CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **6/1/2010**
To: Administrative File, **STN 125360/0**
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT BC 6/7/10
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PHH 6/7/10
Subject: New Biologic License Application (BLA)
Applicant: Merz Pharmaceuticals GmbH
US License: **1830**
Facility: Merz Group Services GmbH, Dessau-Rosslau, Germany
FEI: 3006896175
Product: Xeomin (Botulinum neurotoxin type A, NT201)
Dosage: 50 and 100 LD_{50} units, Lyophilized powder for intramuscular injection
Indication: Cervical dystonia and benign essential blepharospasms
PDUFA Date: August 1, 2010

Recommendation: This application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following four post-market commitments:

1. Revalidate the microbial ingress test (container closure integrity test) to demonstrate the integrity of the drug product container closure. Determine the sensitivity (minimum detectable leak size) of the test. Information and summary data will be submitted in a CBE-0 by 2/1/2011.

2. Re-qualify the crimping machine with media filled vials and the revalidated microbial ingress test. Summary data will be submitted in a CBE-0 supplement by 2/1/2011.

3. Complete shipping validation studies for the drug product vials using the worst shipping temperature and duration. Validation information and summary data should be submitted in a Changes Being Effected in 30 days (CBE30) at the end of study by 10/31/2011.

4. Develop a container closure integrity test to replace the sterility test in the stability program. Information and summary validation data for the container closure integrity test will be submitted in a Prior Approval Supplement (PAS) by 12/31/2011.

Review Summary

Merz has submitted this BLA for Xeomin (Botulinum neurotoxin type A) to treat cervical dystonia and blepharospasms. Both the drug substance and drug product are manufactured at Merz Pharmaceuticals GmbH, Dessau-Rosslau, Germany. The application contains CMC information in an eCTD format. Amendments submitted on 10/27/2009, 1/22/2010, 2/25/2010, and 5/11/2010 were also reviewed here.

Assessment

Drug Product

Description of the Composition of the Drug Product (3.2.P.1):

The final product is supplied as a sterile lyophilized powder for injection packed (b) (4) in glass vials. The vials are sealed with rubber stoppers and aluminium caps. The product is reconstituted with commercially available 0.9% physiological saline which is not supplied in the pack. Each vial contains 100 (b) (4) or 50 (b) (4) mouse LD_{50} units of *Clostridium Botulinum* neurotoxin type A with no preservative. The final formulation contains sucrose and human albumin as excipients.

The composition of Xeomin 50-Units is the same as that of 100-Units except for the amount of neurotoxin, which has been reduced by half in the lower dosage strength. The composition of the other components is exactly the same in both the 50-Units and the 100-Units presentations.

Botulinum Neurotoxin Type A is synthesized by a (b) (4) strain of the anaerobic bacterium *Clostridium botulinum*. This product is a single chain polypeptide with a molecular weight of approximately 150kDa, free from complexing proteins.

(b) (4)

Reviewer comment: The information provided is adequate.

Microbiological Attributes (3.2.P.2.5):

Container-closure and package integrity (CCI):

The microbial challenge test was used to validate the integrity of the container closure system for the final product.

(b) (4)

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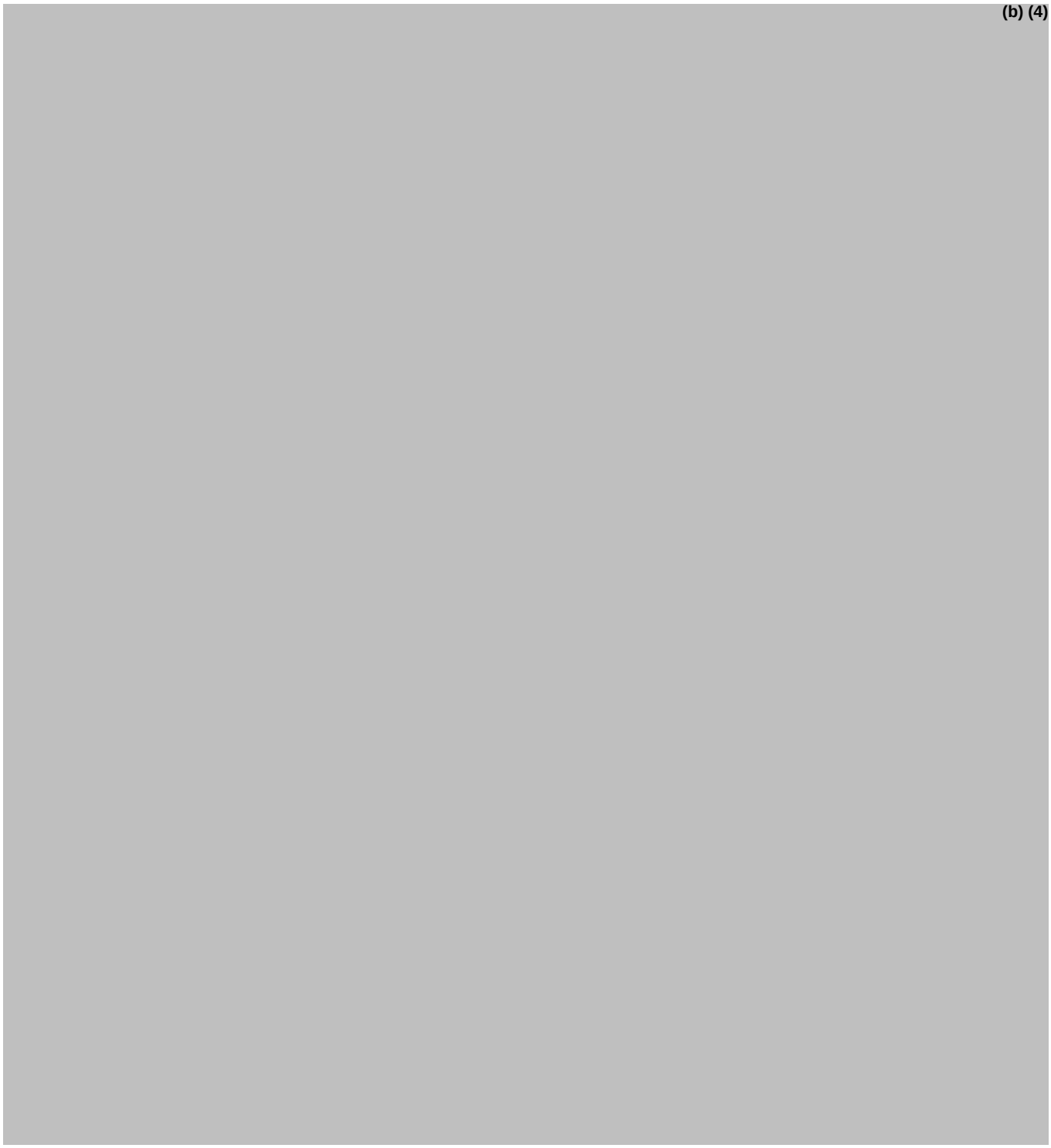
(b) (4)



Environmental Assessment:

The regulations in 21 CFR 25.31 (Environmental Impact Considerations) provide for a categorical exclusion as follows: (a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety. Merz provided justifications for this submission to be qualified for a categorical exclusion.

cGMP Status:

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for Merz Pharmaceuticals, LLC's STN 125360/0 on May 19, 2010. There are no pending or ongoing compliance actions to prevent approval of this BLA.

Conclusion

I. This application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following four post-market commitments:

1. Revalidate the microbial ingress test (container closure integrity test) to demonstrate the integrity of the drug product container closure. Determine the sensitivity (minimum detectable leak size) of the test. Information and summary data will be submitted in a CBE-0 by 2/1/2011.

2. Re-qualify the crimping machine with media filled vials and the revalidated microbial ingress test. Summary data will be submitted in a CBE-0 supplement by 2/1/2011.

3. Complete shipping validation studies for the drug product vials using the worst shipping temperature and duration. Validation information and summary data should be submitted in a Changes Being Effected in 30 days (CBE30) at the end of study by 10/31/2011.

4. Develop a container closure integrity test to replace the sterility test in the stability program. Information and summary validation data for the container closure integrity test will be submitted in a Prior Approval Supplement (PAS) by 12/31/2011.

II. Information and data in this submission not related to drug product sterility assurance and product quality microbiology were not evaluated and should be reviewed by an OBP reviewer.

III. The pre-approval inspection of the drug substance and drug product manufacturing site at Merz Group Services GmbH, Dessau-Rosslau, Germany was conducted on 11/5-13/2009. Ten Form FDA 483 observations were issued at the conclusion of the inspection on 11/13/09. The inspection has been classified as voluntary action indicated (VAI). The BLA is recommended for approval from GMP compliance perspective.

Cc: WO51: Chi
WO51: Hughes
WO22: Kishore
HFD-328, TFRB Blue Files (STN 125360)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

Date: June 11, 2010
To: Administrative File, STN 125360/0
From: Mary E. Farbman, Ph.D., CDER/OC/DMPQ/MAPCB/BMT BC for MF 6/11/10
Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT PFH 6/11/10
Endorsement: Bo Chi, Ph.D., Peer reviewer, CDER/OC/DMPQ/BMT BC 6/11/10
Subject: New BLA
US License: #1830
Applicant: Merz Pharmaceuticals GmbH
Facility: Merz Group Services GmbH Site Dessau, Dessau-Rosslau, Germany (FEI 3006896175)
Product: Xeomin® (botulinum neurotoxin type A)
Dosage: 50 and 100 LD50 units
Indication: Treatment of cervical dystonia, benign essential blepharospasm
Due Date: August 1, 2010

Recommendation for Approvability

The drug substance portion of the BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post marketing commitments:

1. Conduct studies to determine the resistance of *Clostridium botulinum* spores to (b) (4) inactivation. The (b) (4) inactivation cycle may need to be re-validated in the event the *Clostridium* spores are determined to be more resistant to (b) (4) inactivation than *Geobacillus stearothermophilus* biological indicator spores. Submit results of the study in a CBE-0 by August 2010.
2. Include a culture purity test at the end of the (b) (4) step capable of detecting contaminating anaerobes. Submit assay qualification data and information in a CBE-0 by December 2010.
3. Re-validate the drug substance release bioburden assay to include the use of (b) of sample volume without dilution and submit results in a CBE-0 by December 2010.
4. Qualify the spore recovery test method for all intermediates tested routinely and during process validation. Submit summary data in a CBE-0 by December 2010.

Summary

Merz Pharmaceuticals GmbH has submitted a BLA for botulinum neurotoxin type A, a 150 kDa SNAP-25 protease which prevents acetylcholine exocytosis. An assessment of the CMC drug substance section of the application from a microbiology product quality perspective is provided in this review.

The following amendments were submitted and reviewed in response to CMC information requests:

- Amendment # 18 dated January 22, 2010
- Amendment # 20 dated February 5, 2010
- Amendment # 27 dated March 29, 2010
- Amendment # 28 dated March 31, 2010
- Amendment # 33 dated May 12, 2010

(b) (4)

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Environmental Assessment

In Section 1.12.14, the firm requested a categorical exclusion from performance of an environmental assessment based on the expectation that approval of the drug would not cause a substantial increase use of the active moiety. Because other botulinum toxin products are already on the U.S. market, the firm stipulates that approval of its product will not increase overall use.

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch completed its review and evaluation of the TB-EER on May 19, 2010. All sites listed in the BLA have an acceptable compliance status.

Conclusions

I. The drug substance section of the BLA, as amended, is recommended from a microbiology product quality perspective. The following PMCs should be communicated to the sponsor:

1. Conduct studies to determine the resistance of *Clostridium botulinum* spores to (b) (4) inactivation. The (b) (4) inactivation cycle may need to be re-validated in the event the *Clostridium* spores are determined to be more resistant to (b) (4) inactivation. Submit results of the study in a CBE-0 by August 2010.
2. Include a culture purity test at the end of the (b) (4) step capable of detecting contaminating anaerobes. Submit assay qualification data and information in a CBE-0 by December 2010.
3. Re-validate the drug substance release bioburden assay to include the use of (b) of sample volume without dilution and submit results in a CBE-0 by December 2010.
4. Qualify the spore recovery test method for all intermediates tested routinely and during process validation. Submit summary data in a CBE-0 by December 2010.

II. Information and data in the CMC portion of the BLA not related to microbial control of the drug substance should be reviewed by an OBP reviewer.

III. There are no inspectional follow-up items.

CC: WO Bldg 22: Vandna Kishore, RPM
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List of Microbiology-Related PMCs for Botulinum Neurotoxin Type A Drug Substance

1. Conduct studies to determine the resistance of *Clostridium botulinum* spores to (b) (4) inactivation. The (b) (4) inactivation cycle may need to be re-validated in the event the *Clostridium* spores are determined to be more resistant to (b) (4) inactivation than the *Geobacillus stearothermophilus* biological indicator spores. Submit results of the study in a CBE-0 by August 2010.
2. Include a culture purity test at the end of the (b) (4) step capable of detecting contaminating anaerobes. Submit assay qualification data and information in a CBE-0 by December 2010.
3. Re-validate the drug substance release bioburden assay to include the use of (b) (4) of sample volume without dilution and submit results in a CBE-0 by December 2010.
4. Qualify the spore recovery test method for all intermediates tested routinely and during process validation. Submit summary data in a CBE-0 by December 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51
Silver Spring, MD 20993

Date: June 11, 2010
To: Administrative File, STN 125360/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT PFH 6/11/10
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT
Subject: Team Leader Review Memo: New BLA
US License: #1830
Applicant: Merz Pharmaceuticals GmbH
Facility: Merz Group Services GmbH Site Dessau, Dessau-Rosslau, Germany (FEI 3006896175)
Product: Xeomin® (botulinum neurotoxin type A)
Dosage: 50 and 100 LD50 units
Indication: Treatment of cervical dystonia, benign essential blepharospasm
Due Date: August 1, 2010

Recommendation for Approvability

CMC Microbiology Product Quality Assessment:

The BLA, as amended, is recommended for approval from a microbiology product quality perspective. It is recommended that the following post-marketing commitments (PMCs)be communicated to the sponsor. The PMCs are as follows:

1. Conduct studies to determine the resistance of *Clostridium botulinum* spores to (b) (4) inactivation. The (b) (4) inactivation cycle may need to be re-validated in the event the *Clostridium* spores are determined to be more resistance to (b) (4) inactivation than the *Geobacillus stearothermophilus* biological indicator spores. Submit results of the study in a CBE-0 by August 2010.
2. Include a culture purity test at the end of the (b) (4) step capable of detecting contaminating anaerobes. Submit assay qualification data and information in a CBE-0 by December 2010.
3. Re-validate the drug substance release bioburden assay to include the use of (b) (4) of sample volume without dilution and submit results in a CBE-0 by December 2010.
4. Qualify the spore recovery test method for all intermediates tested routinely and during process validation. Submit summary data in a CBE-0 by December 2010.

5. Revalidate the microbial ingress test (container closure integrity test) to demonstrate the integrity of the drug product container closure. Determine the sensitivity (minimum detectable leak size) of the test. Information and summary data will be submitted in a CBE-0 by 2/1/2011.
6. Re-qualify the crimping machine with media filled vials and the revalidated microbial ingress test. Summary data will be submitted in a CBE-0 supplement by 2/1/2011.
7. Complete shipping validation studies for the drug product vials using the worst shipping temperature and duration. Validation information and summary data should be submitted in CBE-30 by 10/31/2011.
8. Develop a container closure integrity test to replace the sterility test in the stability program. Information and summary validation data fro the container closure integrity test will be submitted in a PAS by 12/31/2011.

Establishment Assessment:

All sites listed in the BLA are acceptable from a CGMP perspective. The Merz Groups Services GmbH, Site Dessau, in Dessau-Rosslau, Germany is the manufacturing site for the drug substance and the drug product. The site was inspected November 5-13, 2009 by CDER/OC/BMT and CDER/OBP/DTP and the establishment was classified as VAI and was found to be acceptable. The analytical testing site, (b) (4) was inspected (b) (4) by BMT and DTP and was classified as VAI and is acceptable from a CGMP perspective. The Potency assay test site, Laboratory (b) (4) was inspected on (b) (4) (b) (4) by BMT and DTP and was classified as VAI and is acceptable from a CGMP perspective.

Summary

Merz Pharmaceuticals GmbH is seeking the approval of BLA 125360 for Xeomin (botulinum neurotoxin type A) for the treatment of cervical dystonia and blepharospasms. Both drug substance and drug product are manufactured at Merz Pharmaceutical GmbH, Dessau-Rosslau, Germany. Additional information in several amendments to the BLA were reviewed (# 11, 10/27/2009, #18, 1/22/2010; # 20, 2/5/2010; # 22, 2/25/2010; # 27, 3/27/2010; # 28, 3/31/2010; #33, 5/12/2010; # 32 5/11/2010).

Botulinum Neurotoxin Type A is produced by fermentation (b) (4) using anaerobic bacterium, *Clostridium botulinum.* The protein is expressed as a single polypeptide chain of approximately 150 kDa and on release from the producer bacterium, the protein is proteolytically processed into two subunits, a light chain (~50 kDa) and a heavy chain (~100 kDa) that are covalently linked via a disulfide bond. (b) (4)

The final drug product is supplied as a sterile lyophilized powder for injection packed (b) (4) (b) (4) in glass vials. The vials are sealed with rubber stoppers and aluminum caps. The product is reconstituted with commercially available 0.9% physiological saline which is not

supplied in the pack. Each vial contains 100 (b) (4) or 50 (b) (4) mouse LD50 units of *Clostridium botulinum* neurotoxin type A with no preservative. The final formulation contains sucrose and human albumin as excipients. The composition of Xeomin 50-Units is the same as that of 100-Units except that the amount of (b) (4)

(b) (4)

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cGMP Status

A compliance check of all establishments listed in the BLA was conducted on May 19, 2010. All sites listed in the BLA have an acceptable compliance status (attached compliance check).

Conclusions

I. The BLA, as amended, is recommended from a microbiology product quality perspective and from a CGMP perspective with 8 PMCs (see first page). 2010.

II. Information and data in the CMC portion of the BLA not related to microbial control and sterility assurance and product quality microbiology should be assessed by the OBP review team.

III. There are no inspectional follow-up items.

Attachments: Compliance check e-mail
Facility Sheets for RMS/BLA

CC:
WO Bldg 22: Kishore

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