

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125274Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>		NDA NUMBER	
		NAME OF APPLICANT/NDA HOLDER Ipsen Biopharm Limited	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Dysport®			
ACTIVE INGREDIENT(S) botulinum toxin type A hemagglutinin complex		STRENGTH(S) 500 Units	
DOSAGE FORM Lyophilized Powder For Injection			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number		b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner		Address (of Patent Owner)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <span style="float: right;"><input type="checkbox"/> Yes    <input type="checkbox"/> No</span>			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <span style="float: right;"><input type="checkbox"/> Yes    <input type="checkbox"/> No</span>			

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

*Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:*

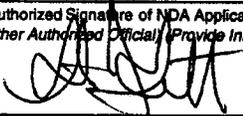
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent)  Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

<b>6. Declaration Certification</b>	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 508 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>US Agent for IPSEN Biopharm Limited</p> <p>11/1/07</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Steve Scott, Senior Director - Regulatory Affairs (US Agent for Ipsen Biopharm Limited)</p>	
<p>Address</p> <p>27 Maple Street</p>	<p>City/State</p> <p>Milford, MA</p>
<p>ZIP Code</p> <p>02466</p>	<p>Telephone Number</p> <p>(508) 478-0144</p>
<p>FAX Number (if available)</p>	<p>E-Mail Address (if available)</p> <p>steve.scott@ipsen.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

1.3.5.2 PATENT CERTIFICATION

1.3.5.2 *Patent Certification*

The original Biologics License Application for Dysport® for Injection is submitted under with Section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), as amended.

Patent Certification is not required.

1.3.3 DEBARMENT CERTIFICATION

PAGE 1

1.3.3 *Debarment Certification*

Ipsen Limited hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

APPLICANT:

Alistair Stokes

Dr. Alistair Stokes  
Ipsen, Ltd.  
190 Bath Road  
Slough

31 October 2007

Date

US AGENT:

Steven R. Scott

Steven R. Scott  
Biomeasure, Inc.  
27 Maple Street  
Milford, MA 01757

11/19/07

Date

**1.3.3 Debarment Certification (continued)**

Biomeasure, Incorporated hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



\_\_\_\_\_  
Jacques-Pierre Moreau  
Biomeasure, Inc.  
27 Maple Street  
Milford, MA 01757  
USA

11/09/07

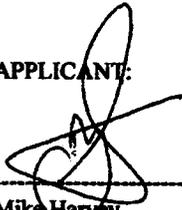
Date

1.3.3 DEBARMENT CERTIFICATION

1.3.3 *Debarment Certification (continued)*

Ipsen Biopharm Limited hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

APPLICANT:



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Mike Harvey  
Ipsen Biopharm Limited  
Unit 9 Ash Road  
Wrexham Industrial Estate  
Wrexham LL139UF  
United Kingdom

14-16-07

Date

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 125274	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Dysport Established/Proper Name: abobotulinumtoxinA Dosage Form: Injection		Applicant: Ipsen Biopharm Limited Agent for Applicant (if applicable): Steven Scott
RPM: Tamy Kim		Division: 120
<p><b>NDAs:</b>            NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)            Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>            Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>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.</b></p> <p><input type="checkbox"/> No changes      <input type="checkbox"/> Updated            Date of check:</p> <p><b>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.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		4/29/09
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input type="checkbox"/> None Extension on 9/26/08 Complete Response on 12/23/08

<sup>1</sup> 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.

➤ 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](http://www.fda.gov/cder/guidance/2197dft.pdf)). If not submitted, explain \_\_\_\_\_

Received

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

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	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

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

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

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

Yes       No

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

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

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

Yes       No

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

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

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

Yes       No

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

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

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

Yes       No

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

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

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

❖ Copy of this Action Package Checklist <sup>3</sup>	Yes.
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**Officer/Employee List**

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	X Included
Documentation of consent/non-consent by officers/employees	X Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Complete Response: 12/23/08 Approval: 12/29/09
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**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 9/5/08

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date at upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	Included
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	X RPM 6/19/08 X DMEPA 8/29/08, 4/24/09 X DRISK 9/15/08, 12/19/08 X DDMAC 9/17/08, 12/11/08 <input type="checkbox"/> CSS X Other reviews OBP Carton and container 9/12/08, 4/29/09
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul>	4/24/09 Acceptability
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	December 18, 2007
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	This is not included, since this is a BLA.
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP                             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )	Not included since this is an orphan product.
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	X Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	X Yes
<ul style="list-style-type: none"> <li>• Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submissions/communications</li> </ul>	Yes. Via email.
❖ Postmarketing Commitment (PMC) Studies	X Yes

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

<ul style="list-style-type: none"> <li>Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	Yes. Via email. 4/29/09
<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	Yes. Via email 4/29/09
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	Yes.
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>PeRC (<i>indicate date; approvals only</i>)</li> </ul>	X Not applicable
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	X Not applicable (Memo dated 3/5/09)
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date</i>)</li> </ul>	X No mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg 12/5/06; 10/26/06
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	X No mtg
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	CMC 4/12/07
❖ Advisory Committee Meeting(s)	X No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>48-hour alert or minutes, if available</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/29/09
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/26/09
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/18/08
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	12/18/08
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	07/29/08
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	X None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	Clin Safety reviewer 8/19/08; Safety TL 9/15/08
❖ 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	07/29/08
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	X Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> <li>REMS Memo (<i>indicate date</i>)</li> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> </ul>	<input type="checkbox"/> None DDMAC REMS Review: 12/08/08 DRISK REMS: 4/15/09  REMS Memo 12/23/08 04/29/09 – See AP Letter
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested Included

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 9/5/08

<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	X None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	X None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	X None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/12/08
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/3/08
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/10/08
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/10/08
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	X None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/23/08
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/18/08, 4/29/09
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/18/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	X None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	X No carc
❖ ECAC/CAC report/memo of meeting	X None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	X None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/24/08
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/24/08
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None 12/11/08
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 12/11/08
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	

<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	12/11/08
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs:             <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	Date completed: 9/9/08 & 4/1/09 X Acceptable <input type="checkbox"/> Withhold recommendation Date completed: 4/1/09 <input type="checkbox"/> Requested X Accepted <input type="checkbox"/> Hold

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

**MEMORANDUM**

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

**DATE:** March 5, 2009

**APPLICATION:** BLA 125274: Dysport (Botulinum Toxin Type A)

**FROM:** Russell Katz, M.D., Director, Division of Neurology Products  
DNP) (HFD-120)  
Mark Avigan, M.D., Division Director, Division of  
Pharmacovigilance I (HFD-430)

**PROJECT MANAGER:** Tamy Kim, Pharm.D., Regulatory Project Manager, DNP

**SUBJECT:** Preapproval Safety Conference for 125274/ Dysport (Botulinum Toxin Type A)

The Division of Neurology Products and the Division of Pharmacovigilance I have concurred that a Pre-approval Safety Conference is not required for Dysport (Botulinum Toxin Type A).

Two botulinum toxin products (botulinum toxin type A marketed as Botox and botulinum toxin type B marketed as Myobloc) are currently approved in the United States (US) for the same indication (cervical dystonia) as that proposed for Dysport. In addition, Botox and Botox Cosmetic are approved for other indications. Postmarketing safety data from DYSPORT and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The risk of these symptoms is probably greatest in children treated for spasticity but can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. It is also known that the potency units of the three products (Botox, Myobloc and Dysport) are specific to the preparation and assay method utilized, that the units cannot be compared or converted into units of any other botulinum toxin product, and that the products are not interchangeable. As a consequence, we are requiring the approved products and Dysport to have a Medication Guide and revised labeling with language to reflect the above concerns. In addition, we are requiring the approved products and Dysport to change their established names from Botulinum Toxin Type A (or B) to prefix+botulinumtoxinA. Further, under FDAAA we are requiring the manufacturers of Dysport and of the approved products to conduct clinical trials in children and in adults with lower limb spasticity.

It is known that potentially life-threatening dysphagia, respiratory depression, and other serious events can occur following spread of botulinum toxin effects beyond the intended site of injection. It is also known that the potency units of the three products (Botox, Myobloc and Dysport) are specific to the preparation and assay method utilized, that the

units cannot be compared or converted into units of any other botulinum toxin product, and that the products are not interchangeable.

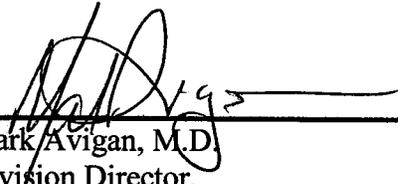
A potential difference between Dysport, and Botox and Myobloc is that Dysport contains bovine-derived lactose as an inactive ingredient, and a small amount (approximately 15-45 µg per 500 units of Dysport) of contaminant milk protein. Theoretically, there is a risk of allergy in patients with allergy to cow's milk protein. However, the potential resulting toxicity following Dysport injection is expected to be similar following oral ingestion of cow's milk protein in a patient with this allergy. This risk is mitigated by language in the Contraindication section of the label stating that Dysport contains cow's milk protein, and that patients known to be allergic to cow's milk protein should not be treated with DYSPORT.

Therefore, while Dysport (Botulinum Toxin Type A) is officially designated an Original Biologics Application, there is significant cumulative experience in the US with other botulinum toxin products already approved (Botox and Myobloc) as well significant cumulative experience with Dysport outside the US, since its first approval in UK in 1990 and subsequently in over 72 countries. Therefore, the safety profile of Dysport is not expected to be significantly different from similar botulinum toxins currently approved in the US.



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



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Mark Avigan, M.D.  
Division Director,  
Division of Pharmacovigilance I

**Hughes, Patricia**

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**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 observations were issued. the inspection was classified as NAI. The PDUFA date is Dec 28, 2008 and the approval letter is currently being drafted.

Thank you.

Patricia



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NOV 26 2008

Our STN: BL 125274/0

Ipsen Biopharm Limited  
Attn: Steven Scott  
Senior Director, Regulatory Affairs  
27 Maple Street  
Milford MA 01757

Dear Mr. Scott,

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

We have reviewed the Chemistry, Manufacturing, and Controls section of your application dated 29 November 2007 for Clostridium botulinum toxin type a hemagglutinin complex and have determined that additional information is necessary to take a complete action on your application.

For ease of reference, we divided our information request into six parts. Please submit information to address the following:



**V. Microbiological Monitoring of the Environment**

- a. Please clarify the term [REDACTED] <sup>(b) (4)</sup> of the Production Area Environmental Monitoring Schedule.
- b. Please provide environmental monitoring data regarding the sampling volume, frequency, and location in the critical area during filling.

**VI. Container Closure Integrity**

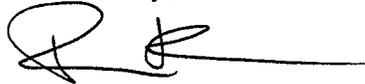
- a. Please provide stability test plan for Container Closure Integrity testing.

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

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 Project Management Officer, Giuseppe Randazzo, at (301) 796-3277 or the Regulatory Project Manager, Tamy Kim at (301) 796-1125.

Sincerely,



Patricia Hughes, Ph.D.  
Biotech Manufacturing Team Leader  
Division of Manufacturing and Product Quality  
Office of Compliance  
Center for Drug Evaluation and Research



INFORMATION REQUEST LETTER

Our STN: BL 125274

COMPLETED NOV 06 2008

Ipsen Biopharm Limited  
Attention: Steven Scott  
Senior Director, Regulatory Affairs  
27 Maple Street  
Milford, MA 01757

Dear Mr. Scott:

Please refer to your November 29, 2007, Biologics Licensing Application (BLA) 125274, submitted under section 351(a) of the Public Health Service Act for Dysport® (botulinum toxin Type A) for the treatment of cervical dystonia.

Please also refer to the August 20, 2008, teleconference in which the Division of Neurology Products informed you that a Risk Evaluation and Mitigation Strategy (REMS) will be required for this application. This letter is the formal notification of the REMS requirement.

We acknowledge receipt of your draft Dysport® (botulinum toxin Type A) communication plan dated September 8, 2008. You may incorporate applicable materials that were described in the September 8, 2008, submission in response to requests cited in this letter.

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Dysport® (botulinum toxin Type A) to ensure that the benefits of the drug outweigh the risk of potential systemic spread of botulinum toxin after local injection and the risk of potential medication errors related to the lack of interchangeability of Dysport® (botulinum toxin Type A) with other licensed botulinum toxin products. One postmarketing case of death in a patient with symptoms consistent with systemic botulism was reported in the Dysport® (botulinum toxin Type A) submission. There have been postmarketing cases of systemic botulism reported for

other botulinum toxin Type A and botulinum toxin Type B products. Once Dysport® (botulinum toxin Type A) is approved, there will be three botulinum toxin products on the market, two of them type A, and one type B. There is a different dose to potency ratio between the various botulinum toxin products. In addition, each of these three botulinum toxin products will have different units of dosing for cervical dystonia. Therefore, the three botulinum toxin products are not interchangeable.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Dysport® (botulinum toxin Type A) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Dysport® (botulinum toxin Type A). FDA has determined that Dysport® (botulinum toxin Type A) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Dysport® (botulinum toxin Type A). FDA has also determined that Dysport® (botulinum toxin Type A) is a product for which patient labeling could help prevent the consequences of serious adverse events. Under 21 CFR 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who receive Dysport® (botulinum toxin Type A) injections.

**Communication Plan:** We have determined that a communication plan targeted to healthcare providers who are likely to prescribe and/or inject Dysport® (botulinum toxin Type A) to disseminate information regarding the risks of potential systemic spread of botulinum toxin after local injection and lack of interchangeability of Dysport® (botulinum toxin Type A) units with those of other licensed botulinum toxin products will support implementation of the elements of your REMS.

The communication plan must include, at minimum, the following:

- Dear Healthcare Provider Letters to be distributed at launch of the approval of Dysport® (botulinum toxin Type A) to neurologists, dermatologists, and other specialties and healthcare professional staff who prescribe or inject Dysport® (botulinum toxin Type A) or other botulinum toxin products.
- Dosing Guide for Physicians that includes information on correct dose selection including lack of interchangeability of Dysport® (botulinum toxin Type A) units with those of other licensed botulinum toxin products, reconstitution and volume of injection, and technique of injection.
- A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the Dosing Guide and other communication materials will be directed. This should be inclusive of all Dysport® (botulinum toxin Type A) prescribers.

- A schedule for when and how these letters/materials are to be distributed to healthcare providers.

**Timetable for Assessments:** The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than by 18 months, by 3 years and in the 7th year after the REMS is approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

Your REMS assessments must assess the extent to which the elements of your REMS are meeting the goals of your REMS and whether modifications to the elements or goals are needed.

In accordance with section 505-1, you must submit a proposed REMS. Before we can continue our evaluation of BLA 125274, you will need to submit the proposed Dysport® (botulinum toxin Type A) REMS to this application. The REMS, once approved, will create enforceable obligations.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Dysport® (botulinum toxin Type A). Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for assessment of the REMS may include but may not be limited to:

1. A survey of patients' understanding of the serious risks of Dysport® (botulinum toxin Type A).
2. A survey of prescribers' understanding of the serious risks of Dysport® (botulinum toxin Type A) and the lack of interchangeability of Dysport® (botulinum toxin Type A) units with those of other licensed botulinum toxin products.
3. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
4. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.
5. An assessment of use data including:
  - a. extent of use (denominator estimates)
  - b. number of patients by age
6. A summary of reports of all potential or diagnosed cases of systemic spread of botulinum toxin after local injection with Dysport® (botulinum toxin Type A).

7. A summary of reports of all medication errors involving interchangeability of Dysport® (botulinum toxin Type A) units with those of other licensed botulinum toxin products.

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your BLA. Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NEW PROPOSED REMS FOR BLA 125274**

On the first page of subsequent submissions related to an already-submitted proposed REMS, prominently identify the submission by including this wording in bold, capital letters at the top of the letter:

**BLA 125274 PROPOSED REMS-AMENDMENT**

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

Sincerely,



11/6/08

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

**Attachment A**

**REMS Template**

**Application number TRADE NAME (DRUG NAME)**

**Class of Product as per label**

**Applicant name**

**Address**

**Contact Information**

**PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

List the goals and objectives of the REMS.

**II. REMS ELEMENTS:**

**A. Medication Guide or PPI**

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

**B. Communication Plan**

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

**C. Elements To Assure Safe Use**

List elements to assure safe use included in this REMS if applicable. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

**A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;**

- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

**D. Implementation System**

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above.

**E. Timetable for Submission of Assessments**

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

## **Appendix B**

### **REMS Supporting Document Template**

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
  - a. Additional Potential Elements
    - i. Medication Guide
    - ii. Patient Package Insert
    - iii. Communication Plan
  - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
  - c. Implementation System
  - d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125274

Ipsen Biopharm Limited  
Attention: Steven Scott  
Senior Director, Regulatory Affairs  
27 Maple Street  
Milford, MA 01757

**COMPLETED SEP 26 2008**

Dear Mr. Scott:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Dysport.

We received your September 8, 2008 amendment to this application on September 10, 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 December 28, 2008, 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 Tamy Kim, PharmD, Regulatory Project Manager at (301) 796-1125.

Sincerely,

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

**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**

\*\*\*\*\*

**THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify me via e-mail or telephone.**

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

The Manufacturing Assessment and Preapproval Compliance Branch has completed 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 Biopharm, 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 Biopharm, 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**

**Kim, Tamy**

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**From:** Brent-Steele, Tammie  
**Sent:** Wednesday, September 10, 2008 11:07 AM  
**To:** Kim, Tamy  
**Cc:** Sahin, Leyla  
**Subject:** Dysport Label from MHT

**Attachments:** FINAL MHT Revisions Dysportfordystonia-label 9-10-08 .doc

Hi Tamy,

Please find attached the Dysport label with revisions and comments from the Maternal Health Team. Please let me know if you have any questions at all.

Thank you very much for your consult and have a great day!

Tammie



FINAL MHT  
Revisions Dysportfor.

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

Our STN: BL 125274/0

Ipsen Biopharm Limited  
ATTENTION: Steven Scott  
Senior Director  
Regulatory Affairs  
27 Maple Street  
Milford, MA 01757

Dear Mr. Scott:

This letter is in regard to your biologics license application (BLA) dated November 29, 2007, received November 29, 2007, submitted under section 351 of the Public Health Service Act, for Dysport® (Clostridium botulinum toxin type A 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 September 28, 2008. 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.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of 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.

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

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

Sincerely,

 1/29/08  
Russell Katz, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research



**BLA ACKNOWLEDGEMENT**

Our STN: BL [125274/0]

Ipsen Biopharm Limited  
ATTENTION: Steven Scott  
Senior Director, Regulatory Affairs  
27 Maple Street  
Milford, MA 01757

Dear Mr. Scott:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following:

**Name of Biological Product:** Dysport® for injection (Clostridium botulinum toxin type A hemagglutinin complex)

**Date of Application:** November 29, 2007

**Date of Receipt:** November 29, 2007

**Our Submission Tracking Number (STN):** BL 125274/0

**Proposed Use:** Cervical dystonia

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Therapeutic Biological Products Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-1125.

Sincerely,



Tamy Kim, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research



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**Meeting Date and Time:** December 5, 2006  
**Meeting Type:** B  
**Meeting Category:** Pre-BLA  
**Meeting Location:** White Oak, Bldg 22, Rm 1311  
**Application Number:** IND 7434  
**Product Name:** Botulinum Toxin Type A (Dysport®)  
**Sponsor Name:** Ipsen  
**Meeting Chair:** Russell Katz, MD  
**Meeting Recorder:** James Reese, PhD  
**Meeting Attendees:**

**FDA Attendees**  
Russell Katz, MD  
Wilson Bryan, MD  
Carole Davis, MD  
Barbara Wilcox, PhD  
Lois Freed, PhD  
Jingyu Luan, PhD  
Sally Yasuda, PhD  
James Reese, PhD

**Ipsen Attendees**  
Patrick Merat, MD, MBA  
Jean-Loic Robin, MD  
Philippe Picaut  
Rosendo Obach  
Phil Weatherill  
John McKellar  
Steven Morrison  
Carric Cascio  
Steven R. Scott  
Gail Head  
Juergen Froehlich

## 1.0 BACKGROUND

- This meeting was held to discuss the content, format, and other developmental topics related to the proposed BLA for cervical dystonia.

## 2.0 DISCUSSION

### 2.1 Clinical

#### Question 1:

Dysport (Botulinum Type A Toxin - Hemagglutinin Complex) was designated as an Orphan Drug, as a treatment for patients with cervical dystonia.

The sponsor proposes to base the demonstration of efficacy on two randomized, double-blind, single dose, placebo controlled studies (Studies Y-47-52120-051 and Y-97-52120-045) each conducted in approximately 100 patients. The primary efficacy parameter (TWSTR Score) was evaluated at Week 4. These pivotal studies will be supported by two additional open label extension studies (Study Y-47-52120-731 and Y-97-52120-045b) evaluating up to 3 to 4 injection cycles to assess long term safety and efficacy. The sponsor believes that the design of the pivotal studies and the efficacy endpoints chosen are adequate to provide substantial evidence of effectiveness of Dysport as a treatment of patients with cervical dystonia as Protocol Y-47-52120-051 underwent a Special Protocol Assessment. Does the FDA agree?

**FDA Response** – The TWSTR score at Week 4 is an acceptable primary efficacy endpoint for Phase 3 studies to provide evidence of effectiveness of Dysport as a treatment of cervical dystonia. The Special Protocol Assessment determined that the design of Protocol Y-47-52120-051 is acceptable to provide evidence of effectiveness. The design of Study Y-97-52120-045 is very similar to Study Y-47-52120-051, and is therefore likely to be acceptable to provide evidence of effectiveness. Based on limited review of the synopsis of Protocol Y-97-52120-045 that you submitted for this meeting, we have not identified any critical deficiencies in the study design. However, your submission does not include the complete protocol for Study Y-47-52120-051 for our consideration; therefore, we will reserve further comment on the design of that study, pending submission of the BLA.

#### *Meeting Discussion:*

*The Agency clarified that paragraph 1 refers to the study 045 protocol (not submitted).*

Your submission does not specify the number of subjects in your pivotal studies who were naïve to botulinum toxin prior to enrollment. We are concerned that your pivotal studies may have enrolled insufficient botulinum toxin naïve subjects for us to assess the safety, efficacy, and appropriate starting dose in these subjects. In order for us to write appropriate labeling for a treatment of cervical dystonia, you must provide data on the safety and effectiveness of Dysport in subjects who were previously naïve to botulinum toxin. We are also interested in your assessment of the appropriate starting dose in patients who were botulinum toxin naïve.

#### *Meeting Discussion:*

*Ipsen: In Study 045, 35/137 (26%) patients were naïve to botulinum toxin treatment. In the main efficacy analysis (second randomization of 80 patients) 21/80 (26%) were botulinum toxin naïve. Enrollment in Study 051 will add additional toxin naïve patients - approximately 18/121 (15%). The % enrollment rate is consistent with the proportion of newly diagnosed cervical dystonia patients. Since CD is an orphan indication and the fact that there are two approved toxin*

*products in the US on the market, it is increasingly difficult to recruit toxin naïve patients. In the statistical analysis of both placebo controlled clinical studies, naïve vs. non-naïve patients will be assessed.*

*Study 020 (dose ranging study) was performed in 75 toxin naïve patients and determined the dose for phase 3 (045 and 051) pivotal studies.*

*Does FDA agree that this is an adequate number of toxin naïve patients?*

*The Agency responded that the number of patients appears to be adequate for filing. However, after review the number may prove to be inadequate. Ipsen will consider evaluating sub-groups and make a proposal in the BLA.*

In the BLA submission, please provide the complete statistical analysis plan for each study.

***Meeting Discussion:***

*Ipsen agreed to provide the SAPs for each study in the BLA.*

For pivotal studies, you must provide the derived variables and the raw variables from which the derived variables were produced in efficacy data sets, and you must provide all SAS programs by which the derived variables were produced from the raw variables and all SAS programs that produced all efficacy results. Programs should be provided as both ASCII text and PDF files and should include sufficient documentation. Moreover, you must provide a detailed description of all the variables in efficacy data sets, e.g., type, length, label, code.

***Meeting Discussion:***

*Ipsen agreed to provide the derived variables, and the raw variables from which the derived variables were produced in efficacy data sets, and will provide all SAS programs by which the derived variables will be produced from the raw variables and all SAS programs for all efficacy results in accordance with eCTD requirements.*

**Question 2:**

Dysport (Botulinum Type A Toxin - Hemagglutinin Complex) is an extremely potent neurotoxin injected directly into the target muscle where it exerts its paralytic action and, therefore, is considered a localized treatment. Treatment occurs approximately every 3 to 4 months, typically coinciding with the return of clinical signs and representing a series of acute treatments.

Botulinum Type A Toxin is not expected to be present in the peripheral blood at measurable levels following intramuscular injection at the therapeutic dose. Based on Dysport high potency, low therapeutic dose, localized action and well published and understood pharmacodynamic properties and mechanism of action, the sponsor believes that formal systemic pharmacokinetic studies will not contribute to the assessment of safety and efficacy profile of the product. Therefore, for the BLA, the primary pharmacodynamic, pharmacokinetic data will consist of published literature. Does FDA agree with this approach?

**FDA Response --** This appears to be reasonable. However, please include in your BLA a justification of your rationale for the lack of contribution of pharmacokinetic studies.

***Meeting Discussion:***

*The BLA will provide the appropriate rationale for lack of contribution of the pharmacokinetic studies. It was clarified that this should also include a justification of the rationale that Botulinum Toxin Type A is not present in peripheral blood.*

**Question 3:**

Over the last 18 years, Dysport has been studied in over 80 clinical trials in a wide variety of neuromuscular indications throughout the world. Dysport has also been approved in a number of indications outside the US. Many of these trials are open label studies and were conducted by Ipsen affiliated companies according to local standards at the time the studies were conducted. As a result, the sponsor proposes to classify and report appropriate levels of clinical safety and efficacy information based on its ability to meaningfully contribute to the safety and efficacy evaluation of Dysport as a treatment for cervical dystonia (i.e., quality of the information, source of data and the indication studied).

The sponsor proposes the following:

**Table 2: Study Categorization**

Category	Purpose	General Criteria	Safety Reporting
Category 1 – Substantial Evidence of Effectiveness	Definitive Efficacy and Safety	Studies conducted in the targeted indication (cervical dystonia) relied on by the sponsor to establish dose, efficacy/safety (including long term) or to address any important BLA specific issues. These studies will have complete Clinical Study Reports supported by CRFs, CRTs and reliable databases.	Full Safety and Efficacy  Full Clinical Study Reports Case Report Tabulations Case Report Forms
Category 2 – Safety and Supportive Efficacy Studies	Supportive Efficacy and Safety	Controlled studies intended to support efficacy conclusions (i.e., not conducted with FDA agreed endpoints) and open label studies conducted in the targeted indication. These studies will have Complete Clinical Study Reports supported by CRFs, CRTs and reliable databases.	Full Safety  Full Clinical Study Reports Case Report Tabulations Case Report Forms
Category 3 – Post-Marketing / Other Information	Supportive Safety	Spontaneous reports from post marketing surveillance in patients treated for cervical dystonia and Post-Marketing Studies and other less reliable study information in the targeted indication (i.e., studies without reports, CRTs, CRFs or reliable databases).	Limited Safety Reporting* <ul style="list-style-type: none"> <li>o Deaths</li> <li>o Serious Adverse Experiences</li> <li>o AEs leading to withdrawal (where available)</li> </ul> Abbreviated Clinical Study Report (copy of the report describing the conduct and findings of the study without most appendices and with limited only CRTs presented electronically) under Marketing Information  *All spontaneous reports from post marketing surveillance use in patients treated for cervical dystonia will be reported as a matter necessary and customary for safety.
Category 4: Studies or PK/PD Data in Other Indications	Supportive Safety	Studies in other indications and spontaneous reports from post marketing surveillance use in other indications.	Limited Safety Reporting <ul style="list-style-type: none"> <li>o Serious Adverse Experiences (SAEs) related to the study drug)</li> </ul> No clinical study reports to be submitted  All spontaneous reports from post marketing surveillance use in the other indications will be reported as a matter necessary.

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Does FDA agree with the general classification and approach to safety and efficacy reporting for the BLA?

FDA Response - The classification system seems to be adequate for review, with the following exceptions:

- In Category 4, you propose to provide "limited safety reporting" on serious adverse events that are "related to the study drug." Attribution of an event as related, or not related, to the study drug is a review issue. Therefore, please provide safety reports on all serious adverse events, regardless of attribution. For these Category 4 events, "limited safety reporting" is acceptable for the BLA submission, pending review.

*Meeting Discussion:*

*For clinical studies conducted in other indications, Ipsen agreed to report all SAEs available regardless of attribution.*

*For Spontaneous Reports, the sponsor commits to reporting all events.*

- Your pivotal studies permitted enrollment of both subjects who were botulinum toxin naïve and subjects who were previously exposed to botulinum toxin. Subjects who were previously exposed to botulinum toxin may have a safety profile that is different from subjects who were naïve to botulinum toxin. Therefore, the BLA submission must include separate safety analyses for previously botulinum toxin naïve subjects and for previously botulinum toxin exposed subjects, in addition to a safety analysis that combines data from all subjects (i.e., both naïve and previously exposed).

*Meeting Discussion:*

*Ipsen agreed to provide a separate safety analysis of toxin naïve and previously treated patients and combined data from all subjects.*

- Similarly, the BLA submission should provide a separate safety analysis for all subjects who received specific Dysport doses or higher (e.g., 200 units or higher, 300 units or higher, etc.), along with an analysis of all subjects who received any dose of Dysport.

*Meeting Discussion:*

*Ipsen: Would FDA please clarify whether they wish to have a cumulative tally of a specific dose and higher (250 and more) or a separate safety analysis by dose or dose range received.*

*The Agency did not make a recommendation. Both ways should be considered.*

Please submit a placebo-controlled safety analysis for all subjects who received the recommended starting dose or higher. In preparing the BLA submission, please consider that we have not yet agreed on a recommended starting dose; therefore, you should submit a separate safety analysis for each likely recommended starting dose.

*Meeting Discussion:*

*Ipsen agreed to provide an analysis of all subjects who receive the starting dose or higher, in addition to safety analysis for any recommended starting dose.*

*The 500 unit starting dose was determined in Study 020 (toxin naïve patients). This dose was used as the starting dose in study 051 and study 045. These studies recruited toxin naïve and previously treated patients. The sponsor plans to confirm the appropriateness of this starting dose in previously treated patients through subgroup analysis.*

All of the above analyses of various dose levels must include separate analyses for previously botulinum toxin naïve subjects and for previously botulinum toxin exposed subjects, in addition to a safety analysis that combines data from all subjects (i.e., both naïve and previously exposed).

*Meeting Discussion:*

*Ipsen agreed to address the toxin naïve and previously treated patient analyses in the BLA submission.*

- Just as the safety of Dysport may be different in the two populations (i.e., previously exposed vs. naïve), the efficacy of Dysport may be different in these two populations. Therefore, please submit separate efficacy analyses for these two populations, with considerations of dose (similar to the safety analyses outlined above).

*Meeting Discussion:*

*Ipsen agreed to address separate efficacy analysis for toxin naïve and previously treated patients for the primary efficacy variables.*

- Please see additional comments in the response to Question 6 below.

**Question 4:**

The sponsor proposes to submit all safety information (including all adverse events, serious adverse experiences, deaths and withdrawals due to adverse events) for Category 1 and 2 studies. These studies comprise approximately 320 cervical dystonia patients receiving at least one dose. Of these, approximately 100 patients will have been treated with 3 to 4 treatments at the time of BLA submission. In addition, the sponsor will submit safety data, as described in Table 2, for Category 3 data comprising approximately 3500 patients and Category 4 studies comprising several thousand patients.

The sponsor believes that the number of patients exposed to Dysport and the duration of exposure are adequate to characterize the Dysport safety profile and support the filing of a BLA for Dysport as a treatment for the orphan indication, cervical dystonia. Does FDA agree?

FDA Response - The number of patients exposed and the duration of exposure appear to be adequate to support filing the BLA. Whether the number of patients exposed and the duration of exposure are adequate to characterize the Dysport safety profile is a review issue.

However, as indicated in the response to Question 1 above, we are concerned that you may not have sufficient safety data on subjects who were botulinum toxin naïve at the time of initial Dysport administration. Your data on botulinum toxin naïve subjects may be insufficient to support filing the BLA.

*Meeting Discussion:*

*As previously discussed, the dose range finding study 020 and pivotal studies 045 and 051 have enrolled toxin naïve patients.*

*Ipsen asked whether having 25% of the patients be naïve would be adequate. The Agency indicated that that question would be a review issue.*

**Question 5:**

At the time of BLA submission, the sponsor will have completed and included the two Category 1 adequate and well controlled studies (Studies 045 and 051). In addition, the open label long-term treatment extension study (Study 045b) in approximately 100 patients will also be included. The sponsor plans to submit interim safety data from the ongoing open label long-term treatment extension study (Study 731) at the time of BLA submission and update the application with additional safety and efficacy results. It is anticipated that this update will occur at the 120 day safety update. Does FDA agree with our plan?

FDA Response - Yes. When submitting the 120-day update, please provide separate analyses for the new data (i.e., the data collected since the original filing) and for the combination of the new data with the data from the original filing.

**Meeting Discussion:**

*Ipsen agreed to perform a separate analysis of new data and a combination of new data and data from the original filing.*

**Question 6:**

The sponsor proposes to organize the Integrated Summary of Safety into three subsections. Since full safety is reported for Category 1 and 2 studies, it is proposed that this data is integrated and utilized to define the adverse experience profile for the package insert. For studies designed to explicitly solicit specific adverse experiences, a separate presentation will be made. Category 3 (cervical dystonia) safety data will comprise Deaths, Serious Adverse Experiences, AEs leading to withdrawal (where available) and spontaneous reports in cervical dystonia patients. For Category 4 (other indications), PMS and other safety data will consist of Serious Adverse Reactions. Each of these Categories will be addressed in separate subsections of the ISS. Does FDA agree with the organizational approach of the ISS?

FDA Response - Please consider the following recommendations on the organization of the ISS:

- The ISS should clearly state what safety assessments were carried out in each study included in the ISS. A tabular presentation of schedule of events might be helpful.
- All deaths that occurred in the clinical development program or found during a literature search and from various commercial and non-commercial databases (e.g., AERS) should be described in a single section and individual deaths should be listed in a table.
- All non-fatal serious adverse events, regardless of assigned causality, that occurred during the clinical development program or were reported from secondary sources (i.e., literature and/or post-marketing reports) should be described in a single section. Serious adverse events may, in addition to signs, symptoms, and diagnosable events, include changes in laboratory parameters, vital signs, ECG, or other parameters of sufficient magnitude to meet the regulatory definition of a serious adverse event [21 CFR 312.32(a); 314.80(a)].
- Dropouts due to adverse events should be clearly described in a single section of the ISS. Case Report Form (CRF)/narratives should be provided for all dropouts. An overall profile of these patients by reason for dropping out (e.g., adverse events, treatment failures, lost to follow-up) should be provided. For the more common adverse events associated with dropouts, the ISS should present the incidence of these adverse events, preferably in a table. Investigator causality assessment can be described but should be justified. The ISS should also describe any dose-response, time dependency of the dropout, drug-demographic, drug-disease, and drug-drug interactions. With respect to rarer events that could represent an important adverse event, the ISS should critically assess whether any of these may represent

treatment-induced injury. Finally, the ISS should consider these events individually with narratives and reference to other data as appropriate.

- The ISS should contain a section entitled "Other Significant Adverse Events." This section should describe significant safety findings such as marked hematological or other lab abnormalities not meeting the definition of serious, any events that led to an adverse dropout or any other intervention such as dose reduction or significant additional concomitant therapy (an expansion of the adverse dropout concept) and potentially important abnormalities not meeting the above definition of serious and not leading to death or modification of therapy (e.g., a single seizure, syncopal episode, orthostatic symptoms). Those adverse events that did not lead to discontinuation but otherwise meet the definition described above should be described in this section.
- If preclinical pharmacology/toxicology, post-marketing, and/or literature reports provide insight into possible safety signals with the investigational drug product, the ISS should describe any findings relative to these signals. This is especially important for new chemical entities. Similarly, if there are particular safety concerns evident from other drug products that are members of the same pharmacological class as the investigational drug product, the ISS should include a thorough safety analysis to address these concerns.
- The ISS should contain a section entitled "Common Adverse Events". You should include a table (or tables) that present the best overall display of commonly occurring adverse events, generally those occurring at a rate of 1% or more (but lower rates can be presented for very large databases). This table or tables will be the basis for the adverse drug reaction (ADR) table in labeling, which may, however, use a higher cut off if this does not lose important information, and will eliminate ADRs that are equally common on drug and placebo. This table or tables should compare the incidence of common adverse events between cohorts regardless of the investigator's assignment of causality from the pooled studies. You should justify any decision for not including a particular study in the pooled adverse event incidence tables. For development programs with a significant number of severe adverse events, it would be helpful to include a table that compares the incidence of severe adverse events between cohorts from the pooled studies. [For drug products used intermittently (e.g., acute migraine products) the incidence of adverse events at the subject and attack level should be described separately.]
- For adverse events that seem clearly drug related (i.e., consistent difference from control across studies, evidence of dose response etc.), you should provide the following additional analysis as appropriate:
  1. exploration for dose dependency, exploration of time to onset (for those that show a delay in onset)
  2. exploration of adaptation (for common, troublesome events such as somnolence, nausea)
  3. explorations of demographic interactions, explorations of drug-disease and drug-drug interactions (if there is a strong signal for an interaction, or a good rationale for expecting an interaction)
  4. Selective exploration of individual cases in an attempt to better characterize the events.
- For each trial described in the ISS you should include a brief discussion on how adverse events were captured (i.e. checklist, open-ended questions on follow up visits etc.). The frequency of assessments should also be described.
- For each trial described in the ISS you should clearly state which translation dictionary (MedDRA, COSTART) was used to categorize verbatim adverse event terms.
- The ISS should include a discussion of the less common adverse events of significant concern seen across all studies in the clinical development program. Since the overall database is typically very heterogeneous, it is unlikely to lend itself to meaningful

estimations of rates or assessments of causality. Thus it may be sufficient to group these events by incidence and by body system. For example, it may be useful to categorize less common adverse events in order of decreasing frequency within certain ranges: e.g.  $\leq 1\%$ , between 0.1% and 1%;  $\leq 0.1\%$ .

- The ISS should clearly provide an overview of what laboratory testing (chemistry, hematology, and urinalysis) was carried out in each study. It is best to summarize the overall approach, rather than provide detailed comments about laboratory testing for each study. The ISS should also describe any discrepancies between planned analyses and those actually conducted, as well as the procedures used to evaluate abnormal values. Provide a summary table identifying the numbers of patients exposed to test drug who had baseline laboratory values and follow-up assessments.
- The ISS should include an integrated discussion of significant laboratory findings from the clinical development program. Controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. However placebo-controlled trials are generally short term, and unsuitable for assessing late-developing abnormalities, so that longer term data also need to be examined. If there is no concomitant control in the long-term studies, the comparison may need to be with similar populations outside the NDA/BLA. The ISS should explain which studies were pooled relative to the evaluation of laboratory findings and why they were selected.
- The ISS should generally include three standard approaches to the analysis of laboratory data. The first two analyses are based on comparative trial data. The third analysis should focus on all patients in the phase 2-3 experience. Analyses are intended to be descriptive and should not be thought of as hypothesis testing. P-values or confidence intervals can provide some evidence of the strength of the finding, but unless the trials are designed for hypothesis testing (rarely the case), these should be thought of as descriptive. The analysis of all laboratory findings should include a comparative description of mean or median changes from baseline across treatment groups. The ISS should include a discussion of individual patients whose laboratory values deviate substantially from the reference range and describe what criteria were used to identify outliers. Additional analyses may be appropriate for certain laboratory findings, including analyses for dose dependency, time dependency, and also drug-demographic, drug-disease, and drug-drug interactions. The ISS should discuss the rationale for additional explorations, the methods used, and the results and interpretations.
- The ISS should include an evaluation of vital sign assessment using a similar approach as described for laboratory data (i.e., description of vital sign assessment in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers, etc.).
- The ISS should include an evaluation of ECG findings using a similar approach as described for laboratory data (i.e., description of ECG assessments in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers, etc.). Particular attention should be given to ECG findings where the timing of the assessment was done at or near the time of maximum concentration for the drug product (generally during phase I or phase II studies) in order to assess QT prolongation effects. A brief discussion on any preclinical cardiac findings would be helpful in orienting the reviewer to any potential concerns.
- The ISS should include a discussion of the impact of immunogenicity (if applicable) on safety, efficacy, and/or clinical pharmacology and pharmacokinetics.
- The ISS should include a brief discussion of human carcinogenicity data if available. A systematic discussion of all human tumors reported during drug development can provide

- useful safety information, particularly in the case of drugs or biologics that have positive genotoxicity or animal carcinogenicity findings, or those that are known immune modulators.
- The ISS should include a summary of any studies designed to evaluate a specific safety concern(s). These studies may include:
    1. studies to assess whether a drug has safety concerns common to its pharmacological class
    2. studies in topical products to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity
    3. studies to characterize the effect on the QT interval (part of most modern development efforts)
    4. studies intended to demonstrate a safety advantage over therapeutic alternatives
  - The ISS should contain a discussion of abuse potential and any apparent withdrawal symptoms seen during the clinical development program. This discussion should contain a summary of findings from any non-clinical and clinical abuse liability studies (if done), problems in medication accounting encountered while monitoring the investigational supply of medication, chemistry and pharmacology issues that relate to abuse potential, and relevant adverse events and epidemiologic data. The ISS should describe any adverse events that emerge after discontinuation of the drug in order to determine whether they may indicate a withdrawal phenomenon. If studies evaluated the potential for withdrawal phenomena, the ISS should indicate whether there was a prospective or post-hoc assessment of withdrawal emergent signs and symptoms (during drug taper or following discontinuation) and discuss the implications of the approach used on the reliability of the findings.
  - The ISS should include a discussion of all pregnancies that occur during the clinical development program. A brief description of each pregnancy should include outcome, duration on therapy, and use of drug relative to trimester.
  - The ISS should summarize all overdose experience with the investigational drug/biologic in humans. The summary should include a description of the constellation of signs and symptoms that might be associated with overdose. A description of phase I or phase II safety findings in subjects exposed to doses higher than planned for marketing should be included. Patients with certain physiological differences that would compromise their ability to clear the drug (e.g. renal impairment, limited CYP450 2D6 activity for a drug cleared by this isozyme) may provide relevant data to the clinical implications of overdose.
  - The ISS should include relevant findings from U.S. and foreign post-marketing experience if available.
  - The ISS should include a clear description of all patient exposures from the entire clinical development program. The exposure summary should describe various demographic subsets such as race, gender and age. Additionally the summary should include a clear description of dose and duration of exposure. Tables and graphs may be helpful in describing the data sources for the ISS. If applicable the ISS should describe any secondary sources of safety data (ex. studies not conducted under the IND and not meeting the standards for inclusion as primary, post marketing data, and/or literature reports). Secondary sources should be briefly described. Original articles and study reports should be provided.
  - The ISS should briefly describe the findings from any preclinical studies that were conducted in order to explore certain potential adverse events, using preclinical models based either on a drug's pharmacology or on clinical findings that emerged early in clinical development. For example, for a drug anticipated to cause QT prolongation because of its drug class or because QT prolongation was seen in phase I studies, were there any preclinical (in-vitro) studies done to evaluate this potential.
  - The ISS should include a discussion of any in vitro and in vivo studies done to evaluate how a drug is metabolized and excreted. Issues to be included should include the following:

1. The enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins.
  2. The effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds.
  3. The major potential safety consequences of drug-drug interactions.
- The ISS should describe the general methodology used to construct the integrated safety review. This discussion should include a rationale for pooling safety data (if done) and the method employed. For example a justification for pooling safety data may include an argument that a larger data base will permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population or pooling data from different studies can improve the precision of an incidence estimate (i.e., narrow the confidence intervals by enlarging the sample size). In pooling safety data, usually the numerator events and denominators for the selected studies are simply combined. If other more formal weighting methods are used (e.g., weighting studies on the basis of study size or inversely to their variance) the ISS should justify why and how the weighting was done. Information on baseline risk factors of concern should be retrievable from the case report tabulations.
  - Since adverse reaction rates may differ considerably from one patient population to another and may change over time, the ISS should explore factors that may affect the safety profile of a drug. For example, the ISS could explore common drug related predictive factors, such as dose, plasma level, duration of treatment and concomitant medications, and patient related predictive factors such as age, sex, race, concomitant illnesses. In general, these explorations are meaningful only for adverse reactions that appear to be drug-related. The ISS may present these explorations using the following subheadings: exploration of dose-dependency for adverse findings, explorations for time dependency for adverse findings, exploration for drug-demographic interactions, exploration for drug-disease interactions and exploration for drug-drug interactions. It may be helpful to link individual safety observations with other on-therapy data such as dose, duration of treatment, concomitant therapy, other adverse effects, lab data, or effectiveness results.
  - It is very helpful if the sponsor provides an overview of the various primary data sets, and clarification of the definitions provided in the define.pdf. Additionally, it is helpful to make full use of links between sections, such as when describing deaths, to provide a link to the case report forms, etc.

**Meeting Discussion:**

*Ipsen will prepare an ISS in accordance with the guidance provided. The main focus will be on the Category 1 and 2 studies (full safety information). The other sources of information Category 3 (limited reliability) and Category 4 (information in other indications) will provide supportive data confirming the safety of Dysport. The relevance of the Category 4 data in the cervical dystonia indication is limited, as the observed safety profile is specific to the disease (muscles being injected). The appropriate analyses where relevant will be presented according level of detail appropriate to the study classification. For example, dose relationship of non-serious AEs will be addressed with Category 1 and 2 studies, while only SAE information is reported for Category 3 and 4. Also, spontaneous reporting of post marketing events has limitation with respect to the types of analyses that can be performed. The Agency acknowledged that not all of the ISS comments above were pertinent at this time.*

**Question 7:**

The sponsor intends to submit the dossier in eCTD format. The eCTD will be prepared in compliance with the "Guidance for Industry - Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, April 2006".

For legacy studies, Clinical Study Reports will be provided as text-based documents, where possible, otherwise as scanned portable document format (PDF).

Case Report Forms will be provided as pdf files.

For clinical studies with full safety reporting, the data will be migrated to Study Data Tabulation Model (SDTM) datasets and analysis datasets will be prepared in accordance with the Analysis Data Model (ADaM). Data complying with these CDISC (SDTM and ADaM) standards will be submitted in electronic format, in lieu of separate Case Report Tabulations and Listings. It is anticipated that FDA will use their electronic review tools to create the Case Report Tabulations (CRTs) and patient profiles from the SDTM and ADaM datasets.

Limited safety data for Category 3 and 4 studies will be provided in Analyses Datasets in accordance with the ADaM standard, where possible. Other details of the eCTD proposal are described in the briefing document.

Does FDA agree with the approach, as described in for submission of an eCTD for Dysport as a treatment for cervical dystonia?

FDA Response - Yes.

*Meeting Discussion:*  
*No comment.*

**Question 8:**

Does FDA agree with the sponsor's proposed approach for summarizing individual efficacy data by dose and efficacy parameters as listed in the briefing document?

FDA Response - Summarizing individual efficacy data by dose and efficacy parameters is acceptable but not sufficient. Efficacy data should also consider whether subjects were naïve or previously exposed to botulinum toxin (see response to Question 3 above).

*Meeting Discussion:*  
*Ipsen agreed to address efficacy analyses by subgroups specifically looking at toxin naïve and previously treated patients.*

**Question 9:**

The sponsor intends to submit the dossier in eCTD format. Safety data will be presented in the clinical overview and summary sections in module 2. An Integrated Summary of Safety will also be included in module 5.3.5.3.

A side-by-side presentation of efficacy data will be presented to facilitate comparison of results between studies. Considering that efficacy data will not be integrated, efficacy analyses will be

presented in the clinical overview and clinical summary sections of the eCTD, an ISE will not be prepared. Does FDA agree with the proposal?

- FDA Response - The eCTD format is acceptable. Please see comments above, under Question 6, regarding the data in the ISS. The BLA submission must include the final protocol, with a detailed description of protocol amendments, for each controlled study. An ISE may be of interest, but is not required.

**Meeting Discussion:**

*Ipsen is not planning to provide category 4 studies for any other indications. The Agency stated that this was acceptable for the submission of the BLA, but indicated that we may ask for the studies later.*

**Question 10:**

Does FDA have any additional comments or recommendations regarding the clinical efficacy and safety package or organization of the BLA?

FDA Response - Please provide copies of any assessment tool used (scales, questionnaires, exams, etc., including the Tsui scale) along with the instructions on how they were administered and rated, and documents to support the validity and interpretation of each assessment tool. Please also provide your rationale for selecting the TWSTR scale as the primary endpoint for the Phase 3 studies.

**Meeting Discussion:**

*Ipsen agreed to provide the assessment tools along with instructions on how they were administered and rated with supporting validity documentation. In addition, the BLA will address the rationale for selection of the TWSTR scale as the primary endpoint.*

**Additional clinical discussion**

- *The Agency asked for more information about the secondary variables. Ipsen discussed numerous secondary variables. The Agency stated its concern about secondary variables that are intended for inclusion in the label.*  
*The criteria for secondary variables included in the label are:*
  - *Replication*
  - *The secondary outcome must be for a different clinical domain than the primary outcome.*
  - *FDA agreement in advance is required as to the acceptability of the secondary variables.*
  - *A statistical plan is needed for the secondary variables that lists the order in which the variables will be evaluated.*
- *In regard to the TWSTR scale, the three evaluations must not be evaluated separately. They must be evaluated together, as a whole.*  
*Ipsen stated that the primary endpoint in the TWSTR scale is evaluated at 4 weeks. Can the secondary endpoints be evaluated at 8 and 12 weeks? Evaluation of the duration of effectiveness is important and should be included among the secondary endpoints. A variety of secondary endpoints is useful to provide other perspectives, such as change in subject-evaluated pain, or quality of life. All secondary variables data submitted will be*

*evaluated. The Agency responded that the hierarchical technique should be used to evaluate the secondary variables.*

## 2.2 Nonclinical

### Question 1

Botulinum type A toxin is a well-characterized, potent neurotoxin with a well-known mechanism of action. The toxin's paralytic action is exerted by binding to presynaptic cholinergic nerve terminals at the neuromuscular junction resulting in the inhibition of acetylcholine exocytosis, the diminishment of endplate potential and the eventual paralysis of the exposed muscle tissue. Paralysis is temporary and recovery occurs gradually as new nerve terminals sprout and contact is made with the post synaptic motor endplate.

The Sponsor has extensive experience with the use of botulinum type A toxin as a therapeutic agent for both medical and aesthetic indications. The first marketing authorization was awarded in 1990 and since then the product has been approved in over 72 countries worldwide resulting in more than 2,000,000 patient exposures.

Cervical dystonia is characterized as an Orphan Indication (affecting less than 200,000 persons in the US) with the average age of peak onset between 40 and 49 years. Given that the pharmacological effect of the drug is local to the injection site and, on occasion, the adjacent muscles as reflected by the results of the clinical studies, the Sponsor believes that the non-clinical package is adequate to support the filing of a BLA for Dysport in this indication for this population. Does FDA agree?

FDA response – No.

- We do not agree that a fertility study of Dysport is without scientific merit. Experience with similar molecules indicates that there may be effects on fertility independent of the reduced mobility caused by such products. Therefore, a fertility and early embryonic development (to implantation) study will be needed to support approval of Dysport for cervical dystonia.

*Meeting Discussion:*

*Ipsen agreed to conduct a fertility study and a pre- and post- natal study in rats. These studies will need to be included in the original BLA submission, not in the 120-day safety update as proposed by the sponsor.*

- The usual treatment regimen for botulinum toxin, i.e., once every 3 months, is considered to be chronic-intermittent and would require the completion of chronic toxicology studies in two species. The duration of such studies should be 6 months in rodent and 12 months in non-rodent. However, if adequate human safety data are available, then chronic toxicology studies may not be needed. A final determination on the adequacy of your non-clinical package will be a matter of review.

*Meeting Discussion:*

*The sponsor noted that the toxicology package supporting the BLA will be consistent with guidance provided.*

- We agree that genotoxicity and carcinogenicity studies would not be appropriate for Dysport.

*Meeting Discussion:*  
*No further comment.*

**Additional Notes:**

- Please provide (in the BLA submission) copies of all letters to/from the FDA relevant to the development of Dysport.
- Please provide (in the BLA submission) your rationale for the dose levels selected for your Phase 3 studies.

*Meeting Discussion:*  
*The BLA will contain all letters to and from FDA relevant to Dysport development in cervical dystonia. In addition, the BLA will contain the rationale for dose levels selected for phase 3.*

Linked Applications

Sponsor Name

Drug Name

IND 7434

IPSEN LTD

Botulinum Toxin Type A Hemagglutinin  
Complex

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

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/s/

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RUSSELL G KATZ  
01/18/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

August 12, 1998

**RECEIVED**

AUG 14 1998

P. V. BUDAY

Porton International, Inc.  
7114 Springbrook Terrace, Suite 200  
Spotsylvania, VA 22553

Attention: Paul V. Buday, Ph.D., J.D.  
Director, Regulatory Affairs

Dear Dr. Buday:

Reference is made to the orphan product application of May 7, 1998 submitted pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (FFDCA), and sponsored by Ipsen Limited, for the designation of Dysport (botulinum type A toxin) as an orphan product (application #98-1141). We also refer to the supplemental information provided in your submission dated May 12, 1998.

We have completed the review of this application and have determined that Dysport qualifies for orphan designation for the treatment of cervical dystonia (spasmodic torticollis). Please note that it is Dysport and not its formulation that has received orphan designation.

Please be advised that if Dysport were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of Dysport as designated. Also an annual progress report must be submitted within 14 months

after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Donald R. Haggerty, M.D. at (301) 827-0986.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan product designation.

Sincerely yours,

Handwritten signature of Marlene E. Haffner in cursive script.

Marlene E. Haffner, M.D., M.P.H.  
Rear Admiral, United States Public Health Service  
Director, Office of Orphan Products Development