

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125274Orig1s000

OTHER REVIEW(S)



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

Office of Biotechnology Products
Rockville, MD 20852
Tel. 301-796-1672

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125274/0

Name of Drug: *Dysport*[®] (*abobotulinumtoxinA*)

Sponsor: Ipsen Biopharm Limited

Material Reviewed: *Dysport*[®] (*abobotulinumtoxinA*) Carton and Container Labels

OBP PM Previous Reviews: August 8, 2008; September 10, 2008

OBP PM Receipt Date: December 5, 2008

Final Review: April 29, 2009

Background:

Ipsen Biopharm Limited has submitted a Biologic License Application (BLA) for *Dysport*[®] (*AbobotulinumtoxinA*) for Intramuscular Injection. The product is a purified neurotoxin complex indicated for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position, disability and neck pain in both toxin naïve and previously treated patients. *Dysport*[®] (*abobotulinumtoxinA*) is supplied in a 3 ml glass vial containing 500 Units of *Dysport*[®]. Each vial is individually labeled and placed in either a carton containing one vial of *Dysport*[®] or a carton containing two vials of *Dysport*[®].

Labels Reviewed:

DYSPO[®]RT (*abobotulinumtoxinA*) Container Label

3 ml Vial label

DYSPO[®]RT (*abobotulinumtoxinA*) Carton Label

Two vial carton

One vial carton

Review

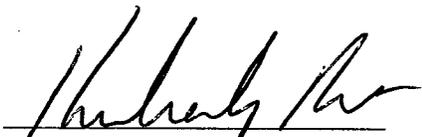
The carton and container labels for *Dysport*[®] (*AbobotulinumtoxinA*) were reviewed and conformed regulations under 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100; and The U.S. Pharmacopeia, USP31/NF36 (12/1/08-4/30/09). Please see the comments in the conclusions section.

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

Conclusions:

- Per 21 CFR 610.61 and 21 CFR 61.62, please display the proper name, AbobotulinumtoxinA above the Tradename, Dysport, followed by the route of administration,” for intramuscular use only” on all labeling. Requested change made.
- Consider revising the strength presentation, 500 units /vial to bold type and moving it directly below the recommended new position for “for intramuscular use” on carton and containers. This change will increase readability. Requested change made.
- Per 21 CFR 610.60(2), please provide the license number with the manufacturer information on the container label. Requested change made.
- Per USPC Official 12/1/08-4/30/09, USP 31/NF26, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients from the current edition of one of the following reference works (in the following order of precedence): (1) the United States Pharmacopeia or the National Formulary; (2) USAN and the USP Dictionary of Drug Names; (3) CTFA Cosmetic Ingredient Dictionary; (4) Food chemicals codex. The ingredients must also be listed in alphabetical order. Requested change made.
- Per 21 CFR 610.60(e), a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents when the label is affixed to the container. Please verify this information. Information verified per sponsor.
- Please consider adding the tradename on the side panel above the lot and expiration information so that the tradename is visible on every panel. Requested change made.
- Per 21 CFR 201.35(3)(i), the NDC number does not appear prominently in the top third of the principal display panel of the label on the carton, please move the NDC number to comply with this regulation. Requested change made.
- Per 21 CFR 201.55, please provide a reference to the package insert for dosage and dilution information on the carton label. Requested change made.
- Per 21 CFR 610.64, please complete “Distributed by:” information or remove the statement from the carton. Requested change made.
- Consider removing the statement “No U.S. Standard of Potency” from the container label to provide space for recommended changes. Requested change made.

- Consider removing the vial quantity designations in the triangles from the carton and container labels to prevent errors. Requested change made.
- Consider revising the statement “DO NOT FREEZE AFTER RECONSTITUTION” to “DO NOT FREEZE” to avoid confusion that the product can be frozen before reconstitution. The package insert does clarify the statement in the “Instructions for Preparation and Administration section”. Requested change made.

 4/29/09

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

Comment/Concurrence:

_____
Ennan Guan, Ph.D.
Product Reviewer
CDER/OPS/OBP/DTP

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

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: April 20, 2009

To: Tamika White, Regulatory Project Manager, DDDP
Denise Cook, M.D., Medical Officer, DDDP
Tamy Kim, Regulatory Project Manager, DNP

From: Shefali Doshi, Regulatory Review Officer, DDMAC *SSD*
Sharon Watson, Regulatory Review Officer, DDMAC *SSD signing for Sharon Watson*

CC: Robert Dean, DTC Group Leader, DDMAC
Marci Kiester, DTC Group Leader, DDMAC
Andrew Haffer, Regulatory Review Officer, DDMAC
Amy Toscano, Regulatory Review Officer, DDMAC

Subject: BLA 125274 & 124286
DDMAC labeling comments for Dysport (abobotulinumtoxin A)
Injection Medication Guide

DDMAC has reviewed the draft Medication Guide for Dysport (abobotulinumtoxin A). These comments are based on the draft PI from April 2009/revision 6. DDMAC's comments on the draft Medication Guide for Dysport begin on the following page.

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

**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

MEMORANDUM

****Pre-Decisional Agency Information****

Date: December 8, 2008

To: Division of Risk Management
Office of Surveillance and Epidemiology

From: Michelle Safarik, PA-C – Regulatory Review Officer *Michelle Safarik MAB/08*
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC comments on Dysport for Injection (prefix + botulinum toxin A)
BLA 125274

DDMAC has reviewed the proposed REMS for Dysport for Injection (prefix + botulinum toxin A) (Dysport) submitted for consult on December 4, 2008. We offer the following comments based on the draft labeling dated December 5, 2008.

REMS Supporting Document

1. We note use of the phrase (b) (4) throughout the proposed REMS Supporting Document. While the sponsor provides context for this phrase (i.e., the incidence) on page 3, the numerous mentions of this phrase throughout the proposed REMS Supporting Document minimizes the risks of Dysport therapy and detracts from the purposes of the REMS. Therefore, we recommend deletion of the phrase (b) (4) throughout.
2. Per the IR letter for Dysport dated November 6, 2008, we recommend the sponsor propose an implementation system for the REMS.
3. The sponsor has proposed a REMS assessment of 18 months, 3 years, and 7 years from product launch. While this is consistent with FDAAA, in light of recent drug approvals with REMS (e.g., Nplate, Promacta), is it appropriate to decrease the REMS assessment time intervals (e.g., every 6 months for the first 24 months, then annually thereafter)?
4. We defer to Social Science expertise in DRISK for review of the proposed Physician and Patient Surveys.

REMS

Please see comments addressed to the proposed REMS Supporting Document. DDMAC has the following additional comments:

Goals

- 1) While the REMS Supporting Document goes into detail about the potential of side effects remote from the injection site, would it be possible to provide further context for "undesirable effects" (i.e., list symptoms found in section 5.2 (Spread of Toxin Effect) of the draft PI such as asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties)?

Medication Guide

- 1) Comments on the proposed Medication Guide will be provided under separate cover.

Dear Healthcare Provider Letter (DHCP Letter)

- 1) We recommend including that Dysport is an "acetylcholine release inhibitor and neuromuscular blocking agent" for consistency with the Indications and Usage section of the draft PI.
- 2) The second paragraph of the proposed DHCP Letter, and the statement ^{(b) (4)} in the fourth paragraph, are promotional in tone and inappropriate in a REMS designed to educate health care providers on the risks of the drug. Therefore, we recommend deleting the second paragraph and the above statement in the fourth paragraph.
- 3) We recommend providing more detail about why a REMS is necessary for this drug. As proposed, the general tone of the DHCP Letter suggests that this is a "casual/nice-to-have" program rather than a program instituted to manage the risks of the drug.

Non-Interchangeability of Botulinum Toxin Units

- 1) We recommend revising the language in this section to match that of the bolded text under the Dosage and Administration section of the draft PI, as well as that of sections 2.1 (Cervical Dystonia) and 2.2 (Dose Modification).

Dosing Guide

- 1) We note that this is a sample of the text which will be shipped with each vial of the drug. The sponsor should submit a mockup of the vial with the proposed text for FDA review.
- 2) We recommend including that Dysport is an "acetylcholine release inhibitor and neuromuscular blocking agent" for consistency with the Indications and Usage section of the draft PI.
- 3) We recommend revising the language in the proposed Dosing Guide to match that of the bolded text under the Dosage and Administration section of the draft PI, as well as that of sections 2.1 (Cervical Dystonia), 2.2 (Dose Modification), and 2.4 (Instructions for Preparation and Administration). Because this proposed piece is dedicated to dosage and administration information, we also recommend stating that "The safety and effectiveness of DYSPORT in the treatment of cervical dystonia in children below 18 years of age has not been assessed" for consistency with section 2.3 (Special Populations) of the draft PI.



Memorandum

Pre-Decisional Agency Information

Date: September 17, 2008

To: Tamy Kim, Pharm.D.
Regulatory Health Project Manager
DNP

From: Amy Toscano, Pharm.D., CPA *Amy Toscano 9/17/08*
Regulatory Review Officer
DDMAC

Subject: DDMAC comments on Dysport® (botulinum toxin type A) draft PI label
BLA 125274

Background

I have considered the current proposed product labeling for Dysport (PI), as well as the Botox (botulinum toxin type A) and Myobloc (botulinum toxin type B) PIs in my review of the Dysport PI.

DDMAC appreciates the opportunity to review the proposed product labeling (PI) for Dysport® (botulinum toxin type A), and provides the following comments.

Use of Brand Name

- DDMAC recommends replacing the generic name "botulinm toxin type A" or "botulinum toxin" with "Dysport" where appropriate. Use of the generic name in lieu of the brand name may be used to disassociate the risks with Dysport.

Examples include:

-  (b) (4)
- Section 5.3: "Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin" (emphasis added).

○ [REDACTED] (b) (4)

WARNINGS AND PRECAUTIONS

[REDACTED] (b) (4)

5.3 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

- “There have been post marketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.”

DDMAC recommends adding “treated with Dysport” to the end of this sentence, to clarify that these adverse events are associated with use of Dysport.

6.1 Clinical Studies Experience

- “*The most commonly reported adverse events (occurring in more than 5% of patients who received 500 Units of DYSPORT in the placebo controlled clinical trials) in cervical dystonia patients were muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, neck pain, musculoskeletal pain, dysphonia, injection site pain, and eye disorders (consisting of blurred vision, diplopia, reduced visual acuity, and accommodation [REDACTED] (b) (4)) (emphasis added).*”

DDMAC recommends changing this to: “occurring in more than 5% of patients and at a rate greater than placebo,” (emphasis added) if applicable.

- [REDACTED] (b) (4)

- **Common Adverse Events:** "Most adverse events were reported as mild to moderate in severity."
- **Injection Site Reactions:** "These events were mainly of mild or moderate intensity."
- **Breathing Difficulties:** "These consisted mainly of dyspnea and were mild in intensity."

DDMAC recommends deleting claims of "mild" and/or "moderate" severity and/or intensity from the PI, as they would also likely be used in a promotional context by the sponsor. Inclusion of such language in the PI minimizes the risks associated with Dysport use.

-  (b) (4)

6.2 Post Marketing Spontaneous Reports in Cervical Dystonia

- *"There is extensive post marketing experience from outside the US."*

DDMAC recommends deleting this sentence from the PI. The sponsor may use this information to minimize the risks associated with Dysport, by claiming the product has been extensively studied outside the US and has a proven safety record.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: September 17, 2008

To: Tamy Kim, PharmD
Safety Regulatory Project Manager
Division of Neurology Products

From: Carrie Newcomer, PharmD *Car Newcomer*
Consumer Promotion Analyst
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Drug: Dysport® for Injection (botulinum toxin type A)
BLA: 125274

DDMAC has reviewed the proposed Medication Guide (Med Guide) for Dysport. We also reviewed the comments on this Med Guide from the Division of Risk Management (DRISK) dated September 15, 2008. We agree with DRISK's comments and offer the following additional comments. If you have any questions or concerns regarding my comments, please contact me.

What is the most important information I should know about Dysport?

- The Warnings and Precautions section of the draft approved product labeling (PI) includes dysphagia as a symptom of botulism; however it is omitted from the list of the symptoms of botulism in the Med Guide. Please consider adding dysphagia or "trouble swallowing" to the list of symptoms in the Med Guide to be consistent with the draft PI.

What is Dysport?

- The Clinical Studies section of the draft PI states, "DYSPORT treatment resulted in improvements in TWSTRS scores **through week 12.**" (emphasis added) The Dosage and Administration section states, "... retreatment every 12 to 16 weeks or **longer, as necessary**" (emphasis added). The Med Guide states "After Dysport is injected into muscles, those muscles are weakened for up to **12 to 16 weeks.**" (emphasis added). Please consider revising this statement to be consistent with the draft PI.

What should I tell my doctor before taking Dysport?

- The Warnings and Precautions section of the draft PI states, "Aspiration complications may result from severe dysphagia and are a particular risk when treating patients in whom **swallowing or respiratory function is already compromised.**" (emphasis added) Please consider adding "problems swallowing" to the list of medical conditions that patients should tell their doctor about.

Thank you. If you have any questions, please contact Carrie Newcomer at 301.796.1233 or Carrie.Newcomer@fda.hhs.gov



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

Date: September 15, 2008

To: Russell M. Katz, M.D., Director
Division of Neurology Products

Through: Jodi Duckhorn, M.A., Team Leader *J. Duckhorn 9/15/2008*
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 9/15/2008*
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: Review of Patient Labeling (Medication Guide)

Drug Name(s): Dysport for Injection (Clostridium botulinum toxin type A hemagglutinin complex)

Application Type/Number: BLA125274

Applicant/sponsor: Ipsen Biophar Ltd.

OSE RCM #: 2008-1386

1 INTRODUCTION

Ipsen Biophar Ltd. submitted an original Biologics Licensing Application, BLA 125274 on November 29, 2007. Dysport is indicated for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position, disability and neck pain in toxin naïve and previously treated patients.

During a teleconference on August 20, 2008, FDA informed the sponsor that a Risk Evaluation and Mitigation Strategy (REMS) will be required for this application. FDA has determined that Dysport® poses a serious and significant public health concern requiring the distribution of a Medication Guide in accordance with 21 CFR 208. The Medication Guide is necessary for patients' safe and effective use of Dysport®. FDA has determined that Dysport® 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' decision to use, or continue to use, Dysport®. FDA has also determined that Dysport is a product for which patient labeling could help prevent serious adverse events.

The review division developed a draft Medication Guide for Dysport on August 28, 2008. The review division requested review of the proposed Medication Guide by the Patient Labeling and Education Team. This review is written in response to that request. Additional aspects of the REMS are being addressed separately from this review by OSE in conjunction with the review division.

MATERIAL REVIEWED

- DRAFT Dysport Professional Information (PI) as submitted by the sponsor on November 29, 2007, and further revised by the review division on August 28, 2008.
- DRAFT Dysport Medication Guide (MG), developed by the review division, dated August 28, 2008.

2 DISCUSSION

The purpose of Medication Guides (MG) is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG developed by the review division has a Flesch Kinkaid grade level of 9.2, and a Flesch Reading Ease score of 47.8%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 7.5 and a Flesch Reading Ease score of 62.5%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- made the MG consistent with the PI,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

3 CONCLUSIONS AND RECOMMENDATIONS

1. Dysport is intended for use only by doctors. The sponsor should state how they intend to ensure that each patient will receive the MG in accordance with 21CFR208.26 (2) (e).
2. We have more clearly delineated the problems with swallowing, speaking, or breathing, which may be life threatening, from issue of systemic spread of the botulinum toxin. We have listed the reportable signs and symptoms of systemic spread.
3. In the MG section “What is the most important information I should know about Dysport?”:
 - Section 5.1 General, under Warnings and Precautions says that patients may require immediate medical attention if they develop problems with swallowing, speech or respiratory problems. Given that the concern about spread of botulinum toxin is the adverse reaction that is driving the need for the MG, should there be an instruction to get medical help right away if patients get symptoms of botulism?
 - Clarify whether it should be any of the symptoms, or the constellation of symptoms.
 - We do not object to including information under this section and “What should I avoid while receiving Dysport?” related to driving or doing other dangerous activities as suggested by DPV; however, this information is not in the PI and should be added to section 17. The language in the MG must be consistent with the language in the PI. Information should be added to section 17 Patient Counseling Information about the important side effects of Dysport. We have revised the MG section “What are the possible side effects of Dysport?” to make it consistent with the PI. A number of side effects were not listed in the draft MG.
4. Section 17 should be further developed to include information that is important to healthcare providers in educating patients about the safe use of the product.
5. We have added the list of ingredients in Dysport at the end of the MG.

Please let us know if you have any questions.

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

Cc List:

Division of Neurology Products

Russell Katz

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OSE/Division of Risk Management

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MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 3, 2008

TO: Tammy Kim, Regulatory Project Manager
Carole Davis, M.D., Medical Officer
Division of Neuropharmacological Products (DNP)

FROM: Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125274

APPLICANT: Biomeasure, Inc. (US Agent for Ipsen Biopharm Limited)

DRUG: Dysport® (Clostridium botulinum toxin type A hemagglutinin complex)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Cervical Dystonia

CONSULTATION REQUEST DATE: February 8, 2008

DIVISION ACTION GOAL DATE: September 28, 2008

PDUFA DATE: September 28, 2008

I. BACKGROUND

Clinical investigator inspections were requested at four clinical sites that performed studies for which the sponsor submitted data in BLA 125274. In addition, a sponsor inspection was requested because Dysport is a new molecular entity product. The clinical investigator and sponsor inspections were conducted according to the Compliance Programs 7348.811 (Inspection Program for Clinical Investigators) and 7348.810 (Inspection Program for Sponsors, Contract Research Organizations and Monitors), respectively. The inspections covered work performed under protocols Y-47-52120-051 and Y-97-52120-045 entitled “A phase III multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of intramuscular administration Dysport® (500 units) for the treatment of cervical dystonia.”

Study Y-47-52120-051 (conducted in the US and Russia) was designed to evaluate the efficacy and safety profile of a single dose (500 Units) of Dysport manufactured by Ipsen Biopharm, Ltd (IBL) for the treatment of cervical dystonia using bulk active substance (BAS) from the site intended for commercialization (IBL, Wrexham), as well as to provide clinical data to register the new BAS facility in Europe. The design of the trial is similar to Study Y-97-52120-045 (done in the US) which used BAS material produced at the (b) (4)

Studies Y-47-52120-051 and Y-97-52120-045 were a multicenter, randomized, double-blind, placebo-controlled, outpatient investigation of Dysport for the treatment of cervical dystonia. Efficacy evaluations were to include Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total and subscale scores, visual analog pain scores (VAS), and subject and investigator’s VAS for symptom assessments. Safety evaluations were to include neurological and physical examinations (including vital signs), routine laboratory tests and blood samples (including chemistry, hematology, and urinalysis), and a blood sample was to be drawn for Botulinum toxin type A antibody testing.

Basis for Site Selection: Four clinical sites (Drs. Truong, Duane, Orlova, and Timerbaeva) were inspected. These four clinical sites were recommended for inspection because they enrolled the largest numbers of subjects in the two pivotal studies for this BLA. The goals of the inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

The sponsor site was inspected because Dysport is a new molecular entity product. The goals of the inspection included validation of submitted data and compliance of specific responsibilities of the sponsor of clinical studies with FDA regulations. Among the elements reviewed for compliance were data collection and handling, study monitoring procedures, and subject records and reports.

II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)/# of subjects	Inspection Date	Final Classification
Daniel Truong, M.D. The Parkinson's Movement Disorder Institute 9940 Talbert Avenue, Fountain Valley, CA 92708	Y-97-52120-045 21 subjects	4/7-10/2008	NAI
Drake Duane, M.D. Arizona Dystonia Institute 10210 North 92 nd Street Suite 300 Scottsdale, AZ 85258	Y-97-52120-045 18 subjects	4/16-18/2008	NAI
Sofia Timerbaeva, M.D. Scientific Research Institute of Neurology, RAMS, Neuropharmacological Group 80 Volokolamskoye Sh. Moscow, 125367 Russia	Y-47-52120-051 8 subjects	7/28 - 8/1/2008	NAI
Olga Orlova, M.D. Clinic "Cecil Plus" 5 Fadeeva St. Moscow, 125047 Russia	Y-47-52120-051 12 subjects	8/4-8/2008	NAI

Sponsor/Site	Protocol(s)	Inspection Date	Final Classification
Biomeasure, Inc./Ipsen Group 27 Maple Street Milford, MA 01757-3650	Y-47-52120-051	4/8-17/2008	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

**1. Dr. Daniel Truong
 Fountain Valley, CA**

a. What was inspected?

At this site, 21 subjects were randomized and completed the study. The FDA investigator performed a complete review of 10 subjects' records. Records were reviewed, including study regulatory records, case report forms (CRFs), and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the BLA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

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Summary Report of U.S. and Foreign Inspections

b. General observations/commentary:

In general, Dr. Truong complied with protocol-specified requirements. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

c. Assessment of data integrity:

Data generated for protocol Y-97-52120-045 at this clinical site appear acceptable for use in support of BLA 125274.

2. **Dr. Drake Duane**
Scottsdale, AZ

a. What was inspected?

At this site, 19 subjects were screened, 18 subjects were randomized and 13 subjects completed the open label portion of the study. The FDA investigator performed a complete review of 18 subjects' records. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. The FDA investigator reviewed the source documents and case report forms, and compared these with data listings provided by the sponsor as part of the BLA submission. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

There were no significant inspectional findings that would adversely impact data acceptability. There was adequate documentation in the source documents to assure all subjects were actually enrolled in the study and treated throughout the study. No underreporting of adverse events was noted. Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms.

In general, Dr. Duane complied with protocol-specified requirements. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

c. Assessment of data integrity:

Overall, data generated for protocol Y-97-52120-045 at this clinical site appear acceptable for use in support of BLA 125274.

**3. Dr. Sofia Timerbaeva
Moscow, Russia**

a. What was inspected?

A total of 8 subjects were randomized into the study. The FDA investigator performed a complete review of study records for all 8 subjects enrolled in the study. Complete files were reviewed including study regulatory records, CRFs, and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the BLA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

In general, Dr. Timerbaeva complied with protocol-specified requirements. There were no significant inspectional findings that would adversely impact data acceptability. There was adequate documentation in the source documents to assure all subjects were actually enrolled in the study and treated throughout the study. No underreporting of adverse events was noted. Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms.

c. Assessment of data integrity:

Data generated for protocol Y-47-52120-051 at this clinical site appear acceptable for use in support of BLA 125274.

**4. Dr. Olga Orlova
Moscow, Russia**

a. What was inspected?

A total of 12 subjects were randomized into the study. The FDA investigator performed a complete review of study records for all 12 subjects enrolled in the study. Complete files were reviewed for all subjects including study regulatory records, CRFs, and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the BLA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

In general, Dr. Orlova complied with protocol-specified requirements. There were no significant inspectional findings that would adversely impact data acceptability. Data in sponsor-provided data listings were supported by data in source documents and case report forms. No underreporting of adverse events was noted.

c. Assessment of data integrity:

Data generated for protocol Y-47-52120-051 at this clinical site appear acceptable for use in support of BLA 125274.

**5. Biomeasure, Inc./Ipsen Group
Milford, MA**

a. What was inspected?

The inspection was conducted in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program (7348.810). The inspection covered work performed under protocol Y-47-52120-051. The inspection reviewed the following: quality assurance and clinical operations, study monitoring procedures, data collection and handling, subject records and reports, participating clinical investigators, monitoring reports, CRFs, data collection, and study drug accountability. Drs. Auerbach, Roper, Young, and Meissner were among the clinical investigators for whom sponsor responsibilities were evaluated.

b. General observations/commentary:

In general, the sponsor adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted.

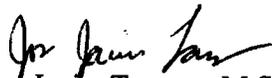
c. Assessment of data integrity:

The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL
RECOMMENDATIONS**

In general, for the four clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events noted. Overall, data from these clinical sites that had been inspected appear acceptable for use in support of BLA 125274.

Page 7 of 7 - BLA 125274 Dysport
Summary Report of U.S. and Foreign Inspections



Jose Javier Tavaréz, M.S.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:



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



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

Date: June 19, 2008
To: Russell Katz, M.D., Director
Division of Neurology Products

From: Tamy Kim, PharmD, Regulatory Project Manager
Division of Neurology Products
Subject: PLR Labeling Review

Drug Name(s): Dysport
(Botulinum type A Toxin) 500 units/vial

Application BLA: 125274

Licensee: Biomeasure Inc.

Highlights:

- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance] OK.
- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)] OK.
- The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)] OK.
- The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)] OK.
- The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4). N/A.
- Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)

- For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

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

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

- Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
- A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]. OK.
- Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble] OK.
- The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)] OK.
- A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval. OK.
- A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)] OK.

Contents (Table of Contents):

- The headings and subheadings in the Contents must match the headings and subheadings in the FPI. [See 21 CFR 201.57(b)] OK.
- The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)] Fix second part?
- Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading. Fix “General” in section 5.1 and change this in CONTENTS section
- Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
- When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

• When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”
OK.

Full Prescribing Information (FPI):

- Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System). OK.
- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format. OK.
- Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>. OK.
- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance] OK.
- Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)] OK.
- Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)] OK.
- The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence. OK.
- There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section. OK.

- The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling. OK.
- If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG. OK.
- Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
- Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

Lack of SPL Submission:

We note that structured product labeling (SPL) has not been submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf>], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Created: JMDelasko/SEALD: 1/29/07; SEALD Updated: 3/1/07; 11/14/07; 4/17/08

BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

BLA #: 125274-Original BLA
Trade Name: Dysport
Generic Name: Botulinum Type A Toxin-Hemagglutinin Complex
Strengths:

Applicant: Ipsen

Date of Application: November 29, 2007
Date of Receipt: November 29, 2007
Date clock started after UN:
Date of Filing Meeting: January 16, 2008
Filing Date: January 28, 2008
Action Goal Date (optional):

User Fee Goal Date: September 28, 2008
After Complete response on December 23, 2008,
PDUFA was April 29, 2009

Indication(s) requested: Cervical Dystonia

Type of Original BLA: N/A (b)(1) _____ (b)(2) _____
OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: 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). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S Standard P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) _____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid _____ Exempt (orphan, government) Orphan
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES[√] NO
User Fee ID # PD3007826
Clinical data? YES[√] _____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO
If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES[√] NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO√
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES√ NO

• Was form 356h included with an authorized signature? YES√ NO
If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES√ NO
If no, explain:

• If an electronic NDA, does it follow the Guidance? N/A YES√ NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A YES√ NO

• Is it an electronic CTD? N/A YES√ NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information submitted on form FDA 3542a? YES√ NO

• Exclusivity requested? Orphan Product exclusivity granted. Sponsor references this. YES 7 years NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES√ NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
“*[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.*” Applicant may not use wording such as “To the best of my knowledge . . .”

- Financial Disclosure forms included with authorized signature? YES[√] NO
 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES[√] NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? RMS-BLA? YES[√] NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 7,434
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 12/05/06 _____ NO
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES[√] NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES[√] NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES[√] NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A[√] YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A[√] YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES[√] NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES[√] NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

- : _____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
 _____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

• Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 16, 2008

BACKGROUND:

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

Dysport (abobotulinumtoxinA) is an original BLA that was submitted for review for the treatment of cervical dystonia. This product is marketed in Europe. Reloxin, which is identical to Dysport is under review in DDDP for the treatment of glabellar lines.

ATTENDEES: Russell Katz, Tamy Kim, Elizabeth McNeil, Carole Davis, Barry Cherney, Elizabeth Shores, Susan Kirshner, Ennan Guan, Lois Freed, Barbara Wilcox, Marc Stone, Jose Tavarez-Pagan, Kun Jin, Kay Schneider, Veneeta Tandon, Ohidul Siddiqui, Sally Yasuda, Michelle Clark-Stuart

Discipline

Reviewer

Medical:	Carole Davis
Safety Medical:	Marc Stone
Statistical:	Ohidul Siddiqui
Nonclinical:	Barbara Wilcox
Clinical Pharmacology:	Veneeta Tandon
Chemistry:	Ennan Guan
Environmental Assessment (if needed):	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Jose Tavarez-Pagan
Regulatory Project Management:	Tamy Kim
Other Consults:	

Per reviewers, are all parts in English or English translation? YES[√] NO
 If no, explain:

CLINICAL FILE √ REFUSE TO FILE _____

- Clinical site inspection needed: YES[√] NO
- Advisory Committee Meeting needed? YES, date if known _____ NO[√]
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A[√] YES NO

CLINICAL MICROBIOLOGY NA[√] FILE _____ REFUSE TO FILE _____

STATISTICS FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA FILE REFUSE TO FILE

- GLP inspection needed: YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments: No.

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.


Regulatory Project Manager, HFD-

Regulatory Filing Review Memo for BLAs and Supplements

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

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

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

STN: 125274/0 Product: clostridium A, DYSPORT Applicant: Ipsen

Final Review Designation (circle one): Standard Priority

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

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 1/16/08 Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

____ Part A – RPM

Part B – Product/CMC/Facility Reviewer(s): Michelle Clark-Sevart Susan F. Lasker

____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____

____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____

- Memo of Filing Meeting

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Quality overall summary [2.3]	(Y) N	
<input type="checkbox"/> Drug Substance	(Y) N	
<input type="checkbox"/> Drug Product	(Y) N	
<input type="checkbox"/> Facilities and Equipment	(Y) N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	(Y) N	
<input type="checkbox"/> Novel Excipients	(Y) N	
<input type="checkbox"/> Executed Batch Records	(Y) N	
<input type="checkbox"/> Method Validation Package	(Y) N	
<input type="checkbox"/> Comparability Protocols	(X) (N)	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	(Y) N	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	(Y) N	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
<input type="checkbox"/> description of manufacturing process	(Y) N	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	(Y) N	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	(Y) N	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> analytical method validation		
<input type="checkbox"/> reference standards		
<input type="checkbox"/> stability		
<input type="checkbox"/> process validation (prospective	(Y) N	

CIP Module Contents	Present	If not justification action
<p>plan, results, analysis, and conclusions)</p> <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> specification <ul style="list-style-type: none"> <input type="checkbox"/> justification of specs. <input type="checkbox"/> analytical procedures <input type="checkbox"/> analytical method validation <input type="checkbox"/> batch analyses <ul style="list-style-type: none"> <input type="checkbox"/> consistency (3 consecutive lots) <input type="checkbox"/> justification of specs. <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	<p>(Y) N</p>	
<p>Drug Product [3.2.P]</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> 3 consecutive lots <input type="checkbox"/> other needed validation data <input type="checkbox"/> control of excipients (justification of specifications; analytical method 	<p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p>	

CTD Module Contents	Present?	File justification action & date
<ul style="list-style-type: none"> validation; excipients of human/animal origin) <input type="checkbox"/> control of drug product (justification of specifications; analytical method validation) <input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF <input type="checkbox"/> closure integrity <input type="checkbox"/> administration device(s) <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	<p style="text-align: center;">Y</p> <p style="text-align: center;">Y</p> <p style="text-align: center;">Y</p>	
<ul style="list-style-type: none"> Diluent (vials or filled syringes) [3.2P'] <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> 3 consecutive lots <input type="checkbox"/> other needed validation data <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) 	<p style="text-align: center;">Y</p>	

CTD Module 3 Contents	Present?	Justification, action & status
<input type="checkbox"/> comparability protocols	Y N	
Literature references and copies [3.3]	Y N	

Example of filing issues	Yes?	Justification, action & status
content, presentation, and organization sufficient to permit substantive review?	Y N	
<input type="checkbox"/> legible	Y N	
<input type="checkbox"/> English (or translated into English)	Y N	
<input type="checkbox"/> compatible file formats	Y N	
<input type="checkbox"/> navigable hyper-links	Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> all electronic submission components usable	Y N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y N	
includes data demonstrating consistency of manufacture	Y N	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
certification that all facilities are ready for inspection	Y N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
if not using a test or process specified by regulation, data is provided to show the	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility <input type="checkbox"/> <input type="checkbox"/>	Y N Y N Y N 	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	

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

Recommendation (circle one): File (RTF)

Reviewer: Michelle W. Clark - Stuart 1/16/08 Type (circle one): Product (Chair) Facility (DMPQ)
 (signature/ date)

Concurrence: [Signature] / 1/15/08 Division, Director: _____
 Branch/Lab Chief: _____ (signature/ date) (signature/ date)