CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	7/30/2010
From	Ellis F. Unger, M.D., Deputy Director, ODE-I
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	BLA STN 125360 /1 (b)(4)
Applicant Name	Merz Pharmaceuticals GmbH
Date of Submission	7/1/2009
PDUFA Goal Date	5/2/2010, extended (major amendment) to 8/1/2010
Proprietary Name / **Established (USAN) Name**	Xeomin® incobotulinumtoxinA
Dosage Forms / Strength	For injection: lyophilized powder, 50- and 100-Unit single-use glass vials
Proposed Indication(s)	…for the treatment of adults with cervical dystonia, to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients; and blepharospasm in adults previously treated with onabotulinumtoxinA (Botox®)
Action:	*Approval*

Material Reviewed/Consulted Action Package, including:	
Project Manager	Vandna Kishore
Medical Officer cervical dystonia	Anne Constantino
Medical Officer blepharospasm	Kenneth Bergmann
Medical Officer Safety Review	Lisa M. Jones
Safety Team	Alice Hughes, Sally Yasuda
Statistical Review	Ohidul I Siddiqui, Kun Jin, Kooros Mahjoob
Pharmacology Toxicology	Barbara J. Wilcox, Lois M Freed, Paul C. Brown
CMC/Office of Biotechnology Products	Kimberly E Rains
Division of Therapeutic Proteins	Ennan Guan, Joao Pedras-Vasconcelos, Jinhai Wang, Susan Kirshner, and Amy Rosenberg
Clinical Pharmacology	Ta-Chen Wu, Angela Y. Men
Microbiology	Bo Chi, Patricia Hughes
Division of Scientific Investigations	Antoine N El Hage
Office of Compliance	Kendra Biddick, Kendra Worthy
Division of Medication Error and Prevention, Office of Surveillance and Epidemiology	Walter Fava, Marcia Britt, Mary Dempsey
Division of Risk Management, Office of Surveillance and Epidemiology	Melissa Hulett, LaShawn Griffiths
Cross-Discipline Team Leader	Gerald D. Podskalny
Director, Division of Neurology Products	Russell Katz

Introduction:

The Division of Neurology Products recommends approval of incobotulinumtoxinA (Xeomin) for the indications of cervical dystonia (CD) and benign essential blepharospasm, and I concur with their recommendation.

Xeomin (incobotulinumtoxinA) is a botulinum toxin Type A, a therapeutic protein that causes neuromuscular blockade by blocking fusion of neurosecretory vesicles with the synaptic membrane, preventing release of the neurotransmitter acetylcholine. With a lethal dose of approximately 1 ng/kg, these neurotoxins are among the most deadly substances known. Used locally in extremely low doses, however, botulinum toxins have salutary effects related to their ability to cause muscle relaxation.

IncobotulinumtoxinA is closely related to two approved botulinum toxin Type A products, onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport), as well as to an approved botulinum B product, rimabotulinumtoxinB (Myobloc). IncobotulinumtoxinA has been approved in Germany since 2005, and in a number of other EU countries since 2007. The product is also approved in Argentina, Canada, Korea, Mexico, and Uruguay.

(b) (4)

The chief safety concern common to all botulinum toxin products is directly related to their pharmacodynamic effect: in essence, having the desired effect in undesired locations. All botulinum toxin products have the potential to spread to contiguous muscles and cause weakness or paralysis through local spread. Because treatment of CD involves injection of neck muscles in proximity to muscles used in deglutition and accessory muscles of respiration, local spread is a particular concern for the CD indication. Of greater concern is the potential for these products to spread systemically, causing neuromuscular blockade at distant sites (including muscles of respiration), which can be fatal. The risk of distant spread tends to be dose-related, and is of greatest concern when relatively large doses are used to treat large muscle groups. Rarely, these products cause allergic reactions, and they can induce neutralizing antibodies associated with loss of efficacy, although this association is not strong.

Advisory Committee:

This application was not referred to an FDA advisory committee. Although incobotulinumtoxinA is a new molecular entity, its mechanism of action is well-understood and comparable to that of onabotulinumtoxinA (Botox), which was approved under section 351 of the Public Health Service Act in 1991, and abobotulinumtoxinA (Dysport), which was approved under the same Act in April, 2009. On preliminary review of the BLA, the safety and efficacy profile of incobotulinumtoxinA appeared to be

consistent with expectations. For these reasons, therefore, the Division decided not to refer Xeomin to an advisory committee, and the Office supported this decision. Following completion of the reviews, this view has not changed.

Nonclinical Findings:

Chemistry Manufacturing Controls

The Division of Therapeutic Proteins, Office of Biotechnology Products, recommends approval of incobotulinumtoxinA. They concluded that the manufacture of purified *C. botulinum* neurotoxin type A is well-controlled, leading to a product that is free from endogenous or adventitious infectious agents, and potent and safe when used according to the label. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. IncobotulinumtoxinA will be on lot release per 21CFR 610.

Xeomin is to be supplied as lyophilized powder in single-use vials of 50 and 100 U that can be stored at room temperature (b) (4), in a refrigerator (b) (4) or in a freezer (b) (4). (b) (4)

The recommended expiration dating period for Xeomin is 36 months.

The product is to be reconstituted with preservative-free 0.9% saline prior to use. The potency of the reconstituted drug product stored at 2-8°C for 24 hours was in compliance with specified release limits.

Anti-Xeomin neutralizing antibody responses were measured using a hemidiaphragm assay. The assay assesses the ability of patient sera to inhibit the ability of incobotulinumtoxinA to prevent the contraction of mouse diaphragm muscles *ex vivo*. The sensitivity of this assay is such that it can detect the quantity of antibody needed to neutralize 32 U of drug. In the clinical development program, 1.1% of subjects who were antibody negative at baseline developed neutralizing antibodies to botulinum toxin. These subjects had received another botulinum toxin prior to incobotulinumtoxinA, rendering interpretation difficult. One botulinum toxin-naïve subject developed neutralizing antibodies transiently, and reverted to negative at study termination. The significance of antibody positivity is unclear, however. For other botulinum toxins, some patients appear to continue to experience clinical benefit even in the presence of neutralizing antibodies.

Clinical Microbiology

The drug substance portion of the BLA, as amended, is recommended for approval from a microbiology product quality perspective. There were concerns regarding the use of (b) (4), particularly because *C. botulinum* is a spore-forming organism, and spores are resistant to sterilization. These concerns

will be addressed through a number of post-marketing commitments, outlined in their review.

Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review staff has recommended approval of incobotulinumtoxinA. The observed toxicological effects of incobotulinumtoxinA were consistent with the known activity of the product in studies in rats, mice, rabbits and nonhuman primates.

The applicant did not submit a pre- and post-natal developmental toxicology study. Their justification for not performing such studies was based principally on the large size of the incobotulinumtoxinA molecule (i.e., too large to cross the placental barrier) and incobotulinumtoxinA's low systemic exposure. For a number of reasons outlined by the pharmacology/toxicology team, however, the applicant's rationale was rejected, and the team recommended a post-marketing requirement for a pre- and postnatal developmental toxicity study. They also recommend a postmarketing requirement for a juvenile animal toxicology study, to support clinical trials in the pediatric population for treatment of upper and lower extremity spasticity. The team agrees with Pregnancy category C as proposed by the applicant.

Clinical Pharmacology

The sponsor did not submit any pharmacokinetic studies in support of the BLA. The chemical complexity of incobotulinumtoxinA, its extreme potency, and its rapid and irreversible binding to cholinergic nerve terminals preclude informative pharmacokinetic studies in humans.

Clinical Evidence of Effectiveness

Merz submitted the results of one adequate and well-controlled trial for each indication – CD and blepharospasm – reviewed separately. In effect, the two indications are somewhat related, and can be viewed as supportive of each other based on mechanism of action. Moreover, the existence of closely related botulinum toxin products with established efficacy in these indications provides *priors* that help justify approval based on less than the two-trial standard.

- *Cervical Dystonia (CD)*

The applicant submitted a single pivotal trial in support of this indication (MRZ 60201-0408/1). This was a parallel-group double-blind trial wherein patients were randomized 1:1:1 to receive a single treatment of either incobotulinumtoxinA, a total of 120 U (divided by muscle site), a total of 240 U divided by site, or placebo. The actual number and sites of injections were at the investigators' discretion. Patients who had received Botox previously, as well as those who had not, could be enrolled.

The primary outcome was to be the Δ from baseline in the Total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score at Week 4. The analysis of the 1° endpoint was based on the comparison of least square means from an analysis of covariance (ANCOVA) model at Week 4, including terms for treatment, baseline TWSTRS-Total score, gender, age, prior treatment of CD with a botulinum toxin, and pooled center. Missing data were replaced with the baseline value (i.e., no change from baseline). For the multiplicity adjustment, pairwise comparisons between treatment groups were performed by using a fixed-sequence test procedure (step downward) in the intent-to-treat (ITT) population starting with the comparison of the 240 U group with placebo followed by a comparison of the 120 U group with placebo. The biostatistical review had no concerns with the analyses of the 1° endpoint as planned.

The TWSTRS is made up of three sub-scales: severity, disability, and pain. Responses in these sub-scales were evaluated as 2° outcomes, assessed at all post-baseline visits. A patient evaluation of global response (PEGR) was assessed at Week 5. Of note, there was no plan to control for multiplicity within the family of 2° endpoints.

Other measures assessed included time to effect, time to waning of effect, and duration of effect.

A total of 233 patients were randomized (240 U, 81; 120 U, 78; placebo, 74) at 37 centers in the US. The groups were well-balanced for baseline TWSTRS score, age and weight, and fairly well-balanced for concomitant medication use. Approximately 39% of subjects were treatment-naïve in all 3 treatment groups. Over 90% of subjects were Caucasian.

Approximately 94% of subjects completed the double-blind phase of the trial.

The results are shown in the reviews of the primary medical officer and CDTL, and summarized in the Division Director's memorandum. The difference between the120 U group and the placebo group on Δ from baseline TWSTRS score was statistically significant ($p<0.05$), as was the difference between the 240 U group and the placebo group. The results were robust to various sensitivity analyses.

There was no apparent difference between responses of subjects previously treated with Botox and those who were treatment-naïve.

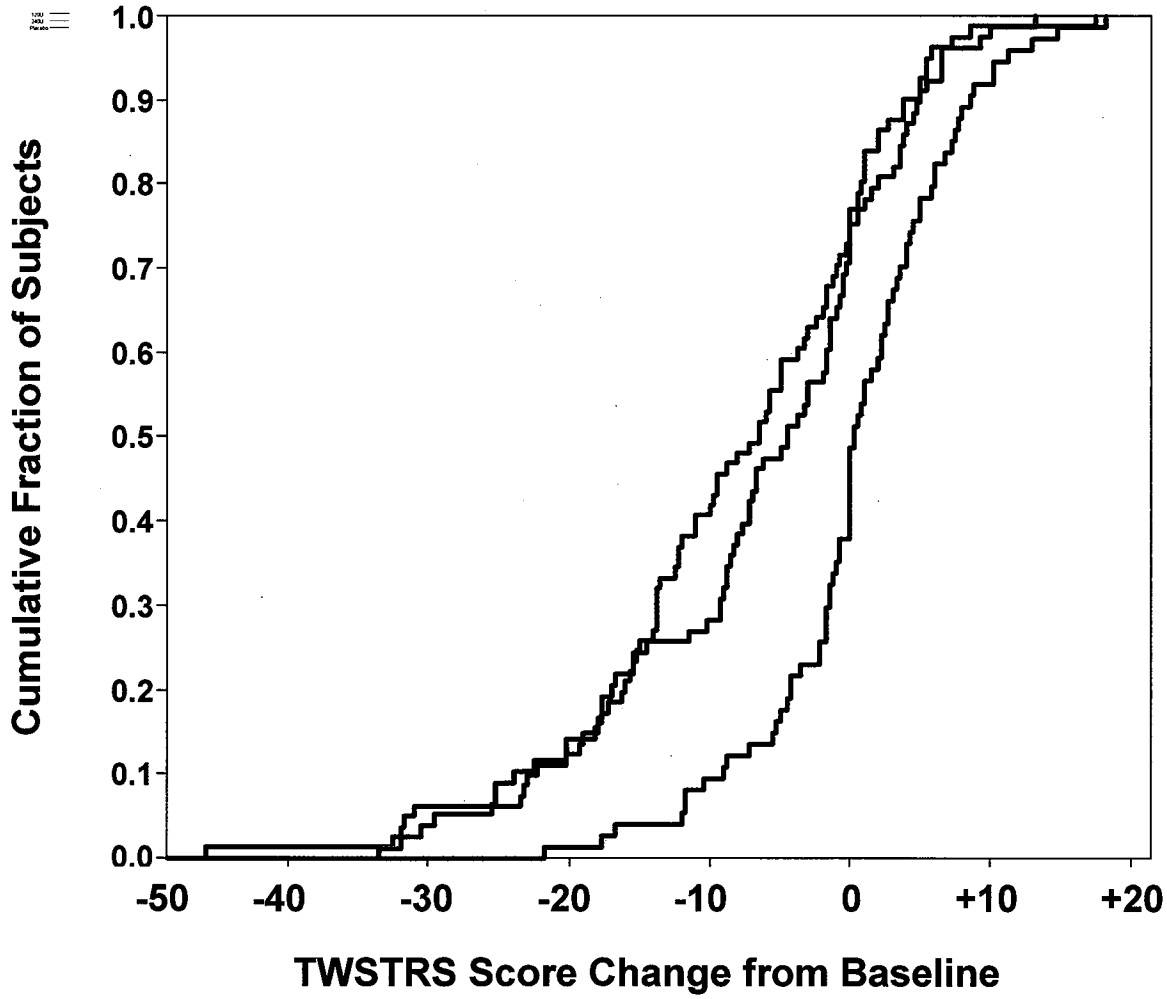
The time to onset of effect was highly variable, but averaged approximately one week in all treatment groups (see Table 27, review of Dr. Anne Constantino).

The mean time to waning of effect was approximately 7.5 weeks in incobotulinumtoxinA treated patients, and 4 weeks in the placebo-treated patients (standard deviation ~3.5 weeks). Importantly, there was no apparent difference in time to waning of treatment between the 120 and 240 U groups.

The mean time to a second treatment was approximately 80 days (range 42-269 days; median 58 days) in both incobotulinumtoxinA groups and approximately 72 days in the placebo group.

The applicant, having performed a fixed-dose study of 120 and 240 U and shown that both doses were effective, (b) (4)

Because toxicity of botulinum toxins is largely dose-related, however, it is critical to consider whether the 240 U dose is more efficacious than the 120 U dose. The cumulative distribution function for all treatment groups allows a critical examination of differences in response between the 120 and 240 U groups, and is not consistent with superiority of the 240 U dose. Moreover, as noted above, the time to onset of effect, time to waning of effect, and time to re-treatment were similar in the 120 and 240 U treatment groups.



[redacted] (b) (4)

- *Blepharospasm*

The applicant performed a double-blind, placebo-controlled, randomized, multi-center trial with an open-label extension period to investigate the efficacy and safety of incobotulinumtoxinA in the treatment of blepharospasm (MRZ 60201-0433/1).

Subjects had to have a diagnosis of benign essential blepharospasm with baseline Jankovic Rating Scale severity subscore (JRS-S) ≥ 2. (The JRS-S measures severity and frequency on a 2-item scale.) A key entrance criterion was having had a satisfactory therapeutic response to Botox® injections on at least two previous occasions; the total administered dose of incobotulinumtoxinA was to be equivalent to the previously administered dose of Botox®. At least 10 weeks had to have elapsed since the most recent Botox administration. Subjects were randomly assigned to receive incobotulinumtoxinA or placebo in a 2:1 ratio. Subjects were treated at a single injection session, and received up to 50 U of incobotulinumtoxinA per eye.

The 1° outcome measure was the Δ from baseline in the JRS-S, as assessed by a masked rater, six weeks following incobotulinumtoxinA administration. The analysis was based on the comparison of least square means from an analysis of covariance (ANCOVA) model at Week 6 between the two treatment groups in the ITT (as randomized) population. The dependent variable in the ANCOVA model was Δ from baseline in the JRS-S, and the independent variables were treatment, baseline JRS-S, sex, age, dose, and center. In case of missing data for the change from baseline in the JRS-S, the last observation was to be carried forward (LOCF).

There were numerous 2° efficacy variables including:

- JRS severity subscale diary
- Blepharospasm Disability Index (DSDI), a self-rated 0-4 scale of 6 items
- patient evaluation of global response (PEGR), ranging from +4 (complete abolishment of signs and symptoms) to -4 (very marked worsening)
- investigator-rated global assessment of efficacy, rated on a 4-point Likert Scale
- time to onset of treatment effect
- time to waning of treatment effect
- duration of treatment effect

A total of 109 patients (incobotulinumtoxinA 75; placebo 34) were enrolled at 31 centers in the US and Canada. Ninety-three percent (93%) of subjects completed the study (same in both groups). All patients were included in the primary efficacy analysis.

Baseline demographic and disease-specific characteristics were well-balanced between the two treatment groups. Approximately two-thirds of subjects were women; average age was approximately 63 years (range 22 to 79 years). Subjects were principally Caucasian (83%) and non-smokers (67%).

The median duration of blepharospasm was 7 years in both treatment arms (range 0.5 – 39 years; mean 9 years). Length of disease after formal diagnosis was 5 years on average. Baseline disease severity as quantified by the JRS-S and BSDI was similar between groups.

The median dose of incobotulinumtoxinA was 65 U (range 20-100 U). There were no important differences in dose between eyes, and no important differences in dose between the incobotulinumtoxinA and placebo groups. Subjects in the incobotulinumtoxinA group averaged 6 injections per eye.

For the 1° endpoint, the mean Δ in JRS-S from baseline to Week 6 decreased by 0.83 points in the incobotulinumtoxinA group and increased by 0.21 points in the placebo group. The inter-group difference of 1.0 point was statistically significant ($p<0.001$) and robust to sensitivity analyses. Analyses on the 2° endpoints were also statistically significant in favor of incobotulinumtoxinA.

Open-label, multiple dosing:

Following the blinded treatment phase, subjects could enroll in an open-label phase, wherein they could receive up to 5 additional treatments, a minimum of 6 weeks apart.

All patients who completed the double-blind phase entered the open-label extension, and the vast majority received either 4 or 5 treatments.

As noted in Dr. Bergmann's review, there was no important change in the incobotulinumtoxinA dose over the course of the open-label extension, and no difference in the change in mean JRS over time.

Study 60201-0003

The sponsor performed a non-inferiority trial comparing incobotulinumtoxinA to Botox. The study enrolled 148 incobotulinumtoxinA subjects and 152 Botox subjects in the ITT analysis. As described by Dr. Bergmann, subjects in both groups received similar mean doses (not surprising, given that patients had to have been treated with Botox previously, using the same rule as in study 0433/1).

The mean change from baseline in the JRS was -2.9 for incobotulinumtoxinA and -3.1 for Botox. Dr. Bergmann's comments are noteworthy:

> "As a non-inferiority design, this trial has deficiencies that affect its interpretation.

It is difficult to estimate from prior experience what the effect size of the primary outcome variable should be. No discussion was presented regarding the rationale for the size of the non-inferiority margin, how much effect one was willing to give up (which changed from 95 to 90% by Amendment 1) and the historical constancy of the effect. In fact, the JRS has not been previously used in an adequately controlled and blinded trial of blepharospasm. The difference in effect size of the JRS for the NT 201 arms in the placebo controlled and active controlled trial graphically demonstrates the difficulty this poses.

Even if the margin had been adequately prespecified, the population in this trial is not the same as other populations used in blepharospasm trials which have led to market approval. A precondition to entry in this trial was an adequate and stable response to a marketed BoNT A product, which is, in effect, enrichment."

Thus, although the trial provided safety experience for incobotulinumtoxinA in blepharospasm, the trial's utility in supporting efficacy is limited.

Overall, the primary reviewer, biostatistical reviewer and CDTL opined that the applicant had adequately demonstrated the efficacy of incobotulinumtoxinA in blepharospasm, although only in patients previously treated successfully with Botox. The starting dose should be based on prior experience with Botox injections.

Safety

With respect to the treatment of CD, the agency has not demanded exposure data that would meet the criteria set in ICH E1 for drugs intended for the long-term treatment of non-life-threatening conditions. The reasoning by some is that these therapies are administered intermittently, although ICH E1 is clear that long-term treatment includes repeated intermittent use for longer than 6 months. The ICH E1 Guideline does provide an exception, however, that seems applicable for diseases such as CD and blepharospasm:

"In some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small."

Thus, ICH E1 subject numbers have not been demanded to support approval for other botulinum toxins for these indications.

During development, the Division discussed appropriate exposure guidelines with Merz on a number of occasions. At the time of BLA submission, 1313 subjects had received at least one dose of incobotulinumtoxinA in all studies combined: 431 with CD, 222 with blepharospasm, 265 with spasticity, 312 with glabellar lines, and 83 with crow's feet. Exposure is summarized by dose, number of doses, and exposure period in the safety and CDTL reviews.

Dr. Jones' safety review provides the following summary of safety (paraphrased here):

Deaths: There were 6 deaths in patients across the development program for all indications (including the non-neurologic indications): 3 patients who received incobotulinumtoxinA, 2 who received placebo, and 1 who received Botox®. The 3 deaths in incobotulinumtoxinA-treated subjects were in a 72 year-old man who died in his sleep >4 months after receiving a single 375 U injection; a 67 year old man with hypertension and a prior cerebrovascular accident (CVA) who died suddenly 6 weeks after a second injection of 400 U; and a 71 year-old man with a similar medical history who died 21 days after a second injection of 400 U. Given the timing and underlying diseases in these subjects, causality seems unlikely.

Serious Adverse Events (SAEs): The SAEs in the incobotulinumtoxinA development program were generally those expected for the background population and demographic group. There were two SAEs of respiratory of failure and dyspnea, but neither fit the clinical presentation of systemic botulinum toxin spread and both cases had clear alternate causes (such as post-surgery blood loss). There has been one post-marketing report of "anaphylaxis," although the details are not highly suggestive of a true anaphylactic event.

Common Adverse Events (AEs): In the controlled portions of blepharospasm studies, adverse events occurring in ≥3% of incobotulinumtoxinA-treated subjects compared to placebo were ptosis (19% vs. 9%), dry eye (16% vs. 12%), dry mouth (16% vs. 3%), diarrhea (8% vs. 0%), headache (7% vs. 3%), visual disturbance (7% vs. 6%), dyspnea (5% vs. 3%) and nasopharyngitis (5% vs. 3%). In the blepharospasm open-label studies, the most common AEs in the repeated dose studies were ptosis (19%), dry eye (16%), dry mouth (16%), and visual disturbance (7%).

In the placebo-controlled CD studies, the most frequent AEs compared to placebo were neck pain (11% vs. 4%), muscular weakness 14 (9% vs. 1%), musculoskeletal pain (5% vs. 1%) and musculoskeletal stiffness (3% vs. 1%).

Discontinuations: The concept of a "discontinuation" has little meaning in the context of therapies where treatment is administered at a single setting; subjects have limited opportunity to "discontinue treatment." Strictly speaking, if a study plans to administer a single treatment at a single session, the number of discontinuations is, by definition, zero. A more accurate assessment of drug tolerance would derive from estimates of the fraction of subjects who refuse a second treatment after a having received a first. In fact, most patients with an option to receive subsequent doses of study agent appeared to agree to re-treatment.

Evidence of Systemic Spread of Toxin Effect: There were no events containing including multiple symptoms (such as respiratory failure, paralysis, the need for intensive inpatient care, etc.) suggestive of broad systemic botulinum toxin poisoning within the incobotulinumtoxinA development program for blepharospasm or CD. One patient experienced dysphagia following injection of incobotulinumtoxinA for upper limb spasticity, suggesting distant spread. The review team recommended that the Boxed

Warning describing systemic spread contained in the label of other botulinum toxin class members also be included in the incobotulinumtoxinA labeling.

Hyperglycemia: Blood glucose was examined closely due to a small elevation of blood glucose in treated versus placebo patients in the Dysport ® development program. There was no obvious signal in the incobotulinumtoxinA development program indicating hyperglycemia.

Overall, the frequency or type of serious and non-serious adverse events seemed consistent with the underlying diseases and patient demographics, and consistent with other botulinum toxins. As noted above, there was a potential case of distant spread in a patient treated for spasticity, and all agree that the label should be consistent with the class in terms of warning statements.

Limitations:

Blepharospasm: For the blepharospasm indication, all subjects had been previously treated with Botox, and the prior experience (total dose; number of injections) was used as the basis for the starting dose of incobotulinumtoxinA. The Division made repeated efforts to encourage the applicant to enroll treatment-naïve subjects, but this never occurred. The inclusion of only subjects who were known responders to Botox functioned, in effect, as an enrichment strategy. Moreover, the starting incobotulinumtoxinA dose was based on the dose of Botox that was known to be effective, presumably providing greater probability of a successful outcome using the starting dose. Although both factors would be expected to lead to overestimation of the treatment effect relative to that in a botulinum toxin-naïve patient population, I agree with Dr. Katz, that approval of the BLA for CD for patients previously treated with Botox is reasonable at this time. The label is quite clear about use in patients previously treated with Botox, and the sponsor has agreed to a post-marketing commitment to study adult patients with blepharospasm who are botulinum toxin-naïve.

Cervical Dystonia: For the CD indication, as noted above, the applicant conducted only a fixed dose study of 120 and 240 U. There is no evidence that subjects gain additional efficacy from the higher dose, whereas we know that toxicity is dose-related. Thus, only the 120 U dose will be recommended in labeling.

Risk Evaluation and Mitigation Strategy (REMS):

Section 505-1 of the Federal Food, Drug, and Cosmetic Act 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)). As noted above, there is concern with all botulinum toxin products regarding the potential for serious adverse events related to systemic (distant) spread of botulinum toxin from the site of injection, producing symptoms consistent with botulism, and in rare cases, death. The risk seems greatest in children treated for spasticity, but symptoms have been reported in adults treated for spasticity and in

patients with underlying conditions that would predispose them to these symptoms. In most of the post-marketing reports of toxicity related to other botulinum toxins, patients received doses comparable to those used to treat neurologic conditions such as CD, or lower doses.

Upon the approval of incobotulinumtoxinA, there will be four botulinum toxin products approved in the US: three botulinum toxin type A products (onabotulinumtoxinA [Botox / Botox Cosmetic], abobotulinumtoxinA [Dysport], and this product), and one botulinum toxin type B product (rimabotulinumtoxinB [Myobloc]). These products have different potencies and different units of dosing, even for the same indication. In this setting, medication errors including overdosing and underdosing can occur due to the potential for healthcare providers to substitute one product for another and interchange dose units.

In accordance with section 505-1 of FDCA and under 21 CFR 208, the review team has opined that a Medication Guide is required for incobotulinumtoxinA, because incobotulinumtoxinA poses a serious and significant public health concern. The Medication Guide is necessary because: 1) patient labeling could help prevent serious adverse effects; and 2) there are serious risks that patients should be made aware of, because information concerning the risks could affect patients' decisions to use, or continue to use the product.

The review team, including pertinent staff from OSE, agrees that the elements of the REMS will be a Medication Guide, a communication plan, and a timetable for the submission of assessments of the REMS.

Postmarketing Requirements and Commitments:

The review team has recommended a number of post-marketing requirements and commitments enumerated in the Approval letter.

Conclusions:

For the reasons stated above, I am approving the incobotulinumtoxinA (Xeomin) BLA for the treatment of patients with CD, and for patients with blepharospasm who were previously treated with Botox. The agreed-upon labeling (including a Medication Guide), post-marketing requirements, post-marketing commitments, and REMS are outlined in the Approval Letter.