

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125360**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

Our STN: BL 125360/0  
BL 125360/1

**BLA APPROVAL**  
July 30, 2010

Merz Pharmaceuticals

Attention: James Kenimer, Ph.D.  
President & CEO, Biologics Consulting Group, Inc.  
US Agent for Merz Pharmaceuticals  
400 N. Washington Street  
Alexandria, VA 22314

Dear Dr. Kenimer:

Please refer to Biologics License Application (BLA) dated July 1, 2009, received July 2, 2009, submitted by Merz Pharmaceuticals under section 351 of the Public Health Service Act for Xeomin (incobotulinumtoxinA) Injection.

We also acknowledge receipt of your amendments dated:

July 29, 2009	December 11, 2009	April 28, 2010	June 30, 2010
August 7, 2009	January 8, 2010	May 5, 2010	July 1, 2010
August 13, 2009	January 19, 2010	May 10, 2010	July 2, 2010
September 1, 2009	January 22, 2010	May 11, 2010	July 6, 2010
September 2, 2009	February 4, 2010	May 12, 2010	July 8, 2010
September 15, 2009	February 5, 2010	May 18, 2010	July 12, 2010
September 25, 2009	February 24, 2010	May 19, 2010	July 14, 2010
September 30, 2009	February 25, 2010	May 20, 2010	July 15, 2010
October 22, 2009	March 1, 2010	May 27, 2010	July 16, 2010
October 23, 2009	March 5, 2010	May 28, 2010	July 19, 2010
October 27, 2009	March 25, 2010	June 8, 2010	July 22, 2010
October 28, 2009	March 26, 2010	June 10, 2010	July 29, 2010
October 30, 2009	March 29, 2010	June 16, 2010	
November 16, 2009	March 31, 2010	June 17, 2010	

We are issuing Department of Health and Human Services U.S. License No. 1830 to Merz Pharmaceuticals, Frankfurt, Germany, 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 Xeomin (incobotulinumtoxinA), indicated for the treatment of Cervical Dystonia and Blepharospasm.

Under this license, you are approved to manufacture Xeomin (incobotulinumtoxinA) at your facility in Dessau, Germany. You may label your product with the proprietary name Xeomin and will market it in 50 Unit and 100 Unit vials.

Your application for Xeomin (incobotulinumtoxinA) was not referred to an FDA advisory committee because this biologic is not the first in its class, and the safety profile is similar to that of other drugs approved for these indications.

The dating period for Xeomin (incobotulinumtoxinA) shall be 36 months from the date of manufacture when stored at -20° C, 5° C and 25° C. The date of manufacture shall be defined as the date of final (b) (4) of the formulated drug product. The dating period for your drug substance shall be 36 months from the date of manufacture when stored at -80 °C.

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the 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.

Please submit Lot Release Protocols showing 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).

Any changes in the manufacturing, testing, packaging, or labeling of Xeomin (incobotulinumtoxinA), or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide).

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved BLA STN 125360/0 & 125360/1.**”

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

We acknowledge your July 15, 2010 submission containing final printed carton and container labels.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.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 indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application for the indication of cervical dystonia because necessary studies are impossible or highly impracticable because there are too few children with the disease to study.

We are waiving the pediatric study requirement for this application for the indication of blepharospasm because necessary studies are impossible or highly impracticable because there are too few children with the disease to study.

### **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 on pre-natal development or post-natal growth and development. 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 Xeomin (incobotulinumtoxinA). A case report consistent with spread of toxin effect following treatment with Xeomin (incobotulinumtoxinA) was submitted in this application. In addition, there are several published reports of spread of toxin effect associated with similar botulinum toxin type A products.

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 assess 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 of Xeomin (incobotulinumtoxinA) 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 Xeomin (incobotulinumtoxinA) on growth, reproductive development, and neurological and neurobehavioral development.

The timetable you submitted on July 8, 2010 states that this study is ongoing and the final report will be submitted according to the following schedule:

<b>PMR #1: Juvenile Rat Toxicology Study</b>	
<b>Milestone</b>	<b>Date of Submission</b>
Final Protocol Submission	July 21, 2010 (submitted)
Study Completion Date	September 30, 2010
Final Report Submission	November 30, 2010

2. A prenatal and postnatal development (including maternal function) study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on stages of development and endpoints not evaluated in an embryo-fetal development study, in accordance with guidance set forth in ICH S5(R2): *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility* (2005).

<b>PMR #2: Prenatal and Postnatal Development Study</b>	
<b>Milestone</b>	<b>Date of Submission</b>
Final Protocol Submission	July 21, 2010 (submitted)
Study Completion Date	May 31, 2010 (completed)
Final Report Submission	November 30, 2010

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the serious risk of distant spread of toxin effects in pediatric and adult patients with spasticity treated with Xeomin (incobotulinumtoxinA).

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

3. Submit safety data assessing distant spread of toxin effects after multiple administrations of Xeomin (incobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years). Approximately one half of the patients must be treated for upper and the other half treated for lower limb extremity spasticity. Patients can be enrolled in either an upper or lower limb safety trial, but not both, and should not receive concomitant botulinum toxin injections for another reason. These safety data could come from open-label extensions of the clinical trials you have committed to perform (see below), from separate longer-term open-label safety trials, or from a long-term controlled safety and efficacy trial. The doses evaluated must be at least as high as those shown effective in these trials, or those commonly used to treat spasticity.

The timetable you submitted on July 8, 2010 states that you will conduct this trial according to the following schedule:

<b>PMR #3: Safety data assessing distant spread of toxin effects after multiple administrations of XEOMIN in pediatric patients</b>	
<b>Milestone</b>	<b>Date of Submission</b>
• Final protocol submission*	July 31, 2012
• Trial Completion Date	March 31, 2018
• Final Report Submission <sup>^</sup>	December 31, 2018

\*Including protocol of already completed studies, and plans for new analyses of data already submitted to the Xeomin BLA

<sup>^</sup> Final Trials reports should be submitted as soon as they are available

4. Submit safety data assessing distant spread of toxin effects after multiple administrations of Xeomin (incobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 adult patients. Approximately one half of the patients must be treated for upper and the other half treated for lower limb extremity spasticity. Patients can be enrolled in either an upper or lower limb safety study, but not both, and should not receive concomitant botulinum toxin injections for another reason. These safety data could come from open-label extensions of the clinical trials you have committed to perform (see below), from separate longer-term open-label safety trials, or from a long-term controlled safety and efficacy trial. The doses evaluated must be at least as high as those shown effective in these trials, or those commonly used to treat spasticity.

The timetable you submitted on July 8, 2010 states that you will conduct this trial according to the following schedule:

<b>PMR #4: Safety data assessing distant spread of toxin effects after multiple administrations of XEOMIN in adult patients</b>	
<b>Milestone</b>	<b>Date of Submission</b>
• Final protocol submission*	December 31, 2011
• Trial Completion Date	September 30, 2016
• Final Report Submission <sup>^</sup>	June 30, 2017

\*Including protocol of already completed studies, and plans for new analyses of data already submitted to the Xeomin BLA

<sup>^</sup> Final Trials reports should be submitted as soon as they are available

Submit the protocols to your IND 100163, with a cross-reference letter to this BLA. Submit all final report(s) to this BLA. 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 UNDER SECTION 506B**

We acknowledge your written commitments as described in your submission dated July 12, 2010 as outlined below:

Regarding clinical efficacy in spasticity, you commit to conduct a:

5. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive children age 2-17 years with lower extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread

of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

<b>PMC # 5: Clinical trial in botulinum toxin-naive children age 2-17 years with lower extremity spasticity</b>	
<b>Milestone</b>	<b>Date of Submission</b>
Final Protocol Submission	January 31, 2012
Trial Completion Date	July 31, 2016
Final Report Submission	March 31, 2017

6. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive children age 2-17 years with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

<b>PMC # 6: Clinical trial in botulinum toxin-naive children age 2-17 years with upper extremity spasticity</b>	
<b>Milestone</b>	<b>Date of Submission</b>
Final Protocol Submission	January 31, 2012
Trial Completion Date	July 31, 2016
Final Report Submission	March 31, 2017

7. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive adults with lower extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

<b>PMC # 7: Clinical trial in botulinum toxin-naive adults with lower extremity spasticity</b>	
<b>Milestone</b>	<b>Date of Submission</b>
Final Protocol Submission	June 30, 2011
Trial Completion Date	December 31, 2014
Final Report Submission	September 30, 2015

8. Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive adults with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).



<b>PMC # 8: Clinical trial in botulinum toxin-naive adults with upper extremity spasticity</b>	
<b>Milestone</b>	<b>Date of Submission</b>
Final Protocol Submission	March 31, 2011
Trial Completion Date	September 30, 2014
Final Report Submission	June 30, 2015

9. Randomized, double-blind, adequate and well controlled, parallel group, clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naive adults with blepharospasm. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

<b>PMC # 9: Clinical trial in botulinum toxin-naive adults with blepharospasm</b>	
<b>Milestone</b>	<b>Date of Submission</b>
Final Protocol Submission	July 31, 2011
Trial Completion Date	January 31, 2016
Final Report Submission	October 31, 2016

Submit clinical protocols to your IND 100163, for this product with a cross-reference letter to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

#### **POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments in your submission dated July 8, 2010. These commitments are listed below.

10. Conduct studies to determine the resistance of *Clostridium botulinum* spores to (b) (4) inactivation. The (b) (4) inactivation cycle may need to be revalidated in the event the *Clostridium* spores are determined to be more resistant to (b) (4) inactivation than the *Geobacillus stearothermophilus* biological indicator spores. Results of the study should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by August 31, 2010.

11. Add a culture purity test at the end of the (b) (4) as an additional in-process control. The assay should be capable of detecting contaminating anaerobes. Assay qualification data and information should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by December 31, 2010.
12. Re-validate the drug substance release bioburden assay to include the use of (b) (4) of sample volume without dilution. Results should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by December 31, 2010.
13. Qualify the spore recovery test method for all intermediates tested routinely and during process validation. Summary data should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by December 31, 2010.
14. 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 should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by February 1, 2011.
15. Re-qualify the crimping machine with media filled vials and the revalidated microbial ingress test. Summary data should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) by February 1, 2011.
16. Complete shipping validation studies for the drug product vials using the worst case shipping temperature and duration. Validation information and summary data should be submitted in a Changes Being Effected in 30 days Supplement (CBE30) at the end of study by October 31, 2011.
17. 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 should be submitted in a Prior Approval Supplement (PAS) by December 31, 2011.
18. Characterize the specificity of the antibody used in the abnormal toxicity test to evaluate whether this antibody recognizes only type A toxin and not other serotypes. Results of this validation study together with the proposed specifications for use in drug product release and in the lot release protocol should be submitted in a Prior Approval Supplement (PAS) by March 31, 2011.
19. Characterize the ability of the SE-HPLC assay to accurately assess the aggregate content of the drug substance at release and on stability. This may be established by demonstrating that SE-HPLC provides similar results in aggregate content evaluations as compared to an orthogonal method that is quantitative and does not disrupt weak protein- protein interactions (e.g., AUC or FFF). Results of this validation study should be submitted in a Prior Approval Supplement (PAS) by February 28, 2011.
20. Investigate the development and implementation of a non-animal based potency assay for drug substance, drug product release and stability testing. A summary report together with

any proposed modifications to the release and stability specifications should be submitted in a Prior Approval Supplement (PAS) by December 31, 2014.

Submit chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the 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 Xeomin (incobotulinumtoxinA) 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 Xeomin (incobotulinumtoxinA) with other licensed botulinum toxin products.

In accordance with section 505-1 of 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 Xeomin (incobotulinumtoxinA) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients’ safe and effective use of Xeomin. FDA has determined that Xeomin (incobotulinumtoxinA) is a product for which patient labeling could help prevent serious adverse effects. FDA has also determined that Xeomin (incobotulinumtoxinA) has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients’ decisions to use, or continue to use, Xeomin (incobotulinumtoxinA) and that the Medication Guide is important to health, and patient adherence to directions for use is crucial to the drug’s effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Xeomin (incobotulinumtoxinA).

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

Your proposed REMS, submitted on July 29, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

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

1. A survey of patients' understanding of the serious risks of Xeomin(incobotulinumtoxinA).
2. A survey of prescribers' understanding of the serious risks of Xeomin and the lack of interchangeability of Xeomin (incobotulinumtoxinA) 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 Xeomin (incobotulinumtoxinA).
7. A summary of reports of all medication errors involving interchangeability of Xeomin (incobotulinumtoxinA) units with those of other licensed botulinum toxin products.
8. For the communication plan, provide the sources of recipient lists for the Dear Healthcare Provider Letter, number of recipients on each mailing list, the date(s) of mailings, and copies of document(s) included in the mailing.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. 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 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 section 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 submission 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:

**BLA 125360  
REMS ASSESSMENT**

**NEW SUPPLEMENT FOR BLA 125360  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR BLA 125360  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

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

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **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:

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 <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.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:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
10903 New Hampshire Avenue, Bldg. 51, Room 4206  
Silver Spring, MD 20992-0002

### **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

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B-05  
5600 Fishers Lane  
Rockville, MD 20857

**POST-ACTION FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Vandna Kishore, R.Ph., Regulatory Project Manager, at (301)796-4193.

Sincerely,

/ Ellis F. Unger /

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

Enclosures: REMS documents; Package Insert