Day 30.

The photography evaluation method, by its very nature, is two-dimensional and thus.. tends to "flatten" facial features, including wrinkles. Discussions with investigators have led to the conclusion that the investigators are able to observe details of the patient that would not be available to independent reviewers through photographs, even if the independent reviewer were given full face photos to evaluate, further justifying the "live assessment" evaluation. The correlation between live assessment of subjects' wrinkles by investigators and independent assessment of photographs of subjects' wrinkles by independent reviewers is, therefore, not exact. Thus, evaluation of photos by the treating physician or by independent reviewers clearly demonstrates clinical efficacy;
The live assessment method is most commonly employed by physicians to select patients for treatment and to evaluate them after treatment; they usually do not take photographs of patients for purposes other than archival documentation.

Based on above discussion, the Sponsor proposes utilizing live investigator assessments in the phase III studies. Does FDA agree?

As stated above, we recommend co-endpoints for the Phase 3 trial consisting of investigator and patient assessments as well as corroborative assessments by panel review. It is essential to ensure appropriate blinding of the investigators.

A discussion ensued about the possibilities for unblinding of the treating physician by the muscle weakness and the potential for bias in the evaluation of the severity of the glabellar lines, and whether the placebo formulation is physically distinguishable from the active formulation.

Ipsen asserted that the use of specific terms and characteristics to describe the clinical result and train the investigators should reduce the subjectivity. Also, based on the ability of the Phase 2 study, to define dose –response Ipsen expects that unblinding will not be a problem.

Question 4:

The Sponsor's clinical experts provided examples of labeled photographs used in the 4-Point Photographic Scales (at rest and at maximum frown) that were utilized in the Phase II study. These photographs depict the key characteristics of the glabellar lines relevant to the classification of severity. Each photograph illustrates the clinical characteristics of the glabellar lines for each category of severity and provides a clear, clinically relevant gradation in severity of glabellar lines which encompasses the full spectrum of observable severities. The severity of the glabellar lines is based on the characteristics of the lines themselves. Based on this, the Sponsor believes that one photograph per category in the 4-Point Photographic Scales

(at rest and at maximum frown) is sufficient for use as a guide in evaluating and categorizing the severity of glabellar lines.
Does FDA agree on the glabellar lines severity classification based on the clinical characteristics for each category of severity, as defined by clinical experts and discussed below? Since the severity of glabellar lines is based on the characteristics of the lines themselves, use of one photograph per category of severity for the 4-Point Photographic Scales is considered sufficient. Does FDA agree?

FDA needs additional confirmation that the levels of severity utilized as reference/ training of investigators during the Phase 2 clinical trial are representative of the entire spectrum of affected patients. Therefore, we would like an opportunity to review the sample facial photograph booklet utilized in the validity studies.

Ipsen provided the booklet.

In addition we would like to review:

- A correlation by patient of the pair-wise assessments for the investigator and the panel reviewers.
- Actual data on the concordant and discordant pairs from the inter-rater data.
- Analysis of the distribution of grading scores for each examiner.

Question 5:

The Sponsor's clinical experts outlined the clinical evaluation of glabellar lines and the specific regions of the face that are evaluated for efficacy. The toxin is injected in the procerus, corrugator and orbicularis oculi muscles, which comprise the frown muscle complex along with the depressor supercilli muscles. Individual muscles can be heavily interwoven or they may merge, so anatomic variance of the muscles may occur. To evaluate the extent of toxin spread and the efficacy of the drug, it is important to evaluate surrounding muscles, since botulinum toxin may diffuse beyond the injection point. In the case of the glabella, this includes the brows, forehead, eyes and nose. Because the injections during treatment extend to the mid-pupillary lines, this area must also be assessed. To accurately evaluate the effect, the areas mentioned above must be visualized.

Follow-up evaluation of glabellar lines treatment must take into account the effect of the frown muscle complex on the glabella, brows, periorbital areas and forehead. An accurate assessment of these areas should be made at rest and at maximum frown.

It is the Sponsor's belief that it is necessary to include the entire periocular area in the lower forehead to the midpupillary line. This supports the Sponsor's method of cropping of photograph by including the glabella and its surrounding area, including the eyes.

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Does FDA agree on the use of cropped photographs containing the critical anatomical region of the face, as described and justified for glabellar lines evaluation?

Yes, use of cropped photographs containing the critical anatomical region of the face would be preferable for this end-point evaluation.

Question 6:

The Sponsor has provided FDA with the formal Validation Report on the 4-Point Photographic Scales that were utilized in the Phase II study. The validation report describes the process of selecting the photographs used in the scales, validation methodology and validation results.

Excellent inter-rater and intra-rater agreement were observed when using the 4-Point Photographic Scales to evaluate and classify fifty (50) photographs of glabellar lines encompassing the full spectrum of glabellar line severity at maximum frown (Kappa values: 0.83 and 0.85). There was also excellent inter-rater and intra-rater agreement using the 4-Point Photographic Scale when evaluating and classifying fifty (50) photographs of glabellar lines encompassing the full spectrum of glabellar line severity at rest (Kappa values: 0.79 and 0.84). These data demonstrate that the 4-Point Photographic Scales used are valid and, therefore, can be used as a guide in evaluating the severity ofglabellar lines in the Phase ill clinical studies.

b(4)

Does FDA agree that the validation method and results demonstrate the validity and utility of the 4-Point Photographic Scales for evaluation of the severity of glabellar lines in the Phase II study? Does FDA agree that the same scales can be used in the Phase III pivotal trials intended to support licensure?

Report —— 52120-003.0 You have performed an exploratory analysis of Principal Investigator assessment vs. Independent Photographic Reviewer assessment of treatment response in your Phase 2 dose ranging study. Using a Chi square test you have determined that the proportion of responders using PI and IPR are not different.

We would like additional statistical analyses to confirm validity of the scales utilized in the Phase 2 study and proposed for evaluation of the Phase 3 studies:

- A plot (scatter plot) and summary (2x2 tables) of individual patient's response/failure overall, by dose group, and by site.

Using both methodologies?

Yes.

- Distribution plots of scale scores obtained by each investigator for subjects evaluated at both maximal frown and rest, by dose group.
- Comparison of live vs. photographic assessments utilizing Cochran- Mantel-Haenszel-statistical method.

Ipsen will provide these comparisons.

A discussion of the relative value of live assessment vs. photographic assessment ensued. FDA stated that photographic assessment should be supportive to live assessment. Photographic assessment is an important secondary endpoint, and FDA would like to see consistency between the live and photographic evaluation.

FDA asked about the relative merits of assessing glabellar lines at rest vs. at maximal frown.

Ipsen responded that the patient's greatest concern is with the lines induced by maximal frown.

Question 7:

In the phase II study the sponsor conducted an exploratory efficacy analysis by using a static Visual Analog Scale (VAS) to assess the patient's global assessment of the appearance of glabellar lines on Days 0 (Baseline), 7, 30, 60, 90, and 120. Using a 10 cm horizontal line, the patient was instructed to make a vertical mark directly on the Case Report Form (CRF) on the line at a location that signifies his or her overall assessment of glabellar lines on that particular visit day. The VAS was oriented such that the extreme LEFT represented no glabellar lines and the extreme RIGHT represented severe glabellar lines. The changes in VAS Score for Days 7, 30, 60, 90, and 120 were calculated with respect to the VAS Score at baseline.

A 9-point dynamic scale was used as a co-primary efficacy endpoint at day 30 and other time-points. In the dynamic scale, patients were asked to assign a score that best describes their current overall assessment of glabellar lines at the time of evaluation compared to how they looked before receiving the injection. The patient was asked: "How would you rate the change in the appearance of your glabellar lines compared with their appearance immediately before the injection?" The ratings of response by patients ranged from +4 (complete improvement, about 100%) to -4 (very marked worsening, about 100%). For this co-primary endpoint, a responder was defined as having a grade of at least +2 at Day 30 (moderate improvement, about 50%).

A correlation between the 9-point dynamic scale, which measures a change from baseline, and the; change from baseline in patient's assessment using the visual analog scale (VAS) was performed as part of the Phase II study analysis plan. A positive value on the 9-point scale

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indicates improvement and a negative change from baseline on the VAS indicates improvement, so a negative correlation between the two scales was expected. Spearman's rank correlation coefficient at Day 30 was -0.666, indicating a moderate negative correlation. The correlation over all patients and all visits was -0.585, which also indicates moderate negative correlation. Both of these correlations are statistically significantly different from zero and indicate a moderate negative monotonic relationship between the two variables. The correlations at Days 60, 90 and 120 were -0.508, -0.452, and -0.395, showing a decreasing correlation between the scales over time.

There was a large variation in responses on the V AS when compared to the 9-point scale and in responses on the 9-point scale when compared to responses using the VAS. Among the 506 measurements where patients who rated themselves as 0 (no change) on the 9-point scale, ratings on the VAS ranged from -5.2 to 7.6, with a standard deviation of 1.9. The mean was 0.2 and the median was 0.0 on the VAS. The standard deviation of the VAS ratings among patients who rated themselves as 0 on the 9-point scale generally increased over time [1.76 at Day 30 (N=92), 1.67 at Day 60 (N=102), 1.84 at Day 90 (N=140) and 2.13 at Day 120 (N=172)].

Among the 41 measurements where patient rating using change in VAS was exactly' 0, ratings on the 9-point scale ranged from 0 (no change) to +4 (complete improvement, about 100%). There did not seem to be any trends over time among patients who rated themselves as 0 using the VAS, but the sample sizes were relatively small. Ratings on the 9-point scale ranged from 0 to +2 at Day 30 (N=7), 0 to +4 at Day 60 (N=11). 0 to +3 at Day 90 (N=13) and 0 to +3 at Day 120 (N=10).

The evidence tends to show that the two scales did not measure the same quantity during this study and that the correlation between the two scales worsened over time.

From a statistical point of view there is nothing to objectively recommend one method over the other. Correlations between both patient self-assessment methods and the Investigator's Assessment at Day 30 (co-primary efficacy end point) were moderate and ®®The Sponsor believes that by using the same 9-point dynamic scale as used by Allergan Inc. in the assessment of BOTOX® COSMETIC in the pivotal studies for this indication for its patients' global assessments, we can support a comparable labeling statement to BOTOX® COSMETIC:

> *"x%. (y/z) of subjects determined that a moderate improvement in their own appearance (+2 or better) occurred by the 30th day following treatment."*

We anticipate that the labeling will be comparable to that approved by FDA for Allergan's BOTOX® COSMETIC for the treatment of glabellar lines.

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Based on the correlation data and the reasons presented above, the Sponsor proposes utilizing the 9-point dynamic scale as a co-primary efficacy endpoint analysis tool in the phase III study. Does FDA agree?

FDA suggested utilizing a patient static global evaluation utilizing a 4-Point Scale similar to that used for the investigator evaluation. This will require defining the four categories. It is important to ensure that the patient's appraisal be performed prior to the appraisal by the investigator and thus maintain independence of the patient's assessment. In our experience, static scales are more reliable. Utilizing similar numeric grading for both scales, will make correlation between the two co-primary end points more meaningful. A visual analog scale may also be acceptable.

Question 8:

The Sponsor proposes a Phase III clinical program consisting of two (2) identical Phase III confirmatory studies and one (1) Phase III open-label study. A database of approximately 345 patients will be available from the randomized Phase II and Phase III studies which will include 93 treated patients with 50 unit dose in the Phase II study (Y-97-52120-717) and approximately 252 Phase ill (Study No's: Y-97-52120-718 and Y-97-52120-719) treatment group patients who have received a one-time treatment of the proposed effective dose of the toxin (i.e., 50 units). Complete follow-up safety evaluation will be carried out. Furthermore, another 95 patients treated with 75 unit dose in the Phase II study and will be added to the database to yield a total of approximately 440 patients. The overall database for this clinical program will also include approximately 1200 patients treated with the recommended effective dose of the toxin (i.e., 50 units) under the Phase III Open Label study. Also an additional 140 patients data (out of which 99 patients having more than 1 cycle of treatment) will be available from the European clinical studies conducted in France and Germany with 52120 for the treatment of glabellar lines.

The above mentioned sample size meets the minimum requirement of the cohort of exposed subjects based on the Guideline for Industry: "The Extent of Population Exposure to Assess Clinical Safety; ICH-E1A, March 1995," which states that "usually 300 to 600 patients should be adequate."

Does FDA agree that there is a sufficient number of patients and patient exposure to support a Marketing Application Approval?

The need exists to rigorously confirm this therapeutic entity's efficacy and safety for long-term or chronic treatment. That will require robust supportive data demonstrating efficacy for repeated treatment in a substantial number of subjects.

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Adequately powered rigorous Phase 3 trials recommended include:

1. Demonstration of efficacy and safety of treatment in two double-blind placebo-controlled trials.
2. Demonstration of efficacy and safety of retreatment in a double-blind placebo-controlled trial. Patients may be randomized to receive two (or more) courses of blinded study treatment. Alternatively, patients who have received multiple active treatments in prior efficacy or open-label studies may be randomized to receive a single blinded study treatment.

In addition, large safety trial (open-label repeated treatment after one or two prior treatments, multi-treated subjects, multi-centers, multi-investigators) would provide supportive data.

We recommend a safety database of at least 1500 patients with the majority having received multiple courses of therapy.

Please provide validated information concerning the anti-drug antibodies assays prior to the potential submission of the BLA licensure application. Evaluate the relationship of antibodies to number of courses of Botulinum Toxin and duration of Botulinum Toxin therapy.

Question 9:

Does FDA agree that the proposed overall clinical development program which includes; two (2) Phase III randomized controlled studies and one (1) Phase III Open Label study for the treatment of glabellar lines is adequate to support a Marketing Application Approval?

No, to support a Marketing Application Approval will require rigorous determination of the benefit to risk ratio among a substantial proportion of subjects exposed to multiple courses of therapy.

FDA Questions/Comments:

1. Treatment allocation

You propose a 3:1 (active: placebo) treatment allocation. This unbalanced allocation may lead to problems with interpretation of results across patient subgroups. We recommend a more balanced allocation (2:1 or more preferably 1:1). Imbalance randomization has the potential to weaken the ability to draw conclusions from the exploratory subset analyses performed during the BLA review. A small placebo group increases the risk that there will be fluke occurrence of a seemingly non-consistent result for safety or efficacy when the subsets are examined, due to a chance occurrence in the small placebo group subset. Thus the Agency may be unable to determine whether it is a chance occurrence of bad luck, or if it is a real signal. If it relates to efficacy with a risky product, or if it relates to a serious AE, then we may not be able to just write it off to chance occurrence, and it has the potential to hold up approval or

to appear in labeling. Therefore, we advise that 1:1 randomization will provide more robust data.

2. Study centers
Your proposed use of five study centers in the two Phase 3 primary treatment efficacy trials is acceptable.

There will be 5 in the U.S. and one in Canada.

3. Study investigators
Please use different investigators for all Phase 3 trials. Please ensure that investigators by specialty, and other professional qualifications are representative of the physicians who are expected to use the product.

Can Phase 3 centers be used in the open label trial?
Yes.

4. Study patients
You plan to enroll patients previously treated with your product or other botulinum toxin (unless treated within 3 months of entry into study). You do not specify how many such patients may be enrolled. Enrollment in the two Phase 3 primary treatment trials of patients previously treated with botulinum toxin will make it more difficult to interpret safety data (due to confounding) and efficacy data (potential enrichment of responders). Please enroll only treatment-naïve subjects in the two Phase 3 trials.

5. Sample size
You propose to expose 126 subjects to active treatment and 42 subjects to placebo in the randomized, double-blinded, controlled portion of each of the two Phase 3 trials (for a total of 252 and 84). Your justification for this sample size is that it will have adequate power to demonstrate and confirm the treatment effect. Please be aware that the numbers may be too small to write an adequate product label if the trial results suggest differences in safety or efficacy in important subgroups (e.g. age, body size etc.).

6. Clinical development
Please describe your plans for study of additional cosmetically significant lines in the face. Do you have plans for evaluating the safety and efficacy of combined areas? Please describe the sites and the manner in which your product may be used off-label.

7. Demonstration of long-term efficacy and safety
Whereas a single injection will not adequately maintain effectiveness long-term, repeated injections will be required to maintain the desired effect. Safety (including antigenicity) and efficacy of retreatment are critical components of the label for this

treatment. Therefore, we recommend a placebo-controlled repeated treatment trial to evaluate the safety and efficacy of repeated treatment, that resembles general physician practice patterns.

The long-term study proposed, would determine such variables associated with chronic treatment as the durability of response, frequency of treatments per year, the antigenic potential associated with repeated injections, and overall safety.

We recommend that you provide the following additional data at the time of filing of your Marketing Application:

- Integrated safety analysis for all available data from clinical trials and post-marketing reports.
- Information on the complete manner of use of this product for both labeled and off-label usage including all usage for facial lines.

8. Minimum interval between treatments.
You require a 90-day interval between treatments. Please justify this interval. We recommend that patients be followed after the first treatment and be retreated when they experience loss of response.

9. Cross-correlation between patient and physician assessments -
Whereas different scales were utilized in the patient and physician assessments, we would like the sponsor to provide an evaluation of the correlation of the different scales.

10. Provisions for subset analyses in Phase 3 trials
Provide provisions for subset analyses such as:

- Individual grade level responses of subjects from baseline (numbers of subjects with each possible grade level change from baseline).
- Summary of patient grade level changes from baseline.
- Individual investigator scoring patterns (patient grading scores at baseline and scoring level change).
- Effect of demographics such as age on response to therapy.
- Inter-rater scoring distribution concordance rates.

11. Provisions to monitor for eye-related adverse events
In the CRF, make provisions to monitor for all possible eye symptoms and signs, ptosis, visual disturbance, itching, eye tearing, etc.

12. Provisions for handling missing data
Please describe how missing data will be imputed for the efficacy analyses.

13. Drug compliance
You state that drug compliance will not be a problem. Please confirm that you will verify the manner of administration of the product (including amount per injection site for each treatment) and the proper disposal of unused materials.

14. Assessment of glabellar lines at rest
Please be aware that presentation of the response data for the secondary end-point (photographs at rest) should be based on the intention-to-treat population. The results you presented of the response for the secondary end-point in the Phase 2 trial only represented a subset of the treated patients.

FDA Attendees:
Louis Marzella, Marc Walton, Aloka Chakravarty, Elizabeth Shores, Rona LeBlanc, J. Lloyd Johnson, Scheldon Kress, James Reese

Ipsen, Ltd. Attendees:
Robin Kingswell, Chris Dott, Phil Weatherill, Ron Ehmsen, Nancy Seretta, Gary Monheit, Corey Maas, Deepak Chadha, Steven Scott, Jeanne Novak, Roger Johnson

APPEARS THIS WAY ON ORIGINAL