# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**125274**

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS

# MEMORANDUM

DATE: April 29, 2009

TO: File, BLA 125274/1 (formerly BLA 125286)
Dysport (abobotulinumtoxinA)

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

RE: Risk Evaluation and Mitigation Strategy (REMS)

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 FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

Ipsen Biopharm's Dysport (abobotulinumtoxinA) has been under review simultaneously in the Division of Neurology Products (DNP) for the treatment of cervical dystonia (BLA 125274) and in the Division of Dermatology and Dental Products (DDDP) for the temporary improvement in the appearance of moderate to severe glabellar lines (BLA 125286). On November 6, 2008, DNP notified the applicant (under BLA 125274) that a REMS will be required for Dysport (abobotulinumtoxinA) and that the elements of the

REMS will be a Medication Guide, Communication Plan, and a timetable for the submission of assessments of the REMS. The applicant submitted a proposed REMS on December 3, 2008 and a revised proposed REMS to reflect the product's use for the dermatologic indication. On April 29, 2009, FDA will approve original BLA 125274/0 and efficacy supplement BLA 125274/1 (formerly BLA 125286). BLA 125286/0 will be voided effective this date.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology (OSE), we have determined that a REMS is necessary to ensure that the benefits of Dysport (abobotulinumtoxinA) outweigh its risks for dermatologic use. The risks that are addressed in the REMS could be expected to affect any patient population taking Dysport (abobotulinumtoxinA), namely the potential for distant spread of botulinum toxin after local injection, and the potential for medication errors related to the lack of interchangeability of Dysport (abobotulinumtoxinA) with other licensed botulinum toxin 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. In this setting, medication errors including overdosing and underdosing can occur due to the potential for healthcare providers to substitute one product for another and interchange dose units.

In reaching this determination, we considered the following:

A. Dysport (abobotulinumtoxinA) will be indicated for the temporary improvement in the appearance of moderate to severe glabellar lines in adults < 65 years of age. The degree to which Dysport (abobotulinumtoxinA) will be used for this purpose is unknown, but may be considerable.

B. Frown lines (or hyperkinetic lines) result from repeated contraction of muscles perpendicular to the wrinkles. In the glabellar region these lines are caused by the contraction of the corrugator and orbicularis muscles which move the brow medially and the procerus and depressor supercilii which pull the brow inferiorly. The muscles targeted for relaxation to temporarily improve these frown lines are the corrugator and procerus muscles, as their only function is to control facial expression. Glabellar lines do not represent a serious medical condition.

C. There were three phase 3 clinical trials submitted to BLA 125286 in support of single and repeat dose efficacy, and short- and long-term safety of Dysport (abobotulinumtoxinA). In these trials, patients treated with Dysport (abobotulinumtoxinA) had a significantly greater improvement, measured as the investigator's and the subject's assessment of glabellar severity score (GLSS) at maximum frown on day 30 after treatment compared to placebo.

D. Dysport (abobotulinumtoxinA) will be approved at a dose of 50 units to be injected intramuscularly into the glabellar region in 5 equal doses. Subsequent treatment should not occur sooner than 90 days after the last treatment.

E. Adverse events associated with botulinum toxin products, of which Dysport (abobotulinumtoxinA) is one, have been reported through the AERS database, medical literature, and manufacturer reports. A serious adverse event with botulinum toxin products is the distant spread of botulinum toxin from the site of injection in amounts sufficient to produce symptoms consistent with botulinum toxin effect. These symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported within hours to weeks after injection, and in some cases, swallowing and breathing difficulties have been life-threatening. The risk appears greatest in children treated for spasticity, but symptoms have been reported in adults treated for spasticity and in patients with underlying conditions that would predispose them to these symptoms. Most cases received doses comparable to those used to treat neurologic conditions such as cervical dystonia, or lower doses.

   Patients who had received botulinum toxin injections in the head, neck and shoulder areas described dysphagia, speech problems, ptosis, and difficulty holding their heads up.

F. Dysport (abobotulinumtoxinA) is considered a new molecular entity.

In accordance with section 505-1 of the FDCA, FDA has determined that a Medication Guide is required for Dysport (abobotulinumtoxinA). Pursuant to 21 CFR Part 208, FDA has determined that Dysport (abobotulinumtoxinA) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Dysport (abobotulinumtoxinA). FDA has determined that Dysport (abobotulinumtoxinA) is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Dysport (abobotulinumtoxinA) and for which patient labeling could help prevent serious adverse effects related to the use of the product.

The elements of the REMS will be a Medication Guide, Communication Plan, and a timetable for submission of the REMS.

Julie Beitz MD

Julie Beitz, M.D.
Director, Office of Drug Evaluation III

Ellis F. Unger, MD
Deputy Director (Acting)
Office of Drug Evaluation I

**BLA STN 125274 AND 125286 DYSPORT™ (ABOBOTULINUMTOXINA)**

Acetylcholine release inhibitor and neuromuscular blocking agent

Ipsen Biopharm Limited
Unit 9 Ash Road Wrexham Industrial Estate
Wrexham LL13 9UF
United Kingdom

Tel: +44 (0)1978 661181

## NEW PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

### I GOAL(S)

DYSPORT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent. The potency units of DYSPORT are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT™ cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

The goal of the REMS is to ensure that the potential benefits of treatment with DYSPORT™ for the treatment of Cervical Dystonia and Glabellar Lines outweigh the potential risks of:

- Medication errors related to the lack of interchangeability of DYSPORT™ units with those of toxins of other manufacturers; and
- the potential for the occurrence of distant spread of toxin effect beyond the injection site discussed in the Warnings and Precautions section of the package insert.

### II REMS ELEMENTS

The DYSPORT™ REMS includes a Medication Guide for patients and a Communication Plan which are further detailed below. The purposes of the REMS elements are to ensure that the potential benefits of treatment with DYSPORT™ for the treatment of Cervical Dystonia and Glabellar Lines outweigh the potential risks.

### A Medication Guide

A Medication Guide will be dispensed with each DYSPORT™ prescription (see REMS Appendix 2).

DYSPORT™ is available in cartons containing either a single or two 500 Unit vials of DYSPORT™ or a single 300 Unit vial of DYSPORT™. The Medication Guide is inserted inside the carton with the vial(s) of DYSPORT. A Medication Guide will be provided for each vial of DYSPORT™. The carton prominently states "Dispense the enclosed Medication Guide to each patient". Each Medication Guide is inspected to ensure that the correct version is being used and that the component is available for insertion into each carton of DYSPORT™.

Because the Medication Guide is included as part of the secondary package for DYSPORT™, IPSEN has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide.

**B** **Communication Plan**

Ipsen will implement a communication plan to healthcare providers to support the implementation of this REMS.

The primary objectives of this Communication Plan are to ensure that the potential risk of serious adverse reactions due to the distant spread of effect of botulinum toxin is minimized when DYSPORT™ is being used in the approved indication for Cervical Dystonia and Glabellar Lines and to inform physicians of the lack of interchangeability of DYSPORT™ units with those of toxins of other manufacturers.

Ipsen will provide a Dear Healthcare Provider Letter (See REMS Appendix 1) to healthcare professionals involved in the prescribing, dispensing, or administration of DYSPORT™. The Dear Healthcare Provider Letter will be distributed at launch of the approval of DYSPORT™ to neurologists, dermatologists, and other specialties and healthcare professional staff who prescribe or inject DYSPORT™ or other botulinum toxin products (i.e., physical medical and rehabilitation specialists, dermatologists, ophthalmologists and other specialists who have previously dispensed botulinum toxins).

**C** **Elements to Assure Safe Use**

The REMS for DYSPORT™ does not require Elements to Assure Safe Use.

**D** **Implementation System**

The REMS for DYSPORT™ does not require an Implementation System.

**E** **Timetable for Submission of Assessments**

Ipsen will continually review the success of the Communication Plan and make any changes necessary to ensure efficient communication of the potential risks to patients and treating physicians. In particular, the number and nature of reports of

undesirable effects, medication errors indicated by the lack of effect, overdose, etc. will be carefully monitored.

The estimated timetable for Submission of Assessments is as follows:

- 1st Assessment: 18 months from product launch
- 2nd Assessment: 3 years from product launch
- 3rd Assessment: 7 years from product launch

Ipsen will submit the assessments within 60 days of the close of the intervals as noted above.

APPEARS THIS WAY
ON ORIGINAL

# NEW PROPOSED REMS FOR BLA 125274 AND BLA 125286 – REMS SUPPORTING DOCUMENT

**BLA STN 125274 DYSPORT™ (abobotulinumtoxinA)**

Acetylcholine release inhibitor and neuromuscular blocking agent

Ipsen Biopharm Limited
Unit 9 Ash Road Wrexham Industrial Estate
Wrexham LL13 9UF
United Kingdom

Tel: +44 (0)1978 661181

**REMS SUPPORTING DOCUMENT**

14 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

**DYSPORT™ New Proposed REMS Appendix 1: Dear Healthcare Provider Letter**

**Dear Healthcare Provider Letter for the treatment of Cervical Dystonia**

Announcing the Approval of DYSPORT™ (abobotulinumtoxinA)

Dear Healthcare Provider:

Ipsen Biopharm Limited, the makers of DYSPORT™, and Tercica, Inc. the distributor of the product for medical use, would like to notify you that DYSPORT™ has been approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients. DYSPORT™ has also been approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients <65 years of age. DYSPORT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent.

In order to ensure that the benefits of DYSPORT™ treatment outweigh the potential risks of DYSPORT™ treatment, a Risk Evaluation and Mitigation Strategy has been implemented. The goals of the Risk Evaluation and Mitigation Strategy are:

- to reduce the potential for medication errors related to the lack of interchangeability of DYSPORT™ units with those of other botulinum toxin products from other manufacturers, and
- to communicate the potential for the distant spread of toxin effect beyond the injection site.

**Non-Interchangeability of botulinum toxin Units:**
It is important to note that the potency units of DYSPORT™ are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT™ cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

The approved DYSPORT™ starting dose for the treatment of cervical dystonia in botulinum toxin-naïve and previously treated patients is 500 Units. Further doses of DYSPORT™ to treat cervical dystonia should be given no less than 12 weeks apart. Depending on patient response, doses may be increased or decreased in 250 Unit increments. The maximum recommended dose for cervical dystonia is 1000 Units every 12 weeks.

The approved total dose of DYSPORT™ for the temporary improvement of glabellar lines is 50 Units given in 5 equal aliquots in naïve and previously treated patients. When used for retreatment, DYSPORT™ should be administered no more frequently than every 3 months.

When prescribing DYSPORT™ to your patients, please take care to appropriately document DYSPORT™'s unique established drug name *"abobotulinumtoxinA"* to reduce the potential for medication errors that may arise from confusion between botulinum toxins from different manufacturers.

**Spread of Toxin Effect:**
All botulinum toxins including DYSPORT™ have the potential to cause clinically detectable effects that occur in areas beyond and not contiguous with the site of injection. These effects are consistent with the pharmacological action of botulinum toxin. The risk of adverse events may be reduced by using the lowest effective dose and not exceeding the recommended dose for each indication.

Patients with, or at risk of, peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be closely supervised when treated with DYSPORT™.

Patients and/or their care partner should be informed of the potential risk of distant spread of botulinum toxin effect associated with the use of DYSPORT™. They should be instructed to recognize the early symptoms of toxicity (difficulty swallowing, breathing, or speaking) and urged to seek immediate medical advice if they experience any of them. Patients and/or their care partner should also be instructed to inform other healthcare providers about their use of botulinum toxin when being treated for other medical conditions.

Information on the Spread of Toxin Effect (Boxed Warning and section 5.2), Dysphagia and Breathing Difficulties in the Treatment of Cervical Dystonia (section 5.3), and Pre-Existing Neuromuscular Disorders (section 5.5) is provided in the enclosed copy of the FDA approved DYSPORT™ Full Prescribing Information as well as below.

**Distant Spread of Toxin Effect**

Postmarketing reports indicate that the effects of DYSPORT™ and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

## *5 WARNINGS AND PRECAUTIONS*

### *5.2 Spread of Toxin Effect*

*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 symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of the symptoms is probably greatest in children treated for spasticity but symptoms 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. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with the spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.*

### *5.3 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia*

*Treatment with DYSPORT™ and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or*

*swallowing. When distant effects occur, additional respiratory muscles may be involved [see Warnings and Precautions (5.2)].*

*Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.*

*Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post marketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.*

*Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].*

***5.5 Pre-Existing Neuromuscular Disorders***
*Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of DYSPORT™ [see Adverse Reactions (6.1)].*

**Patient Medication Guide:**
One of the elements of the Risk Evaluation and Mitigation Strategy is the FDA approved Patient Medication Guide. When discussing the risks above and other risks identified in the Full Prescribing Information with patients and/or their care partner, you must provide them with a copy of the Patient Medication Guide enclosed with each vial of DYSPORT™. The Patient Medication Guide and Full Prescribing Information are also available from your local Tercica, Inc. sales representative, on our website at www.dysport.com, or by calling 1-877-397-7671.

Finally, please remember to report suspected adverse reactions associated with DYSPORT™ treatment at 1-877-397-7671 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

We look forward to serving you and your patients.

Best regards,

Tercica Inc.
Brisbane, CA

**Dear Healthcare Provider Letter for the treatment of Glabellar lines**

Announcing the Approval of DYSPORT™ (abobotulinumtoxinA)

Dear Healthcare Provider:

Ipsen Biopharm Limited, the makers of DYSPORT™, and Medicis Aesthetics, Inc. the distributor of the product for aesthetic use, would like to notify you that DYSPORT™ has been approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients <65 years of age. DYSPORT™ has also been approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients. DYSPORT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent.

In order to ensure that the benefits of DYSPORT™ treatment outweigh the potential risks of DYSPORT™ treatment, a Risk Evaluation and Mitigation Strategy has been implemented. The goals of the Risk Evaluation and Mitigation Strategy are:

- to reduce the potential for medication errors related to the lack of interchangeability of DYSPORT™ units with those of other botulinum toxin products from other manufacturers, and
- to communicate the potential for the distant spread of toxin effect beyond the injection site.

**Non-Interchangeability of botulinum toxin Units:**
It is important to note that the potency units of DYSPORT™ are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT™ cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

The approved total dose of DYSPORT™ for the temporary improvement of glabellar lines is 50 Units given in 5 equal aliquots in naïve and previously treated patients. When used for retreatment, DYSPORT™ should be administered no more frequently than every 3 months.

The approved DYSPORT™ starting dose for the treatment of cervical dystonia in botulinum toxin-naïve and previously treated patients is 500 Units. Further doses of DYSPORT™ to treat cervical dystonia should be given no less than 12 weeks apart. Depending on patient response, doses may be increased or decreased in 250 Unit

increments. The maximum recommended dose for cervical dystonia is 1000 Units every 12 weeks.

When prescribing DYSPORT™ to your patients, please take care to appropriately document DYSPORT's unique established drug name *"abobotulinumtoxinA"* to reduce the potential for medication errors that may arise from confusion between botulinum toxins from different manufacturers.

**Spread of Toxin Effect:**
All botulinum toxins including DYSPORT™ have the potential to cause clinically detectable effects that occur in areas beyond and not contiguous with the site of injection. These effects are consistent with the pharmacological action of botulinum toxin. The risk of adverse events may possibly be reduced by using the lowest effective dose and not exceeding the recommended dose for each indication.

Patients with, or at risk of, peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be closely supervised when treated with DYSPORT™.

Patients and/or their care partner should be informed of the potential risk of distant spread of botulinum toxin effect associated with the use of DYSPORT™. They should be instructed to recognize the early symptoms of toxicity (difficulty swallowing, breathing, or speaking) and urged to seek immediate medical advice if they experience any of them. Patients and/or their care partner should also be instructed to inform other healthcare providers about their use of botulinum toxin when being treated for other medical conditions.

Information on the Spread of Toxin Effect (Boxed Warning and section 5.2), Dysphagia and Breathing Difficulties in the Treatment of Cervical Dystonia (section 5.3), and Pre-Existing Neuromuscular Disorders (section 5.5) is provided in the enclosed copy of the FDA approved DYSPORT™ Full Prescribing Information as well as below.

**Distant Spread of Toxin Effect**

Postmarketing reports indicate that the effects of DYSPORT™ and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms can occur hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

## *5 WARNINGS AND PRECAUTIONS*

### *5.2 Spread of Toxin Effect*

*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 symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms can occur hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of the symptoms is probably greatest in children treated for spasticity but symptoms 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. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with the spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.*

### *5.3 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia*

*Treatment with DYSPORT™ and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or*

*swallowing. When distant effects occur, additional respiratory muscles may be involved [see Warnings and Precautions (5.2)].*

*Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.*

*Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post marketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.*

*Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].*

***5.5 Pre-Existing Neuromuscular Disorders***
*Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of DYSPORT™ [see Adverse Reactions (6.1)].*

**Patient Medication Guide:**
One of the elements of the Risk Evaluation and Mitigation Strategy is the FDA approved Patient Medication Guide. When discussing the risks above and other risks identified in the Full Prescribing Information with patients and/or their care partner, you must provide them with a copy of the Patient Medication Guide enclosed with each vial of DYSPORT™. The Patient Medication Guide and Full Prescribing Information are also available from your local Medicis Aesthetics, Inc. sales representative, on our website at www.DysportUSA.com, or by calling 1-877-397-7671.

Finally, please remember to report suspected adverse reactions associated with DYSPORT™ treatment at 1-877-397-7671 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

We look forward to serving you and your patients.

Best regards,

Medicis Aesthetics, Inc.
Scottsdale, AZ

# HEALTH CARE PROVIDER SURVEY

**Date of the Survey:** |_|_|.|_|_|.|_|_|_|_|
M M D D Y Y Y Y

**HEALTH CARE PROVIDER's details:**

First name: _____

Last Name: _____

Address: _____
_____

Phone: _____ Fax: _____
Email: _____

**Specialty** (select one):

- Neurologist
- Physical Medicine & Rehabilitation Specialist
- Dermatologist
- If other please specify: _____

Before conducting the survey, inform the HEALTH CARE PROVIDER of the following:

*"DYSPORT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent."*

**Experience with botulinum toxin injection and screening criteria:**

You use DYSPORT™ to treat:

(a) adults with cervical dystonia to reduce the severity of abnormal head position, disability and neck pain in both toxin naïve and previously treated patients (please answer questions 1 – 12)

(b) the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age (please answer questions 1 – 8, and 13 – 14)

(c) Both (please answer all questions)

Number of years since first botulinum toxin injection (excluding DYSPORT™):

(a) < 1 year

(b) 1 year – 3 years

(c) >3 years

Number of patients treated with DYSPORT™ injections each week:

(a) <10 patients
(b) 10-20 patients
(c) >20 patients

Number of months since first patient treated with DYSPORT™ injection:

(a) < 6 months
(b) 6 - 12 months
(c) >12 months
(d) I have not treated a patient with DYSPORT™

Number of patients treated with botulinum toxin injections each week:

(a) <10 patients
(b) 10-20 patients
(c) >20 patients

**Physician Survey Questions:**

(1) The dosing Units of DYSPORT™ are specific to the preparation and are not interchangeable with units of other botulinum toxin products.

(a) True
(b) False

(2) When treated with botulinum toxin A patients should be instructed to seek immediate medical advice if they experience:

(a) Difficulty swallowing or breathing
(b) Muscle weakness
(c) Blurred Vision
(d) Difficulty Speaking
(e) a and b only
(f) All of the above

(3) All botulinum toxins should be used with caution in patients with, or at risk of:

(a) Defective neuromuscular transmission

(b) Lambert-Eaton syndrome

(c) Both of the above

(d) Neither of the above

(4) Treatment with DYSPORT™ can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications.

(a) True

(b) False

(5) In order to minimize the risk of serious reactions from botulinum toxin effect spreading in the body beyond the site where it was injected, you should:

(a) Use the lowest effective dose

(b) Avoid intravenous injection

(c) Both of the above

(d) Neither of the above

(6) What resources are available to physicians related to the approved dosing for cervical dystonia and glabellar lines?

(a) The DYSPORT™ full prescribing information

(b) The DYSPORT™ product website

(c) Both

(7) What resources are available to help physicians communicate important information related to the potential for spread of toxin effect to patients?

(a) The DYSPORT™ Patient Medication Guide

(b) The DYSPORT™ full prescribing information

(c) The DYSPORT™ product website

(d) All of the above

(8) Physicians should use caution when using DYSPORT™ with which of the following concomitant treatments?

(a) Aminoglycosides

(b) Anticholinergic agents

(c) Curare-like agents

(d) All of the above

(e) None of the above.

**If you treat patients for cervical dystonia, answer questions 9-12.**

(9) What is the recommended starting dose of DYSPORT™ given intramuscularly as a divided dose amongst the affected muscles for the treatment of cervical dystonia?

(a) 150 Units

(b) 250 Units

(c) 500 Units

(d) 750 Units

(10) What is the incremental or decremental change in dose that can be used to titrate DYSPORT™ to optimize clinical effect for the treatment of cervical dystonia?

(a) 150 Units

(b) 250 Units

(c) 500 Units

(d) 750 Units

(11) What is the maximum recommended dose of DYSPORT™ for the treatment of cervical dystonia?

(a) 500 Units

(b) 750 Units

(c) 1000 Units

(d) 2000 Units

(12) To properly reconstitute a 500 U vial of DYSPORT™ for the treatment of cervical dystonia, dilute with ___ ml of 0.9% sodium chloride for injection USP. (Insert correct amount)

**If you treat patients for glabellar lines, answer questions 13-14.**

(13) What is the recommended dose of DYSPORT™ for the treatment of glabellar lines?

(a) 25 Units

(b) 50 Units

(c) 150 Units

(d) 300 Units

(14) To properly reconstitute a 300 U vial of DYSPORT™ for the treatment of glabellar lines, dilute with ___ or ___ ml of 0.9% sodium chloride for injection USP. (Insert correct amount)

APPEARS THIS WAY ON ORIGINAL

## PATIENT SURVEY

**Date of the Survey:** |_|_|.|_|_|.|_|_|_|_|
M M D D Y Y Y Y

**Patient details:**
**Initials:** |_| |_| |_|
First Middle Last

Before conducting the survey, inform the patient of the following:

*"DYSPORT™ (abobotulinumtoxinA) is a botulinum toxin product that acts as an acetylcholine release inhibitor and neuromuscular blocking agent."*

| **Inclusion Criteria (Patient Response must be "YES" to participate in survey)** | | |
|---|---|---|
| **Criterion** | **YES** | **NO** |
| Have you been treated with Dysport for Cervical Dystonia? | | |
| In the past 12 months, have you received DYSPORT™ as treatment for your Cervical Dystonia? | | |
| Have you been treated with Dysport for Glabellar Lines? | | |
| In the past 12 months, have you received DYSPORT™ as treatment for your Glabellar Lines? | | |

**Patient Survey Questions:**

(1) Did your healthcare provider give you the FDA approved DYSPORT™ Patient Medication Guide?

(a) Yes
(b) No
(c) I don't know

(2) After receiving DYSPORT™, you should get medical help right away if you have which of the following (Please select one of the following):

(a) Trouble breathing or swallowing
(b) Trouble speaking
(c) Blurred Vision
(d) All of the above plus any other condition that concerns you
(e) None of the above
(f) You are unsure

(3) DYSPORT™ is used to treat the symptoms of cervical dystonia (CD) in adults.

(a) TRUE
(b) FALSE
(c) I am unsure

(4) DYSPORT™ is used to treat the symptoms of glabellar lines in adults.

(a) TRUE
(b) FALSE
(c) I am unsure

(5) You should inform your treating physician before treatment if you have ever experienced which of the following (Please select all that apply):

(a) Difficulty breathing or swallowing
(b) Vision problems or droopy eyelids
(c) Any surgery of the face
(d) Any condition which affects the ability of muscles to function (e.g., myasthenia gravis)
(e) Any condition which causes you to have a concern about treatment with botulinum toxin

(6)You should inform your treating physician before treatment if you (Please select all that apply):

(a) Are taking other prescription drugs
(b) Are taking other over the counter drugs
(c) Are taking any herbal or other treatments
(d) Have had an allergic reaction with any botulinum toxin product
(e) Are being treated with any other botulinum toxin product

(7) You should contact your physician if you feel differently or experience symptoms which could indicate a reaction to treatment with botulinum toxin if you experience these (Please select all that apply):

(a) Within hours of the injection

(b) Within days of the injection

(c) Within weeks if the injection

(d) Only if you are certain that the symptoms are related to the treatment

(e) You are not sure

(8) After reviewing the FDA approved DYSPORT™ Medication Guide and discussing the potential risks and benefits of treatment with DYSPORT™ with your healthcare provider, do you feel that your questions were adequately answered?

(a) Yes

(b) No

If no, please provide further details of what questions were unanswered after discussing with your Health Care Provider.

_____

_____

_____

_____

**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: April 15, 2009

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

Susan Walker, M.D., Director
Division of Dermatology and Dental Products (DDDP)

Through: Claudia Karwoski, Pharm.D., Director (Acting)
Division of Risk Management (DRISK)

From: **OSE Dysport REMS Review Team**

**Scientific Lead:** Marcia Britt, Ph.D., Health Education Reviewer (DRISK)

**Team Members:**
Suzanne Berkman, Pharm.D., Team Leader and Senior Drug Risk Management Analyst (DRISK)
Daniel Brounstein, MPH, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Mary Dempsey, Risk Management Program Coordinator (DRISK)
Walter Fava, Pharm.D., Safety Evaluator, Division of Medication Error and Prevention Analysis (DMEPA)
Brian Gordon, MA, Social Science Reviewer (DRISK)
Kendra Worthy, Pharm.D., Senior Drug Risk Management Analyst (DRISK)

Subject: Addendum: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Names: Dysport® (abobotulinumtoxin A)

Application Type/Number: BLA 125274

Applicant/sponsor: Ipsen Biopharm Limited

OSE RCM #: 2008-1425

DRISK completed a review of Ipsen's Risk Evaluation and Mitigation Strategy (REMS) for BLA 125274 Dysport (abobotulinumtoxin A) with the proposed indication of reducing cervical dystonia severity on March 31, 2009 for the Division of Neurology Products (DNP). This addendum follows the April 9, 2009 communication to DRISK regarding the supplemental application for Dysport (BLA 125274/1) currently under review in the Division of Dermatology and Dental Products (DDDP) for glabellar lines. DDDP will be taking a joint action with DNP on April 29, 2009, to approve both the cervical dystonia and glabellar lines indications with a REMS for the product.

DDDP's comments on the Dysport REMS included adding the glabellar line indication to the DHCP letter, updating the number of dermatologists who will be included in random sampling for physician surveys, and indication-specific comments on the physician and patient surveys.

DRISK finds these comments and associated edits to the Dysport REMS acceptable. We note that these changes are limited to the Supporting Document and DHCP Letter. No edits to the REMS document are required.

APPEARS THIS WAY
ON ORIGINAL

**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: March 31, 2009

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: Claudia Karwoski, PharmD, Director (Acting)
Division of Risk Management (DRISK)

From: **OSE Dysport REMS Review Team**

**Scientific Lead:** Marcia Britt, Ph.D., Health Education Reviewer (DRISK)

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Suzanne Berkman, Pharm.D., Team Leader and Senior Drug Risk Management Analyst (DRISK)
Daniel Brounstein, MPH, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Mary Dempsey, Risk Management Program Coordinator (DRISK)
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Brian Gordon, MA, Social Science Reviewer (DRISK)
Amy Toscano, Pharm.D., Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications (DDMAC)
Kendra Worthy, Pharm.D., Senior Drug Risk Management Analyst (DRISK)

Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Names: Dysport® (abobotulinumtoxin A)

Application Type/Number: BLA 125274

Applicant/sponsor: Ipsen Biopharm Limited

OSE RCM #: 2008-1425

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# 1 INTRODUCTION

This review follows a request from the Division of Neurology Products (DNP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Dysport (abobotulinumtoxin A) submitted on March 2, 2009.

# 2 BACKGROUND

Dysport (abobotulinumtoxin A) is a botulinum toxin product with the proposed indication to treat patients with cervical dystonia (spasmodic torticollis) to reduce the severity of abnormal head position, disability, and neck pain in both toxin naïve and previously treated patients. BLA 125274 was originally submitted by Ipsen Biopharm Limited on November 29, 2007 with an Orphan Drug designation.

There are currently two approved botulinum toxin preparations: Botox (botulinum toxin type A, Allergan), and Myobloc (botulinum toxin type B, Solstice). Botulinum toxin preparations are not equivalent; their units are not interchangeable. The potential for medication errors exists if the various preparations of botulinum toxin are considered to be interchangeable by treating physicians. Such medication errors may lead to under-dosing of a patient if Dysport or Myobloc is administered in place of Botox using the recommended Botox dose. Patients may be overdosed when Botox is administered instead of either Myobloc or Dysport at either the Myobloc or Dysport recommended doses. In addition, while botulinum toxin is a treatment localized at the injected muscles and is not intended to enter systemic circulation in measurable quantities, symptoms consistent with systemic spread of toxin have been reported in patients treated with marketed botulinum toxin products.

Therefore, FDA requested Ipsen to submit a risk management plan containing a Communication Plan for Dysport during a teleconference held on August 20, 2008 to address the potential risk of medication errors leading to systemic spread of toxin. Ipsen submitted the proposed REMS on September 10, 2008 (Sequence 0015). The proposed Communication Plan contained information related to the website —— . Ipsen submitted the actual materials on September 24, 2008. b(4)

On November 6, 2008, FDA issued a formal REMS notification letter for a proposed REMS to address the risk of potential systemic spread of botulinum toxin after local injection and the risk of medication errors related to the lack of interchangeability of Dysport with other licensed botulinum toxin products. The letter states that the REMS must consist of a Medication Guide, Communication Plan, and timetable for submission of assessments of the REMS. Specifically, the Communication Plan needed to include a Dear Healthcare Provider Letter ——————— . On December 3, 2008, Ipsen submitted a proposed REMS that included a Medication Guide, communication plan with Dear Healthcare Provider Letter ——

b(4)

[redacted], along with Healthcare Provider and Patient Surveys to assess the patients'/healthcare providers' understanding of these risks. On December 23, 2008, FDA issued a Complete Response letter recommending that t [redacted] be omitted from the REMS, [redacted] in the package insert labeling. FDA also recommended changes to the Dear Healthcare Professional Letter and to the Healthcare Provider and Patient Surveys. Ipsen submitted a revised REMS proposal on March 2, 2009 which is the subject of this review. b(4)

Upon approval of the Dysport REMS, the other botulinum toxin products will also be requested to implement a similar REMS.

## 3 MATERIAL REVIEWED

- Ipsen's cover letter to DNP containing the Communication Plan Outline submitted September 10, 2008.
- Mills S. Review of Patient Labeling (Medication Guide), BLA 125274, preliminary comments dated September 15, 2008.
- Ipsen's cover letter to DNP containing the Communication Plan Tools submitted September 24, 2008.
- Ipsen's proposed REMS for Dysport (BLA 125274) dated December 3, 2008.
- FDA comments to Ipsen dated December 10, 2008.
- FDA CR letter to Ipsen dated December 23, 2008.
- Revised Proposed REMS for Dysport (BLA 125274) submitted March 2, 2009

## 4 PROPOSED REMS

### 4.1 GOALS

The FDA and Ipsen agreed upon REMS goal is:

To communicate the potential risks of:

- medication errors related to the lack of interchangeability of Dysport units with those of licensed botulinum toxins of other manufacturers; and
- the occurrence of spread of toxin effect beyond the injection site.

### 4.2 REMS ELEMENTS

The REMS includes a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. Each element of the REMS is described below. Our comments on the REMS document are presented in Appendix A.

#### 4.2.1 Medication Guide

A review of the proposed Medication Guide (MG) was conducted and comments were provided to Ipsen on September 15, 2008. Ipsen has accepted all comments and has submitted a revised MG with the December 19, 2008 REMS proposal. Final review of the MG will be provided under a separate cover.

Dysport is administered by a healthcare professional; therefore the MG will be provided by the healthcare professional that administered the product. Further copies of the MG may be provided by Ipsen representatives to healthcare professionals if necessary.

A MG will be dispensed with each Dysport prescription in accordance with 21 CFR 208.24. The Medication Guide will be inserted inside the carton with the vial(s) of Dysport.

### 4.2.2 Communication Plan

Ipsen will implement a communication plan consisting of a DHCP Letter disseminated within 60 days of REMS approval. It will be distributed to physicians who prescribe or inject botulinum toxin and may therefore use Dysport in their patient's care. This will include neurologists, physical medical and rehabilitation specialists, dermatologists, ophthalmologists and other specialists who have previously dispensed or administered botulinum toxins. The DHCP Letter will be distributed by mail and will also be presented to physicians, at launch, when called upon by Ipsen sales representatives to healthcare professionals (HCPs, neurologists, neurologists and other specialists) to convey the risks outlined in the REMS:

The letter references FDA links to provide more information and lists contact information for reporting cases of serious adverse events associated with the use of Dysport.

### 4.2.3 Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use.

### 4.2.4 Implementation System

An implementation system is not a required component of the proposed REMS if there are no elements to assure safe use.

### 4.2.5 Timetable For Submission Of Assessments

The sponsor proposes the following timetable for submission of assessments of the Dysport REMS:

1st FDAAA Assessment: 18 months from product launch
2nd FDAAA Assessment: 3 years from product launch
3rd FDAAA Assessment: 7 years from product launch

We recommend that assessments be submitted within 60 days of the close of the interval.

### 4.3 REMS ASSESSMENT PLAN

As described in the REMS Supporting Document, the information needed for assessment of the REMS (REMS Assessment Plan) includes both a healthcare provider and patient surveys to assess the patients' and healthcare providers' understanding of the risks. The target dates for the submitting survey reports are described in the above assessment timetables. Each survey type is discussed below.

A. Patient Survey:

Ipsen will conduct an anonymous patient survey (sample size = 200) to assess patients' understanding of the safe use and potential benefits and risks associated with Dysport. The study design, methodology, and sample survey questions have been reviewed and comments have been provided to Ipsen.

The Sponsor has accepted all recommendations and the current patient survey will be acceptable if they accept one additional recommendation (outlined below).

B. Healthcare Provider Survey:

The sponsor will conduct a healthcare provider survey (sample size = 350) to evaluate physicians' understanding of the safe use and potential benefits and risks associated with Dysport. The sample will include neurologists, physical medical and rehabilitation specialists who received the Dear Healthcare Professional Letter and have purchased Dysport. The study design, methodology, and sample survey questions were submitted with the modified REMS proposal, and comments have been provided to the Sponsor.

Ipsen has accepted all recommendations and the current physician survey is acceptable. We recommend Ipsen submit and note any changes within survey protocols and sample questions to FDA 60 days prior to conducting the survey.
The REMS Assessment submission should include but is not be limited to the following information:

A. Results of a survey of patients' understanding of the serious risks of Dysport (described above)
B. Results of a survey of prescribers' understanding of the serious risks of Dysport (described above)
C. An assessment of use data including – extent of use (denominator estimates), number of patients by age
D. A summary of reports of all potential or diagnosed cases of systemic spread of botulinum toxin after local injection with Dysport
E. A summary of reports of all medication errors involving interchangeability of Dysport units with those of other licensed botulinum toxin products.

F. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
G. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
H. The extent to which the elements of the REMS are meeting the goals of your REMS and whether modifications to the elements or goals are needed.

Information needed for assessment or the REMS Assessment Plan is not a required element of the REMS proposal. However, this information (described above) should be addressed in the REMS approval letter and discussed in the REMS Supporting Document.

## 5 CONCLUSIONS AND RECOMMENDATIONS

The Division of Risk Management in the Office of Surveillance and Epidemiology finds the proposed REMS for Dysport (abobotulinumtoxin A) acceptable with the following revisions below and acceptance of the track changes to the DHCP Letter (Appendix B).

The Division of Medication Error Prevention Analysis (DMEPA) will provide recommendations on the carton and container labeling to further minimize any potential of medication error in a separate review.

We have the following recommendations and comments:

### 5.1 COMMENTS TO DNP

1. We recommend incorporating the information needed for assessment of the REMS Supporting Document and into the approval letter.

   The REMS Assessment should include but is not be limited to the following information:

   A. Results of a survey of patients' understanding of the serious risks of Dysport
   B. Results of a survey of prescribers' understanding of the serious risks of Dysport
   C. An assessment of use data including – extent of use (denominator estimates), number of patients by age
   D. A summary of reports of all potential or diagnosed cases of systemic spread of botulinum toxin after local injection with Dysport
   E. A summary of reports of all medication errors involving interchangeability of Dysport units with those of other licensed botulinum toxin products.
   F. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

G. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
H. The extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed.

## 5.2 COMMENTS TO IPSEN

1. The DHCP Letter is acceptable if you incorporate and accept the proposed changes.
2. The proposed Patient Survey is acceptable if you accept the recommended change to add a possible answer choice of "I don't know" to question #1 of the patient survey.
3. We recommend you submit and note any changes in healthcare provider and patient survey protocols and sample questions to FDA 60 days prior to conducting surveys. This re-submission includes alteration of the healthcare provider survey as recommended above.

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ON ORIGINAL

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)