DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STNs: BL 125274/0
BL 125274/1

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

Dear Mr. Scott:

We are issuing Department of Health and Human Services U.S. License No.1787 to Ipsen Biopharm Limited, Wrexham, United Kingdom, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Dysport (abobotulinumtoxinA), indicated for the treatment of cervical dystonia and 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.

Under this license, you are approved to manufacture Dysport (abobotulinumtoxinA) at your facility in Ipsen Biopharm Ltd., Wrexham UK. You may label your product with the proprietary name Dysport and market it in 500 U and 300 U vials.

The dating period for Dysport (abobotulinumtoxinA) shall be twelve months from the date of manufacture when stored at 2 - 8 °C. (b) (4) We have not approved a stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

We have approved the lot release protocol in your license application. Please submit results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Drug Evaluation and Research (CDER).

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Dysport (abobotulinumtoxinA), or in the manufacturing facilities.

Please note that BLA STN 125286/0, submitted on March 12, 2008, for the use of abobotulinumtoxinA for temporary improvement in the appearance of moderate to severe glabellar lines has been converted into efficacy supplement STN 125274/1 under the parent BLA STN 125274. STN 125286/0 has been voided effective the date of this letter. All future submissions for this indication should be made to STN 125274.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes 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)).

In accordance with 505-1 of the FDCA, we have determined that a REMS is necessary for Dysport (abobotulinumtoxinA) to ensure that the benefits of the drug outweigh the risk of 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.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Dysport (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). In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Dysport (abobotulinumtoxinA).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on April 29, 2009 (via email), and appended to this letter, is approved. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include 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. The REMS assessment plan should include but is not limited to the following:

1. A survey of patients' understanding of the serious risks of Dysport (abobotulinumtoxinA).

2. A survey of prescribers' understanding of the serious risks of Dysport (abobotulinumtoxinA) and the lack of interchangeability of Dysport (abobotulinumtoxinA) units with those of other licensed botulinum toxin products.

3. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

4. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.

5. An assessment of use data including:
   a. extent of use (denominator estimates)
   b. number of patients by age

6. A summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection with Dysport (abobotulinumtoxinA).

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

In addition, as required by section 505-1(g)(3)(B) and (C) of the FDCA, your REMS assessments must include information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the amendment containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BL 125274 REMS ASSESSMENT

NEW SUPPLEMENT FOR BL 125274
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BL 125274
REMS ASSESSMENT

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Dysport (abobotulinumtoxinA) for the treatment cervical dystonia has an orphan designation. Therefore, you are exempt from the requirement under PREA to conduct pediatric studies in cervical dystonia.

We are waiving the pediatric study requirement for the temporary improvement in the appearance of moderate to severe glabellar lines because necessary studies are impossible or highly impracticable. This condition does not exist in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of adverse effects related to: embryo-fetal development or postnatal growth and development, and inadequate potency acceptance criteria. In addition, analysis of spontaneous postmarketing adverse events will not be sufficient to assess signals of serious risk of distant spread of toxin effects in patients with spasticity treated with Dysport (abobotulinumtoxinA), and effects on blood glucose and alkaline phosphatase as a marker of bone metabolism.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

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

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

2. An embryo-fetal development study is required in rabbits to identify the risk of adverse effects on embryo-fetal development. The submitted pivotal embryo-fetal development study (Study #AA28028) was inadequate because the high dose was lethal to pregnant dams. However, in a preliminary study (No. 434/363), the same high dose (20 U/day), administered using the same dosing regimen was tolerated. This apparent discrepancy in the tolerability of Dysport (abobotulinumtoxinA) will need to be explored prior to selection of doses for a repeat pivotal embryo-fetal development study.

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

3. A study to establish tighter potency acceptance criteria for the qualification of new reference standards so that the product is dosed properly. The acceptance criteria should ensure consistent potency assessment when different reference standards are used. This is critical because potency is reported relative to the potency of the reference standard.

   Final Report Submission: by May 2009

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of serious risk of distant spread of toxin effects in patients with spasticity treated with Dysport (abobotulinumtoxinA), and effects on blood glucose and alkaline phosphatase as a marker of bone metabolism.

4. Submit safety data assessing distant spread of toxin effects after multiple administrations of Dysport (abobotulinumtoxinA), during a minimum period of 12 months, collected in at

least 100 pediatric patients (ages 2-17 years) and 100 adult patients (approximately half upper, and half lower extremity spasticity). In addition, submit data assessing the effects of Dysport (abobotulinumtoxinA) on blood glucose and alkaline phosphatase as a marker of bone metabolism. These safety data could come from open-label extensions of the clinical studies specified under #5-8 below, from separate long-term open-label safety studies, or from a long-term controlled safety and efficacy study. The doses evaluated must be at least as high as those shown effective in studies specified under #5-8 below, or those commonly used to treat spasticity.

Adult

Final Protocol Submission:	by March 2010
Trial Completion Date:	by May 2014
Final Report Submission:	by January 2015

Pediatric

Final Protocol Submission:	by July 2010
Trial Completion Date:	by August 2014
Final Report Submission:	by May 2015

Submit the protocols to your IND, with a cross-reference letter to BLA 125274. Submit all final reports to your BLA 125274. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

We acknowledge your written commitments as described in your letter(s) and email communications of April 15, 2009, and April 29, 2009 as outlined below:

Regarding clinical efficacy in spasticity, you commit to conduct:

5. A randomized, double-blind, adequately controlled, multiple fixed doses, parallel group clinical study of Dysport (abobotulinumtoxinA) in botulinum toxin-naïve children age 2-17 years with lower extremity spasticity. The minimum duration of the study is 12 weeks. The study should be submitted to the FDA for special protocol assessment.

   Final Protocol Submission: November 2009
   Study Completion Date: by January 2013
   Final Report Submission: by September 2013

6. A randomized, double-blind, adequately controlled, multiple fixed doses, parallel group clinical study of Dysport (abobotulinumtoxinA) in botulinum toxin-naïve children age 2-17 years with upper extremity spasticity. The minimum duration of the study is 12 weeks. The study should be submitted to the FDA for special protocol assessment.

   Final Protocol Submission: by July 2010
   Study Completion Date: by August 2013
   Final Report Submission: by May 2014

7. A randomized, double-blind, adequately controlled, multiple fixed doses, parallel group clinical study of Dysport (abobotulinumtoxinA) in botulinum toxin-naïve adults with lower extremity spasticity. The minimum duration of the study is 12 weeks. The study should be submitted to the FDA for special protocol assessment.

   Final Protocol Submission: by November 2009
   Study Completion Date: by January 2013
   Final Report Submission: by September 2013

8. A randomized, double-blind, adequately controlled, multiple fixed doses, parallel group clinical study of Dysport (abobotulinumtoxinA) in botulinum toxin-naïve adults with upper extremity spasticity. The minimum duration of the study is 12 weeks. The study should be submitted to the FDA for special protocol assessment.

   Final Protocol Submission: by March 2010
   Study Completion Date: by May 2013
   Final Report Submission: January 2014

Regarding specifications, you commit to:

9. Establish a drug substance release specification for (b) (4). The proposed specification will be submitted by May 15, 2009.

10. Establish a drug substance release specification for aggregates using a validated sensitive method for quantification. As stated in the September 9, 2008 (Sequence 0013) amendment responding to the Division's April 8, 2008 Information Request, the Applicant will employ the SE-FPLC method. The proposed SE-FPLC analytical method, validation data and specification will be submitted by May 15, 2009.

11. Provide data demonstrating the specificity of the capture antibody used in the ELISA based identity release test by July 31, 2009.

Regarding additional characterization tests, you commit to:

12. Develop and validate a Western blot assay for release of the drug substance as an identity test and submit this information by September 30, 2009.

Regarding potency testing, you commit to:

13. Investigate the development and implementation of a non-animal based potency assay(s) for drug substance and drug product release testing by March 31, 2010.

Regarding drug product identity testing, you commit to:

14. Develop and implement a non-animal based identity test for drug product release. The animal based identity test for the first lot of drug product manufactured from every new lot of drug substance should be maintained. A summary report together with any proposed modifications to the process and/or stability protocol will be submitted by May 15, 2009.

Regarding reference standards, you commit to:

15. Provide a protocol that describes extension of reference standard dating period. The protocol will be submitted by May 15, 2009.

Regarding the drug product lot release protocol, you commit to:

16. Add SE-HPLC results for bulk drug substance to the lot release protocol when the SE-HPLC assay(s) is validated. A supplement for approval of this drug substance release specification will be submitted by May 15, 2009.

Regarding a 125 Unit dosage form, you commit to:

17. Develop a 125U single use dosage form appropriate for the dermatologic indication. A supplement for approval of this dosage form will be submitted by March 31, 2010.

We request that you submit clinical protocols to your IND, with a cross-reference letter to BLA 125274. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA 125274. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **Postmarketing Commitment Protocol**
- **Postmarketing Commitment - Final Study Report**
- **Postmarketing Commitment Correspondence**
- **Annual Status Report of Postmarketing Study Commitments**

For each postmarketing commitment subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing commitments for this product. The status report for each commitment should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm for further information).

ADVISORY COMMITTEE

Your application was not referred to an advisory committee because Dysport (abobotulinumtoxinA) is not the first product in its class, the clinical study designs were acceptable, no significant safety or efficacy issues were raised, no significant public health questions were raised regarding the role of the product in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

CONTENT OF LABELING

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125274."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft labels as soon as they are available but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved STN BL 125274**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

When you issue your letter communicating important safety related information about this product (i.e., the "Dear Health Care Professional" letter) as a part of your REMS and if you issue future communications, we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the following address:

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

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance, Risk Management, and Surveillance (HFD-330)
5600 Fishers Lane, Rockville, MD 20857

Biological product deviations sent by courier or overnight mail should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Division of Compliance Risk Management and Surveillance (HFD-330)
Montrose Metro 2
11919 Rockville Pike
Rockville, MD 20852

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

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

Sincerely,

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

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Package Insert
REMS (including Medication Guide and Communication Plan)