CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125274

CHEMISTRY REVIEW(S)

Review Cover Sheet

BLA STN 125286/0

Reloxin
(Botulinum Toxin Type A)

Ipsen Biopharm Limited, UK

Reviewer's Signatures:

Ennan Guan, Product Quality Chair Ennan Guan 3/18/09

Susan Kirshner, Product Quality Team Leader Susan R. Kirshner 3/18/09

Amy Rosenberg, Director, Division of Therapeutic Proteins
Amy Rosenberg 3-18-09

Indication:	Glabellar Lines
Labeled Strength:	300 Units/vial
Stabilizer (HSA):	Human Albumin, Lactose Monohydrate

Table of Contents

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125286 for Reloxin 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, hemificial 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 the 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

CMC Post-Marketing Requirement

- To establish tighter potency acceptance criteria for the qualification of new reference standards. The acceptance criteria should ensure consistent potency assessment when different reference standards are used. This is critical as potency is reported relative to the potency of the reference standard. Amended criteria will be submitted to the Agency by [SPONSOR PROPOSE DATE].

Justification for the post-marketing requirement: The potency units for dosing are relative potency units established by normalizing the results of test lots of drug substance or product to the results obtained using the reference standard. This helps ensure consistent dosing from batch to batch. The potency specifications for drug product and drug substance are wide, but are supported by clinical and manufacturing data. Nevertheless, it is unacceptable to allow such wide limits to be applied to the qualification of new reference standards as this could allow the product to drift in potency over time. New reference standards are only infrequently created so this issue can be safely addressed post-approval.

CMC 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 [SPONSOR PROPOSE 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 [SPONSOR PROPOSE DATE].

   c. To develop and validate a sensitive immunologically based method to replace the FPLC and SDS-PAGE identity tests. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].

   d. To provide information on control of destaining the GelCode Blue gel to prevent over-destaining the minor bands on the gel. The information will be provided to the Agency by [SPONSOR PROPOSE DATE].

2. Regarding stability

   a. To perform a comprehensive analysis of the degradation products and pathways, including the contribution of the Clp protease system to degradation. 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 [SPONSOR PROPOSE 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 the implementation plan for this assay (i.e. specifications or characterization) should be provided to the Agency by [SPONSOR PROPOSE DATE].

4. Regarding potency test

   a. To investigate reducing the observation time period for animal death in the mouse LD50 assay from 96 to 72 hours. A summary report together with any proposed modifications to the method will be submitted to the Agency by [SPONSOR PROPOSE DATE].

   b. To investigate the development and implementation 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 [SPONSOR PROPOSE 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 [SPONSOR PROPOSE DATE].

6. Regarding reference standards:

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 [SPONSOR PROPOSE DATE].

b. To provide a protocol that describes extension of the dating period for reference standards. The protocol will be submitted to the Agency by [SPONSOR PROPOSE DATE].

7. Regarding the drug product lot release protocol:

    a. To add SE-HPLC results for bulk drug substance to the lot release protocol upon validation of the SE-HPLC assay(s). A supplement for approval of this drug substance release specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].

To develop a 125U single use dosage form. A supplement for approval of this dosage form will be submitted to the Agency by [SPONSOR PROPOSE DATE].

II. Chemistry Executive Summary

A. Description of the Drug Product and Drug Substance

Structure

The active pharmaceutical ingredient of Reloxin is purified type A neurotoxin complex, which is produced by the anaerobic fermemtation 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

Reloxin 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 metallopeptidase, hydrolyzes a member of the SNARE protein complex, which is required for vesicle exocytosis. The Zn^{2+} 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_{197}-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, Reloxin 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 Reloxin 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_{50}). The potency of botulinum toxin therapeutic preparations is expressed in LD_{50} 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

Reloxin is supplied as a sterile single use vial. Each vial contains 300 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 [redacted] clear neutral [redacted] glass vials with [redacted] rubber closure and sealed with 13 mm [redacted] flip top overseals. As each vial is for single patient use, no anti-microbial preservatives are included in the formulation. b(4)

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 ——— ——— as a compendial product manufactured in accordance with the NF monograph. b(4)
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. The drug product looses approximately ——— % of its potency over the one year dating period. The instability notwithstanding, clinical studies support the safety and efficacy of b(4)
the product in this time frame. Moreover, a PMC (refer to Dysport BLA) 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 40% range in potency from dose to dose, a range that has been verified as safe. 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:

Reloxin drug substance is produced as a secreted protein complex by 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)

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

Reloxin is produced from bacterial fermentation. Since bacterial fermentation processes do not support the growth of mammalian 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 — %. It is a pro-inflammatory molecule that could b(4)

increase product immunogenicity. Immunogenicity to Reloxin was very low (~3%), 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 Reloxin, but their presence in trace amounts cannot be discounted.

Reloxin appears to [redacted] 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. b(4)

DS Release Tests

The tests for release of DS include appearance ([redacted], pH ([redacted]), protein ([redacted], mouse neutralization test ([redacted] FPLC [redacted] non-reduced SDS-PAGE ([redacted] reduced SDS-PAGE Coomassie stain and densitometric analysis ([redacted], bioburden ([redacted] and endotoxin ([redacted]. FPLC and non-reduced SDS-PAGE are inadequate identity tests because they do not measure parameters that are unique to Reloxin. 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, but one is in development for drug substance. Since drug product is formulated with an excess of HSA and DS is present in nanogram quantities, it is not possible to test DP for aggregates. Since the presence of aggregates can promote immunogenicity this is a safety concern, albeit a limited one because the drug is administered at low dose. Clinical experience with Reloxin indicates very low incidence of patients developing anti-Reloxin antibodies. The Sponsor has agreed to develop and implement a release test to assess the aggregates in the DS as a post-marketing commitment. b(4)

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 (Center for Emergence Preparedness and Response, UK)
- VPU (Vaccine Production Unit, UK) 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 — C or higher. Exposure to light also causes degradation. Real-time stability data indicate that drug substance is stable when stored frozen (—) and protected from light. A comprehensive characterization of product degradation was not reported and is a PMC. b(4)

The proposed drug substance shelf life of — months when at — 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

- Reloxin is a neuromuscular blocking toxin indicated for reduction of facial wrinkle and improving facial appearance in adults with severe glabellar lines. Reloxin should be administered by intramuscular injection into a maximum of five clinically indicated muscles. The total dose is 50 units in a single session. Recommended dose of Reloxin is 50 units intramuscularly every 3 months.

- Each vial of Reloxin contains 300 units of lyophilized *C. botulinum* toxin type A complex, 125 ug human albumin and 2.5 mg lactose, free of preservatives.

- Reloxin is prepared for intramuscular injection by reconstituting each vial with 1 ml of 0.9% sodium chloride for injection USP.

- Reloxin vials should be refrigerated at 2 to 8 ^{0}C and protected from light. The recommended expiration dating period for Reloxin is 12 months under these storage conditions.

C. Basis for Approvability or Not-Approval Recommendation

- Reloxin'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 and requirement described in the recommendations sections above will provide additional information to assure the continued safety and efficacy of the product.

139 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
methods used and time intervals for product assessment.		
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y N	
☑ LAL instead of rabbit pyrogen	(Y) N	Bacterial product ; not necessary
☐ mycoplasma	Y (N)	
☑ sterility	(Y) N	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y (N)	FDA labs do not accept BNT/A products for testing
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	DMPQ to review
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	DMPQ to review
Information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	DMPQ to review

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Emmn [signature] 4/21/08

Product Quality Reviewer(s) Date

Susan L. Kirshner 4/21/08

Branch Chief/Team Leader/Supervisor Date

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
☑ method validation package	(Y) N	
☑ comparability protocols	(Y) N	
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y N	
☑ legible	(Y) N	
☑ English (or translated into English)	(Y) N	
☑ compatible file formats	(Y) N	
☑ navigable hyper-links	(Y) N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
☑ summary reports reference the location of individual data and records	(Y) N	
☑ all electronic submission components usable	(Y) N	
Includes appropriate process validation data for the manufacturing process at the commercial production facility	(Y) N	
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	(Y) N	
Includes data demonstrating consistency of manufacture	(Y) N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
Certification that all facilities are ready for inspection	(Y) N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test	(Y) N	

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
☑ container closure system ☑ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ☑ stability ☑ summary ☑ post-approval protocol and commitment ☑ pre-approval ☑ protocol ☑ results	✓ ✓	
Other components to be marketed (full description and supporting data, as listed above): ☐ other devices ☐ other marketed chemicals (e.g. part of kit)	 Y (N) Y (N)	
Appendices for Biotech Products [3.2.A] ☐ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination	 Y N	DMPQ to assess
☑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ☑ cell line qualification ☑ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ☑ testing at appropriate stages of production	(Y) N N/A NA	bacterial product
☑ novel excipients	Y (N)	No novel excipients used
USA Regional Information [3.2.R] ☐ executed batch records	(Y) N	

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
☑ description and composition of diluent	(Y) N	
☑ pharmaceutical development	(Y) N	
○ preservative effectiveness	Y (N)	NA
☑ container-closure integrity	(Y) N	
☑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
☑ batch formula		
☑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N (Y) N	
☑ controls of critical steps and intermediates		
☑ process validation including aseptic processing & sterility assurance:	(Y) N	DMPQ to assess
○ 3 consecutive lots		
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation	Y N	
○ Validation of aseptic processing (media simulations)	Y N	
○ Environmental Monitoring Program	Y N	
○ Lyophilizer sterilization validation		
○ Other needed validation data (hold times)	Y N	
☑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)		
☑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)		
☑ reference standards		

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
☑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N (Y) N	
☑ controls of critical steps and intermediates		
☑ process validation including aseptic processing & sterility assurance:	Y N	DMPQ to assess
o 3 consecutive lots		
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program		
o Lyophilizer sterilization validation	Y N	
o Other needed validation data (hold times)		
☑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)		
☑ control of drug product (justification of specifications; analytical method validation)		
☑ container closure system [3.2.P.7]		
☑ specifications (vial, elastomer, drawings)		
☑ availability of DMF & LOAs		
o administration device(s)	none	
☑ stability		
☑ summary		
☑ post-approval protocol and commitment		
☑ pre-approval		
☑ protocol		
☑ results		
☑ method validation		
Diluent (vials or filled syringes) [3.2P']		

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
cell banking system, characterization, and testing		
control of critical steps and intermediates	Y N	
justification of specifications		
analytical method validation		
reference standards		
stability		
process validation (prospective plan, results, analysis, and conclusions)	Y N	
manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
characterization of drug substance		
control of drug substance	Y N	
specifications	Y N	
justification of specs.		
analytical procedures		
analytical method validation		
batch analyses		
consistency (3 consecutive lots)		
justification of specs.		
reference standards		
container closure system	Y N	
stability	Y N	
summary	Y N	
post-approval protocol and commitment		
pre-approval		
protocol		
results		
method validation		
Drug Product [3.2.P]		
description and composition	Y N	
pharmaceutical development	Y N	
preservative effectiveness	Y N	N/A no preservative used
container-closure integrity	Y N	
	Y N	
manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
batch formula		

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action, & status
arrangement		

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

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	
Drug Substance [3.2.S]			
☑ general info	(Y)	N	
☑ nomenclature			
☑ structure (e.g. sequence, glycosylation sites)			
☑ properties			
☑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
☑ description of manufacturing process	(Y)	N	
☑ batch numbering and pooling scheme			
☑ cell culture and harvest			
☑ purification			
☑ filling, storage and shipping			
☑ control of materials	(Y)	N	
☑ raw materials and reagents			
☑ biological source and starting materials			
☑ cell substrate: source, history, and generation			

PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

BLA/NDA Number: 125286 **Applicant:** Ipsen **Stamp Date:** N/A Signed at bottom

Drug Name: Relaxin **BLA/NDA Type:** Original

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	(Y) N	
☑ including list of all establishment sites and their registration numbers	(Y) N	
Comprehensive Table of Contents	(Y) N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	
Labeling:	(Y) N	
☑ PI –non-annotated	(Y) N	
☑ PI –annotated	(Y) N	
☑ PI (electronic)	(Y) N	
☑ Medication Guide	Y (N)	
☑ Patient Insert	Y (N)	
☑ package and container	(Y) N	
☑ diluent	(Y) N	
☑ other components	(Y) N	
☑ established name (e.g. USAN)	Y (N)	
☑ proprietary name (for review)	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y) N	
☑ legible	(Y) N	
☑ English (or translated into English)	(Y) N	
☑ compatible file formats	(Y) N	
☑ navigable hyper-links	(Y) N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
☑ summary reports reference the location of individual data and records	(Y) N	
☑ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
Companion application received if a shared or divided manufacturing	Y N	N/A

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 PFH 12/17/08
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

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 Biobharm 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.

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)

Archived File: S:\archive\BLA\125274\125274.0.rev.mem.BLA.12-17-08.doc