

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125274Orig1s000**

**CHEMISTRY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research

**Date:** December 17, 2008  
**To:** Administrative File, STN 125274/0  
**From:** Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT  
**Subject:** Team Leader Secondary Discipline Review  
**US License:** 1787  
**Applicant:** IPSEN Biopharm Limited  
**Facility:** IPSEN Biopharm Limited, Wrexham, UK (FEI 1000346340)  
**Product:** DYSPORT for Injection (*Clostridium botulinum* toxin Type A haemagglutinin complex)  
**Dosage:** Sterile lyophilized powder (liquid) for intramuscular injection  
**Indication:** Treatment of cervical dystonia  
**Due date:** December 29, 2009

PH 12/17/08

**Recommendation for Approvability:**

The BLA 125274 was reviewed by the Biotech Manufacturing Team reviewers Brenda Uratani, Ph.D. and Donald Obenhuber, Ph.D. The BLA, as amended, is recommended for approval from a microbial control, sterility assurance and product quality perspective.

Several CMC deficiencies were noted in the review of this BLA relating to microbial control in drug substance manufacturing and drug product sterility assurance. The sponsor was contacted and the BLA was appropriately amended (Amendment 27 and 28).

The Ipsen Biopharm Limited manufacturing facility was inspected June 2-10, 2008 and no 483 observations were issued. The facility was found to conform to applicable CGMP standards for manufacturing the drug substance and drug product.

**Conclusion**

- I. The drug substance and drug product sections of the BLA are adequate from a microbiology product quality perspective.
- II. The drug substance and drug product sections not relating to microbiology quality issues were assessed OBP/DTP reviewers.

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III. A list of CGMP items to be followed up at the next surveillance inspection were included in the drug substance review memo from Brenda Uratani. These items will be communicated to the International Operations Group in Office of Regulatory Affairs by The Division of Manufacturing and Product Quality.

Cc: WO Bldg 51, Uratani  
WO Bldg 51, Hughes  
WO Bldg 51, BMT Files (BLA 125274)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research

**Date:** December 11, 2008  
**To:** Administrative File, STN 125274/0  
**From:** Brenda Uratani, Ph.D., CDER/OC/DMPQ/BMT *for BU PFH 12/17/08*  
**Endorsement:** Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT *PFH 12/17/08*  
**Subject:** Review of Biological License Application (BLA): new BLA  
**US License:** 1787  
**Applicant:** IPSEN Biopharm Limited  
**Facility:** IPSEN Biopharm Limited, Wrexham, UK (FEI 1000346340)  
**Product:** DYSPORT for Injection (*Clostridium botulinum* toxin Type A haemagglutinin complex)  
**Dosage:** Sterile lyophilized powder (liquid) for intramuscular injection (300 U/vial and 500 U/vial)  
**Indication:** Treatment of cervical dystonia  
**Due date:** December 29, 2009

**Recommendation:** The drug substance section of the application, 2.3.S, was reviewed from a microbiological product quality perspective. The application, as amended, is recommended for approval.

### Review Summary

IPSEN submitted this BLA in support of the manufacturing of *Clostridium botulinum* toxin Type A haemagglutinin complex bulk active substance (CNT52120 BAS), a 150 kDa polypeptide neurotoxin and a 120 kDa non-toxin haemagglutinin protein, and various smaller haemagglutinin proteins. The 150 kDa neurotoxin is initially produced as a single-chain protein which undergoes post-translational cleavage by endogenous proteases during fermentation into a fully active neurotoxin.

This drug is indicated for the treatment of cervical dystonia. Both the drug substance and drug product are manufactured at IPSEN Biopharm Ltd in Wrexham, UK.

The drug substance CMC sections of the BLA were evaluated in this review for adequacy from a microbiology product quality perspective. The sections evaluated include in part

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3.2.S.2, 3.2.S.4, 3.2.S.6, 3.2.S.7, and 3.2.A.1. The BLA was amended (number 28 on December 9, 2008) to address deficiencies identified during the review of the BLA.

A pre-approval inspection of IPSEN Biopharm manufacturing facility was conducted by BMT (Michelle Clark Stuart), and OBP/DTP on June 02-10, 2008- NAI no 483 observations.

**Drug Substance**

Manufacturer-3.2.S.2

**Table 3.2.S.2.1-1 Sites and Activities for the Manufacture and Testing of the CNT52120 Bulk Active Substance**

Name and Address of Site	Activities Occurring at Site
IPSEN Biopharm Ltd. Wrexham Industrial Estate Ash Road Wrexham LL13 9UF UK Tel.: +44 (0)1978 661181	<ul style="list-style-type: none"><li>• Manufacture of CNT52120 BAS</li><li>• Raw material testing and release</li><li>• In-process testing during the manufacture of CNT52120 BAS</li><li>• Environmental monitoring</li><li>• CNT52120 BAS release testing</li><li>• CNT52120 BAS stability testing</li></ul>
(b) (4)	
(b) (4)	

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### **Environmental Assessment**

Ipsen requests a categorical exclusion from providing an environmental assessment for the commercial manufacture, distribution and use of DYSPORE for Injection.” The BLA states the following:

“Dysport® for Injection (*Clostridium botulinum* type A hemagglutinin complex) is a biologic product manufactured from clostridium botulinum toxin type A, which occurs naturally in the environment. ...For the treatment of this rare disease, Dysport is administered by a small, local, injection in the affected muscle(s) once every 12-16 weeks or longer. Moreover, to the Applicant’s knowledge, no extraordinary circumstances exist that would warrant an environmental assessment [21 CFR Part 25.31(d)]. Therefore, given the rarity of the disease, its localized administration, and the infrequent use of the product, the Agency’s approval of Dysport is not expected to significantly alter the concentration or distribution of clostridium botulinum toxin type A, its metabolites, or degradation products in the environment. Consequently, a categorical exclusion for an Environmental Analysis, as stated in 21 CFR Part 25.31 (c), is requested.”

### **cGMP Status**

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

### **Conclusion**

- I. The drug substance section of the application is adequate from a microbiology product quality perspective.
- II. The drug substance control of Source and Starting Materials of Biological Origin, Generation of Cell Substrate, Cell banking System, Characterization, Batch Analyses, Justification of Specifications, Reference Standards, and Stability sections are reviewed by OBP/DMA.
- III. Additional inspectional follow-up items include:
  - Evaluate methodology, sensitivity of the bioburden test, and trending data.
  - Evaluate endotoxin controls.
  - Evaluate the adequacy of room classification, pressure differentials, and EM trending.
  - Evaluate the type of BI used in sterilization validation of equipment since the D value of *C. botulinum* can be as high as 3 minutes. Has the firm made proper evaluation of the BI suitable for sterilization validation?

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- Evaluated bacterial endotoxin test used for bulk drug substance release.

Cc: WO Bldg 51, Uratani  
WO Bldg 51, Hughes  
WO Bldg 51, Friedman  
WO Bldg 51, BMT Files (BLA 125274)

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## Review Cover Sheet

BLA STN 125274/0

**Dysport**  
**(Botulinum Toxin Type A)**

**Ipsen Biopharm Limited, UK**

**Reviewer's Signatures:**

Ennan Guan, Product Quality Chair *Ennan Guan 10/24/08*

Sheila Rawls, Labeling *Sheila Rawls 10/24/08*

Susan Kirshner, Product Quality Team Leader *Susan L. Kirshner 10/24/08*

Amy Rosenberg, Director, Division of Therapeutic Proteins *Amy Rosenberg 10-24-08*

<b>Indication:</b>	Cervical Dystonia
<b>Labeled Strength:</b>	500 Units/vial
<b>Stabilizer (HSA):</b>	Human Albumin, Lactose Monohydrate

**Review Cover Sheet**

**BLA STN 125274/0**

**Dysport  
(Botulinum Toxin Type A)**

**Ipsen Biopharm Limited, UK**

**Reviewer's Signatures:**

**Ennan Guan, Product Quality Chair**

**Sheila Rawls, Labeling**

**Susan Kirshner, Product Quality Team Leader**

**Amy Rosenberg, Director, Division of Therapeutic Proteins**

<b>Indication:</b>	Cervical Dystonia
<b>Labeled Strength:</b>	500 Units/vial
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## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125274 for Dysport manufactured by IPSEN, Biopharm limited. The data submitted in this application support the conclusion that the manufacture of purified *C. botulinum* neurotoxin type A complex (BoNT/A complex), naturally secreted by *C. botulinum*, is well controlled, and leads to a product that is potent and safe, when used according to the label. The product is free from endogenous or adventitious infectious agents. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs.

The product was first registered for the treatment of blepharospasm and hemifacial spasm in the UK in 1990. Since then, the product has been registered in over 70 countries for various indications (blepharospasm, adult post-stroke arm spasticity, hemifacial spasm, cervical dystonia, pediatric cerebral palsy spasticity, hyperhidrosis and glabellar lines). Of more than 80 IPSEN sponsored clinical trials, 17 were conducted for the treatment of cervical dystonia. The FDA safety group is currently assessing clinical experience from the clinical data generated from rest of the world.

This product will be on lot release per 21CFR 610. It is recommended that this product be approved for human use under the conditions specified in the package insert.

### Recommendation on Phase 4 (Post-Marketing) Commitments and Agreements, if Approvable

We propose the following post-marketing commitments:

#### 1. Regarding specifications

- a. To establish a drug substance release specification for Clp protease. The proposed specification will be submitted to the Agency by [INSERT DATE].
- b. To establish a drug substance release specification for aggregates using a validated sensitive method for quantification. The proposed specification will be submitted to the Agency by [INSERT DATE].
- c. To develop and validate a sensitive immunology based method to replace the FPLC and SDS-PAGE identity tests. The proposed specification will be submitted to the Agency by [INSERT DATE].
- d. Please provide information on control of destaining GelCode Blue gel to prevent over-destaining the minor bands on the gel.

## 2. Regarding stability

- a. To perform a comprehensive analysis of the degradation products and processes, including the contribution of the Clp protease system. A summary report together with any proposed modifications to the process and/or stability protocol that will improve drug product stability will be submitted to the Agency by [INSERT DATE].

## 3. Regarding additional characterization tests

- a. To develop a Western blot assay for further characterization of the drug substance. Results of this analysis together with how this assay will be implemented (i.e. specifications or characterization) should be provided to the Agency by [INSERT DATE].

## 4. Regarding potency test

- a. To investigate reducing the observation time period for animal death in the mouse LD50 assay from 96 hours to 72 hours assay. A summary report together with any proposed modifications to the method will be submitted to the Agency by [INSERT DATE].
- b. To investigate the possibility of a non-animal based potency assay(s) for drug substance and drug product release testing. A summary report together with any proposed modifications to the process and/or stability protocol will be submitted to the Agency by [INSERT DATE].

## 5. Regarding drug product identity test

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

## 6. Regarding reference standard

- a. To develop drug substance and drug product reference standards from material made at the IBL facility. Routine use of new reference standards will be implemented by [INSERT DATE].
- b. To establish tighter potency acceptance criteria around the potency specification center point for the qualification of new reference standards. Amended criteria will be submitted to the Agency by [INSERT DATE].
- c. To provide a protocol that describes extension of the dating period for reference standards. The protocol will be submitted to the Agency by [INSERT DATE].

7. Regarding the drug product lot release protocol:

- a. To add SE-HPLC results for bulk drug substance to the lot release protocol when the SE-HPLC assay(s) is validated.

## II. Chemistry Executive Summary

### A. Description of the Drug Product and Drug Substance

#### Structure

The active pharmaceutical ingredient of Dysport is purified type A neurotoxin complex, which is produced by the anaerobic fermentation of the bacterium *Clostridium botulinum*, Hall strain. The neurotoxin moiety is a 1296 amino acid dichain molecule consisting of a heavy chain (Hc, 100 kDa) and a light chain (Lc, 50 kDa) linked by a disulfide bond. The ~400 kDa complex is also comprised of heamagglutinin (HA) and non-toxin-non-heamagglutinin (NTNH) components. The HA components include several subunits that are transcribed and translated from three open reading frames encoding: HA34 (293 amino acids); HA17(146 amino acids); and HA70 (627 amino acids). HA70 is initially produced as a single protein and is subsequently processed into the smaller polypeptide chains HA70(50 kDa) and HA70(20 kDa). The NTNH component is expressed as a single protein of 1193 amino acids. The final product is a lyophilized material containing type A toxin complex, human albumin and lactose.

#### Biological activity

Dysport blocks neuromuscular transmission by binding to receptor sites on motor or sympathetic nerve terminals, entering the nerve terminal and inhibiting release of neurotransmitter (acetylcholine). The full action of the toxin requires both the Hc and the Lc. The Hc mediates neuron-specific binding, up-take by receptor-mediated endocytosis and transport of Lc across the endosomal membrane into the cytosol. In the cytosol the Lc, a zinc binding metalloproteinase, hydrolyzes a member of the SNARE protein complex, which is required for vesicle exocytosis. The Zn<sup>2+</sup> binding sequence within each Lc, H-E-X-X-H, is a distinct minimal amino acid motif conserved within this toxin family.

The substrate for type A toxin is a 25-kD synaptosomal associated protein (SNAP-25). SNAP-25 is cleaved at the C-terminus (Q<sub>197</sub>-R) by BoNT/A, generating truncated SNAP-25 that can't participate in formation of the SNARE core complex. The HA and NTNH components have not been found to be involved in the therapeutic mechanism of action of the BoNT/A complex following parenteral administration. They are believed to protect the toxin from degradation after ingestion (the natural route of exposure). When injected i.m. at therapeutic doses, Dysport produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. It is indicated for decreasing voluntary muscle power and improving abnormal head position, disability and neck pain in adult patients with severe cervical dystonia.

#### Potency Assays to Measure Activity

The mouse lethal dose assay is used to assess product activity. The assay is conducted by administering pre-set dilutions of Dysport into groups of mice. The number of deaths that occur at each dilution are measured over a fixed period of time. The concentration that leads to death in half of the test animals is the lethal dose (LD<sub>50</sub>). The potency of botulinum toxin therapeutic preparations is expressed in LD<sub>50</sub> units, with one unit of

activity defined as the amount of drug required to kill 50% of the animals. The assay is a good indicator of both light and heavy chain function since both are required for activity *in vivo*. A major drawback of this assay is that hundreds of mice are sacrificed for each potency activity measurement. Because it is an animal based assay there is huge inter-laboratory variability precluding standardization of LD50 units between products. Currently a reliable *in vitro* non-animal based assay to replace the mLD50 test is not available. Therefore the mLD50 assay is still used to assess potency for release of all botulinum toxin products currently on the market in the US and Europe.

#### Drug Product Presentation

Dysport is supplied as a sterile single use vial. Each vial contains 500 units of dried *C. botulinum* toxin type A, lactose monohydrate (2.5 mg) and human albumin (125 ug). The DP is packaged in 3 ml Type I clear neutral (b) (4) glass vials with (b) (4) rubber closure and sealed with 13 mm (b) (4) flip top overseals. As each vial is for single patient use, no anti-microbial preservatives are included in the formulation.

#### Excipients

The product is formulated with lactose monohydrate and human albumin. Lactose monohydrate is a natural disaccharide obtained from bovine milk, containing one glucose and one galactose moiety. Lactose is a common pharmaceutical excipient used in oral, parenteral and inhalational products. Lactose monohydrate is supplied by (b) (4), as a compendial product manufactured in accordance with the NF monograph. Human albumin is manufactured from human plasma. Plasma is received from selected donation centers in the US, authorized by FDA and members of American Blood Resource Association (ABRA) Plasma Quality Certification Program (QPP).

#### Drug Product Storage

Drug product is stored as a lyophile at 2°C – 8°C. Drug product must be used within 4 h of reconstitution and should also be stored at 2°C – 8°C and protected from light. Drug product is unstable, loosing approximately (b) (4) of its potency over the one year dating period. The instability notwithstanding, clinical studies support the safety and efficacy of the product in this time frame. Moreover, a PMC has been negotiated with the sponsor to identify the sources of the instability and to correct them To prevent drug product from becoming out of specification with respect to potency during its shelf life, and to prevent under and overdosing of patients due to fluctuations in product potency over shelf life, the Sponsor has established lot release specifications that ensure that patients will not receive a dose with greater than a (b) (4) range in potency from dose to dose. The clinical safety and efficacy data provided in this application support this range. The Sponsor has made a post-marketing commitment to investigate the cause(s) of drug instability and correct them if possible.

#### DS Manufacture:

Dysport drug substance is produced as a secreted protein complex by small-scale (b) (4) anaerobic fermentation of *Clostridium botulinum* type A, Hall strain. It is purified from the culture solution by a series precipitation, dialysis and chromatography steps to a

complex consisting of the neurotoxin and several accessory proteins. These steps include

(b) (4)

(b) (4) The process is validated and well-controlled both through defined operating and performance parameters. The manufacturing site, Ipsen Biopharm, Limited, (Unit 9 Ash Road, Wrexham industrial Estate, Wrexham, United Kingdom LL139UF) was inspected between June 2 and 10, 2008. No 483 observations were issued.

#### DS Purity

Dysport is produced from bacterial fermentation. Since bacterial fermentation processes do not support the growth of mammal-trophic viruses the purification process is not required to include viral clearance steps or the examination of viral particles in the product. Drug substance contains two process related impurities of interest. One is the bacterial protein flagellin, with a specified limit of (b) (4). It is a pro-inflammatory molecule that could increase product immunogenicity. Immunogenicity to Dysport was very low (b) (4), which suggests that its presence is not a safety concern. The other is the bacterial protein Clp P. Clp P is a non-specific protease that must associate with one of two related bacterial proteases, ATPase subunits Clp A or Clp X, for expression of full proteolytic activity. Neither subunit has been detected in Dysport, but their presence in trace amounts cannot be discounted. Dysport appears to (b) (4) with a concomitant loss of potency over time during storage at 2°C – 8°C. The presence of this protease may be involved in the instability of drug product. As noted above, a post-marketing commitment has been made by the Sponsor to examine drug product instability and ways to promote product stability.

#### DS Release Tests

The tests for release of DS include appearance (b) (4) pH (b) (4) protein (b) (4), mouse neutralization test (b) (4), FPLC (b) (4), non-reduced (b) (4), reduced SDS-PAGE Coomassie stain and densitometric analysis (b) (4), bioburden (b) (4), and endotoxin (b) (4). FPLC and non-reduced SDS-PAGE are inadequate identity tests because they do not measure parameters that are unique to Dysport. The Sponsor has proposed to replace these tests with a new test (ELISA). Implementation of a new identity release test is a post-marketing commitment. There is no test to assess aggregates. Since the presence of aggregates can promote immunogenicity this is a safety concern. Clinical experience with Dysport indicates very low incidence of patients developing anti-Dysport antibodies. The Sponsor has agreed to develop and implement a release test to assess the aggregates in the DS as a post-marketing commitment.

### Development and Comparability

The DS manufacturing process was originally developed over 20 years ago. Over that time three different facilities owned by two separate companies manufactured bulk drug substance:

- IU Facility at CEPR
- VPU Facility at CEPR
- Unit 10 Primary Production Facility at IBL

During the clinical development for cervical dystonia and glabellar lines, drug substance used for formulation of clinical trial drug product was changed from the 96/02 material (manufactured at IU CEPR site) to the IBL material (manufactured at IBL site). The IU material was used in phase 1, 2 and early phase 3 trials. The IBL material was used in phase 3 trials. VPU material was not used in clinical trials to support licensure in the US. There are no significant changes in the manufacturing process from IU to IBL. The comparability of clinical material manufactured at IU and IBL was established by physico-chemical and biological studies.

### Degradation and Stability

Increased cleaved drug substance fragments and loss of potency are observed when drug substance is stored at temperatures of (b) (4) °C or higher. Exposure to light also causes degradation. Real-time stability data indicate that drug substance is stable when stored frozen (b) (4) and protected from light. A comprehensive characterization of product degradation was not reported and is a PMC.

The proposed drug substance shelf life of (b) (4) months when at (b) (4) °C and protected from light is supported by data submitted by the Sponsor.

### **B. Description of How the Drug Product is Intended to be Used**

- Dysport is a neuromuscular blocking toxin indicated for decreasing voluntary muscle power and improving abnormal head position, disability and neck pain in adult patients with severe cervical dystonia. Dysport should be administered by intramuscular injection into a maximum of four clinically indicated muscles. The total dose is 500 units in single session. Recommended dose of Dysport is 500 units intramuscularly every 3 months.
- Each vial of Dysport contains 500 units of lyophilized *C. botulinum* toxin type A complex, 125 ug human albumin and 2.5 mg lactose, free of preservatives.
- Dysport is prepared for intramuscular injection by reconstituting each vial with 1 ml of 0.9% sodium chloride for injection USP.
- Dysport vials should be refrigerated at 2 to 8 °C and protected from light. The recommended expiration dating period for Dysport is 12 months under these storage conditions.

### **C. Basis for Approvability or Not-Approval Recommendation**

- Dysport's manufacturing process is well-controlled and consistently delivers a quality product suitable for its intended use. Therefore based on a quality review it is approvable for the proposed indication.
- Post-marketing commitments described in the recommendations sections above will provide additional information to assure the continued safety and efficacy of the product.

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