



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

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APR 30 2009

Re: Docket No. FDA-2008-P-0061

Dear Dr. Barbehenn, Dr. Lurie, Mr. Stark, and Dr. Wolfe:

This responds to your citizen petition dated January 23, 2008 (Petition), and supplement received on January 28, 2008 (Supplement). Your Petition requests that the Food and Drug Administration (FDA or Agency) immediately require the Biologics License Application (BLA) holders of all formulations of botulinum toxin to issue a Dear Health Care Professional (DHCP) letter to "alert physicians to serious problems, including hospitalizations and deaths, resulting from the spread of the toxin from the site of injection to other parts of the body" (Petition at 1). Your Petition also requests that FDA require BLA holders of botulinum toxin products to provide "additional warnings in the form of a black box" to product labeling regarding the risk of distant spread of the toxin effects from the site of injection and provide an FDA-approved Medication Guide for patients, to be dispensed by physicians at the time of injection. Your request is based on rates of dysphagia and muscle weakness in preapproval clinical trials and postmarketing adverse event reports of dysphagia, aspiration, and/or pneumonia.

We have carefully reviewed your Petition and the Supplement to your Petition enclosing references cited in the Petition. For the reasons described in detail in this response, your Petition is granted in part. We have notified the holders of the BLAs for botulinum toxin products that, pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the Act), the risk of spread of botulinum toxin effects from the site of injection should be included in the labeling of the products (including a boxed warning). We also have sent notification letters to inform the BLA holders for botulinum toxin products that a Risk Evaluation and Mitigation Strategy (REMS) (which must consist of a Medication Guide and Communication Plan, including a Dear Health Care Provider letter, and a timetable for submission of assessments) is necessary to ensure that the benefits of these products outweigh the risks in accordance with section 505-1(a)(2) of the Act.<sup>1</sup> In this manner, we are granting the requests in your Petition in part. As with all FDA-approved drug and biological products, FDA will continue to monitor and review available safety information related to licensed botulinum toxin products throughout the product lifecycles.

<sup>1</sup> The FDA-approved labeling for Dysport, which FDA approved on April 29, 2009, already contains information (including a boxed warning) regarding these risks as well as an approved REMS, which consists of a Medication Guide, a Communication Plan, and a timetable for submission of assessments.

## I. BACKGROUND

### A. Botulinum Toxins

Botulinum toxins are neurotoxic proteins produced by *Clostridium botulinum*, a group of spore-forming, anaerobic, gram-positive bacilli, and described as serotype A, B, C, D, E, F, or G. The different types of botulinum toxins impede, to varying degrees, the release of acetylcholine in the neuromuscular junction, which results in the interruption of neuromuscular transmission. This partial chemical denervation of the muscle results in muscle relaxation and paralysis.<sup>2</sup> Injection of a licensed botulinum toxin product into a muscle<sup>3</sup> may cause the affected muscle(s) to atrophy in the short term, but reinnervation of the muscle may occur as nerve transmission is restored through sprouting of new nerve endings and development of extrajunctional acetylcholine receptors.<sup>4</sup>

FDA has approved Biologic License Applications (BLAs) for two botulinum toxin type A products (Botox/Botox Cosmetic and Dysport) for clinical use. In December 1989, FDA approved Allergan, Inc.'s (Allergan) BLA 103000 for Botox for the treatment of strabismus (crossed eyes) and blepharospasm (spasm of the eyelids) associated with dystonia. In 2000, FDA approved Botox for the treatment of cervical dystonia (severe neck muscle spasms) in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia. In 2004, Botox was approved for the treatment of severe primary axillary hyperhidrosis (excess sweating) that is inadequately managed with topical agents. In 2002, FDA approved Allergan's supplemental BLA for Botox Cosmetic to temporarily improve the appearance of moderate-to-severe glabellar lines (frown lines between the eyebrows) in adult patients 65 years of age or younger.

FDA has approved a BLA for one botulinum toxin type B product (Myobloc) for clinical use. In December 2000, FDA approved Elan Pharmaceuticals' BLA 103846 for Myobloc for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia. The Myobloc BLA is currently held by Solstice Neurosciences, LLC (Solstice).

On April 29, 2009, FDA approved Ipsen's BLA 125274 for Dysport for the treatment of cervical dystonia and to temporarily improve the appearance of moderate-to-severe glabellar lines in adult patients younger than 65 years of age.

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<sup>2</sup> See, e.g., Taylor P. Agents Acting at the Neuromuscular Junction and Autonomic Ganglia. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. New York: McGraw-Hill, 2001, at 206; Hallett M. One Man's Poison – Clinical Applications of Botulinum Toxin. *N Engl J Med* 1999;341(2):118-120.

<sup>3</sup> As discussed in this section of the response, Botox also is licensed for treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents. Intradermal injection of Botox produces temporary chemical denervation of the sweat gland resulting in a local reduction in sweating (see Botox product labeling (approved July 19, 2004), available at <http://www.fda.gov/cder/foi/label/2004/103000s5050lbl.pdf>). However, references to *injection* of a botulinum toxin product in this response are intended to refer primarily to intramuscular injection.

<sup>4</sup> See Botox product labeling (approved July 19, 2004), available at <http://www.fda.gov/cder/foi/label/2004/103000s5050lbl.pdf>.

It is important to note that the relative potencies of the botulinum toxin products differ significantly within botulinum toxin type and among the different botulinum toxin types. The potency of botulinum toxin is measured in functional units that correspond to the calculated median intraperitoneal lethal dose (LD<sub>50</sub>) in mice. Clinical doses range widely depending on the size of the muscle to be treated, the degree of muscle weakness required, and the specific botulinum toxin product used (the potency expressed in *Units* or *U* is not comparable from one botulinum toxin product to another). Although we may not distinguish between botulinum toxin products in this Petition response because the safety issues apply to all, we do not intend to suggest that the three licensed botulinum toxin products are interchangeable.<sup>5</sup>

## **B. Spread of Botulinum Toxin Effects**

Botulism is a serious bacterial toxin-mediated neuromuscular illness whose onset is typically marked by cranial nerve dysfunction (resulting in double vision (diplopia), inability to control or coordinate the muscles used in speaking (dysarthria), and/or difficulty swallowing (dysphagia)), followed by progressive descending muscle weakness or paralysis that can lead to respiratory failure and death.<sup>6</sup> The botulism syndromes may result from absorption of botulinum toxin through a mucosal membrane (intestine or lungs) or from a wound.<sup>7</sup> The clinical use of licensed botulinum toxin products presents the potential for *iatrogenic botulism*, which may be described as the appearance of one or more clinical manifestations of botulism that has the potential to be clinically serious.<sup>8</sup>

Local extension of effect of the botulinum toxin to anatomical structures (nerves and muscles) adjacent (contiguous) to the site of injection may occur and is described in product labeling.<sup>9</sup> For example, dysphagia (difficulty swallowing) is described in product labeling as a “commonly reported adverse event following treatment with all botulinum toxins in cervical dystonia

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<sup>5</sup> We have also informed the BLA holders for botulinum toxin products that a REMS is necessary to ensure that the benefits of these products outweigh the potential for serious risks associated with the lack of interchangeability among the three botulinum toxin products.

<sup>6</sup> See Abrutyn E. Botulism. In *Harrison's Principles of Internal Medicine*, 16<sup>th</sup> ed. New York: McGraw-Hill, 2005, at 920-922.

<sup>7</sup> See Abrutyn E. Botulism. In *Harrison's Principles of Internal Medicine*, 16<sup>th</sup> ed. New York: McGraw-Hill, 2005, at 920-922; see also Sobel J. Botulism. *Clin Infect Dis* 2005;41(8):1167-1173.

<sup>8</sup> We note that there is a lack of uniformity in the terminology used to characterize this adverse event associated with use of botulinum toxin products. Clinical seriousness may be considered with unintended extension of the toxin's neuromuscular blockade effects to anatomical structures beyond the targeted treatment site, whether these structures are contiguous or noncontiguous with the site of injection.

<sup>9</sup> See Botox product labeling (approved July 19, 2004) (stating “[l]ocal weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin”), available at <http://www.fda.gov/cder/foi/label/2004/103000s50501bl.pdf>; see also Botox Cosmetic product labeling (approved April 12, 2002), available at <http://www.fda.gov/cder/foi/label/2002/botuall041202LB.pdf>.

patients.”<sup>10</sup> However, dysphagia may also be a sign of distant spread of botulinum toxin effects when the botulinum toxin is administered at a site other than the neck.

In this Petition response, we are focusing our discussion primarily on distant spread of the botulinum toxin effects from the site of injection resulting in systemic symptoms of botulism. We are using the term *distant spread of botulinum toxin effects* to describe the unintended extension of the toxin’s neuromuscular blockade effects to anatomical structures that are noncontiguous with the site of injection. The mechanism by which distant spread of the toxin effects occurs has not been established.<sup>11</sup> We note, however, that any spread of the toxin beyond the intended site of action can cause serious adverse effects.

In February 2008, FDA issued an *Early Communication About an Ongoing Safety Review* (Early Communication) describing our review of postmarketing cases from the Adverse Event Reporting System (AERS) database and from the medical literature of pediatric and adult patients diagnosed with botulism following local injection with a marketed botulinum toxin product. The Early Communication alerted the public to:

... reports of systemic adverse reactions including respiratory compromise and death following the use of botulinum toxins types A and B for both FDA-approved and unapproved uses. The reactions reported are suggestive of botulism, which occurs when botulinum toxin spreads in the body beyond the site where it was injected. The most serious cases had outcomes that included hospitalization and death, and occurred mostly in children treated for cerebral palsy-associated limb spasticity. Use of botulinum toxins for treatment of limb spasticity (severe arm and leg muscle spasms) in children or adults is not an approved use in the [United States]<sup>12</sup>

Although current product labeling for Botox, Botox Cosmetic, and Myobloc contains a WARNINGS section advising physicians that patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects, including severe dysphagia and respiratory compromise, after local injection of typical doses of botulinum toxin, the Early Communication described evidence suggesting that “similar, potentially life-threatening systemic toxicity from the use of botulinum toxin products can also result after local injection in patients with other underlying conditions such as those with cerebral palsy associated limb spasticity.”

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<sup>10</sup> Myobloc product labeling (approved December 8, 2000), available at <http://www.fda.gov/cder/foi/label/2000/botelan120800lb.pdf>; see also Botox and Botox Cosmetic product labeling. The labeling further advises: “[In the medical literature,] there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.”

<sup>11</sup> See, e.g., Roche N, Schnitzler A, Genet F, et al. Undesirable Distant Effects Following Botulinum Toxin Type A Injection. *Clin Neuropharmacol* 2008;31:272-280.

<sup>12</sup> Early Communication about an Ongoing Safety Review: Botox and Botox Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum toxin Type B) (posted February 8, 2008), available at [http://www.fda.gov/cder/drug/early\\_comm/botulinium\\_toxins.htm](http://www.fda.gov/cder/drug/early_comm/botulinium_toxins.htm).



To further evaluate this emerging drug safety issue,<sup>13</sup> we requested that the BLA holders of the Botox, Botox Cosmetic, and Myobloc BLAs provide FDA with any available information from clinical trials, observational studies, published literature, and postmarketing reports of serious and nonserious adverse events related to distant spread of botulinum toxin effects, including cases of botulism or suspected botulism, in adults and children. In addition, FDA considered data from clinical trials involving Dysport and international post-marketing experience describing serious and nonserious adverse events consistent with the spread of botulinum toxin effects.

FDA has completed its review of the BLA holders' submissions and its independent analysis of spontaneous adverse event reports submitted to the AERS database (see section II.A of this response). FDA also has completed its review of published literature describing adverse events associated with use of botulinum toxin for treatment of cerebral palsy-associated spasticity in pediatric patients, an unapproved use. We are presenting our current findings and describing the regulatory actions that we have taken in an Update to the Early Communication as well as in this Petition response. FDA will continue to monitor and review safety information related to botulinum toxin products and evaluate new data submitted by the BLA holders in accordance with the proposed Risk Evaluation and Mitigation Strategies (REMS) described in sections II.B-D of this response and required postmarketing clinical trials.

### **C. Regulations and Guidance on Warnings in Prescription Drug and Biological Product Labeling and Other Relevant Safety Communications**

#### **1. *Warnings and Precautions and Boxed Warnings***

FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug and biological product labeling (including the product's package insert) must describe clinically significant adverse reactions,<sup>14</sup> other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (21 CFR 201.57(c)(6)(i); see also 21 CFR 201.80(e) through (f)). Labeling must be revised to include a warning as soon as there is reasonable evidence of a causal association of a clinically significant hazard with the product. For products described in § 201.56 (21 CFR 201.56), a summary of the most clinically

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<sup>13</sup> The term *drug* as used in this response generally refers to all drug and biological products reviewed by the Center for Drug Evaluation and Research (CDER).

<sup>14</sup> Section 201.57(c)(7) defines *adverse reaction* as an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. FDA's draft guidance for industry entitled *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Warnings Draft Guidance) (at 11) defines *serious adverse reaction* as any reaction occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect (see also definition of *serious adverse experience* at 21 CFR 600.80(a)). The Warnings Draft Guidance (at 2) states that the clinically significant adverse reactions observed in association with use of a drug that should be listed in the WARNINGS AND PRECAUTIONS section (see § 201.57(c)(6)) include those involving a serious adverse reaction, an adverse reaction that is otherwise clinically significant (e.g., requires discontinuation, could be prevented with appropriate patient selection, significantly affects patient compliance), and product interference with a laboratory test. (Guidances are available on FDA's Web site at <http://www.fda.gov/cder/guidance/index.htm>. The Warnings Draft Guidance, when finalized, will represent FDA's current thinking on this topic.)

significant warnings and precautions information must be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION (HIGHLIGHTS) for the product (§ 201.57(a)(10)).

Under § 201.57(c)(1), a boxed warning (sometimes referred to as a *black box warning*) may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury (see also § 201.80(e)). A boxed warning must contain, in uppercase letters, a heading that includes the word “WARNING” and conveys the general focus of information in the box. A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section (§ 201.57(c)(1)). A summary of a boxed warning (with the heading WARNING and other words identifying the subject of the warning) must be included in the HIGHLIGHTS in a box and in bold type (21 CFR 201.56(d)(1) and 201.57(a)(4)).

FDA’s Warnings Draft Guidance (at 9) states that a boxed warning ordinarily is used to highlight one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug, or
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), or
- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted.

The Warnings Draft Guidance also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber (at 9).

## 2. *Medication Guides*

A Medication Guide is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208 and other applicable regulations. The Agency will require a manufacturer of a prescription drug product to develop a Medication Guide for distribution by physicians to patients when we determine that the drug product poses a serious and significant public health concern and that patient labeling is needed to ensure the safe and effective use of the product (§ 208.1(a) and (b)). Under § 208.1(c), we will require a Medication Guide when we determine that one or more of the following circumstances exist:

- The drug product is one for which patient labeling could help prevent serious adverse effects.
  - The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
  - The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.
3. *Postapproval Labeling Changes and Risk Evaluation and Mitigation Strategies (REMS) Based on New Safety Information*

Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the Federal Food, Drug, and Cosmetic Act (the Act) to authorize FDA to require holders of approved drug and biological product applications to make safety labeling changes for an approved drug based on new safety information<sup>15</sup> that becomes available after the approval of the drug (section 505(o)(4) of the Act (21 U.S.C. 355(o)(4))).

Section 901 of FDAAA also added section 505-1(a)(2) of the Act (21 U.S.C. 355-1(a)(2)), which authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) for an approved drug product if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh its risks.<sup>16</sup>

## II. DISCUSSION

### A. Botulinum Toxin Product Labeling

Your Petition states that botulinum toxin product labeling “must be updated to consistently emphasize that distant spread is possible, that fatal cases have occurred and that the cosmetic form of botulinum toxin also carries dangers of dysphagia and aspiration” (Petition at 10). In support of your request, you reference: (1) rates of dysphagia and muscle weakness reported in randomized, placebo-controlled clinical trials submitted in support of licensure of Botox, Botox Cosmetic, and Myobloc; (2) a previously published analysis by FDA staff of adverse events

<sup>15</sup> As defined in section 505-1(b)(3) of the Act, *new safety information* is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.

<sup>16</sup> Section 505-1(a)(1)(A) through (F) of the Act states that in making a determination on whether a REMS is needed, the Agency considers the following factors: (1) the estimated size of the population likely to use the drug involved, (2) the seriousness of the disease or condition that is to be treated with the drug, (3) the expected benefit of the drug with respect to such disease or condition, (4) the expected or actual duration of treatment with the drug, (5) the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug, and (6) whether the drug is a new molecular entity.

associated with botulinum toxin products; and (3) your analysis of reports of dysphagia, aspiration, and/or pneumonia submitted to the FDA Adverse Event Reporting System (AERS) database. You contend that “the information currently provided to both U.S. patients and physicians is deficient compared to that in the [European Union]” (Petition at 10; see also Petition at 4). However, you acknowledge that “[m]ost of the information in the [European Union] label is present” in the FDA-approved labeling, although the information is presented throughout the product label and does not appear together in one section (see Petition at 4).

Your Petition requests that FDA require “additional warnings in the form of a black box” in product labeling for botulinum toxin products (Petition at 1). However, you also note that the European Union also has not required a boxed warning to date (see Petition at 10).

*FDA Response:*

Based on our review and analysis of AERS reports, postapproval clinical trial data, and published literature related to distant spread of botulinum toxin effects from the site of injection, we have concluded that labeling for all botulinum toxin products should be updated to include a boxed warning describing postmarketing safety data on distant spread of the toxin effects in children and adults following injection of botulinum toxin. As discussed in further detail in section II.A.2 of this response, the risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In addition, we have concluded that the labeling for Botox, Botox Cosmetic, and Myobloc should be updated to include strengthened warnings regarding the spread of toxin effect beyond the site of local injection and regarding dysphagia and breathing difficulties in the treatment of cervical dystonia and pre-existing neuromuscular disorders. Pursuant to our authority in section 505(o)(4) of the Act, we have notified the BLA holders for Botox, Botox Cosmetic, and Myobloc that we have become aware of new safety information regarding these serious risks that we believe should be included in the labeling of the products. In addition, FDA will continue to monitor and review available safety information related to all of the botulinum toxin products, including data submitted as part of the postmarketing clinical trial we are also requiring under section 505(o)(3) of the Act. Below is an analysis of each of the specific issues raised in the Petition in support of your requests.

1. *Dysphagia and Breathing Difficulties Associated with Botulinum Toxin Administration in the Treatment of Cervical Dystonia*

You state that “[p]re-approval clinical studies provide ample proof that botulinum toxin can cause dysphagia” and reference the rates of dysphagia and muscle weakness reported in randomized, placebo-controlled clinical trials submitted in support of licensure of Botox, Botox Cosmetic, and Myobloc (Petition at 6, 7). You also reference a published article by Dr. Timothy R. Côté and others describing FDA staff’s review of the AERS database for serious adverse events associated with botulinum toxin type A, including reports of severe dysphagia. You assert that these adverse event data “emphasize that, although dysphagia was more common in therapeutic than cosmetic clinical trials (presumably due to higher doses and, for many

indications, greater proximity to the esophagus), cosmetic cases have been reported and some have been serious” (Petition at 7 to 8).

### *FDA Response*

The cases of dysphagia reported in the randomized, placebo-controlled clinical trials supporting licensure of Botox and Myobloc occurred in patients treated with botulinum toxin for cervical dystonia. As noted in the Petition, there were “no cases of dysphagia in either the treated or placebo groups” in the clinical trials supporting licensure of Botox Cosmetic for temporary improvement in the appearance of moderate-to-severe glabellar lines (see Petition at 7). Dysphagia is a common, labeled, and well-recognized adverse effect of botulinum toxin when used to treat cervical dystonia (see section I.B of this response). The WARNINGS section of current product labeling for botulinum toxin products states, in relevant part:

Dysphagia is a commonly reported adverse event following treatment with all botulinum toxins in cervical dystonia patients. [In the medical literature,] there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died... Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of [botulinum toxin].<sup>17</sup>

We note that the occurrence of dysphagia in patients treated with botulinum toxin for cervical dystonia may reflect local effects of the toxin at adjacent muscle groups, and is not considered a symptom of distant spread of the toxin effects to noncontiguous structures from the site of injection.<sup>18</sup> The incidence of dysphagia reported in preapproval clinical trials is currently described in product labeling, and additional risk information regarding dysphagia based on the location and dose of botulinum toxin is provided in the PRECAUTIONS section of Botox product labeling.

Similarly, reports of muscle weakness in preapproval clinical trials for Botox Cosmetic are currently described in product labeling and were not considered symptomatic of distant spread of the toxin effects to noncontiguous areas. The product labeling for Botox Cosmetic advises: “While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months.”

FDA’s review of the AERS database from December 1989 (date of initial licensure of Botox) through May 2003 for reports of serious adverse events associated with use of botulinum toxin

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<sup>17</sup> Myobloc product labeling; see also Botox and Botox Cosmetic product labeling.

<sup>18</sup> The ADVERSE REACTIONS section of Botox product labeling notes: “Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles.”



type A for neurologic or dermatologic use is presented in the Coté article<sup>19</sup> (see section II.A.2 of this response for a discussion of FDA's more recent analyses of spontaneous adverse event reports in the AERS database). Dr. Coté and colleagues described 217 serious adverse experiences (as defined in 21 CFR 600.80),<sup>20</sup> including 28 deaths, 26 reports of dysphagia associated with therapeutic use, and 2 reports of dysphagia associated with "cosmetic use."<sup>21</sup> The authors noted that "[m]any of the AEs [adverse events] reported after use of BTA [botulinum toxin type A] were biologically plausible; for example dysphagia and ptosis occurred after injections near the throat and eyes, respectively. . . . These pharmacologically predictable AEs linked to tissue diffusion of BTA constituted a large share of reports to the FDA for BTA."<sup>22</sup> The article concluded that "[s]erious AEs were more likely to be reported for therapeutic than for cosmetic use, which may be related to higher doses, complicated underlying diseases, or both."<sup>23</sup>

Although our current review focused on distant spread of botulinum toxin effects from the site of injection, based in part on this review we also are requesting revisions to product labeling to strengthen current warnings regarding dysphagia and breathing difficulties in patients treated with botulinum toxin for cervical dystonia, and to emphasize that (local) spread of botulinum toxin effects beyond the site of injection may be associated with serious adverse events.

## 2. *Distant Spread of Botulinum Toxin Effects from the Site of Injection*

Your Petition states that "spread of toxin has been implicated in serious adverse events including muscle weakness, dysphagia . . . , and aspiration pneumonia, the latter sometimes resulting in death" (Petition at 1). In the Petition, you provide your own analysis of spontaneous adverse event reports in the AERS database of dysphagia, pneumonia (searched using the truncated term "pneumon\*" as the *Medical Dictionary for Regulatory Activities* (MedDRA) Preferred Term), and aspiration (searched using the truncated term "aspir\*" as the MedDRA Preferred Term) associated with the use of Botox, Botox Cosmetic, Myobloc, or "botulinum" toxin (Petition at 8 to 9). Based on your analysis, you conclude that during the period from November 1, 1997, through December 31, 2006, there were 180 adverse event reports submitted by drug

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<sup>19</sup> Coté TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type A injections: Adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. *J Am Acad Dermatol* 2005; 53:407-415 (Coté article).

<sup>20</sup> As defined in 21 CFR 600.80(a), *serious adverse experience* means "[a]ny adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

<sup>21</sup> Coté article at 412, Table II. We note that the Coté article uses the term "cosmetic use" to describe the approved dermatologic use for temporary improvement in the appearance of glabellar lines and unapproved uses for other facial wrinkles (see Coté article at 411, Table I). The Coté analysis predates the 2004 approval for treatment of severe primary axillary hyperhidrosis, another dermatologic use.

<sup>22</sup> Coté article at 410.

<sup>23</sup> Coté article at 407.

manufacturers associated with aspiration, dysphagia, or pneumonia where botulinum toxin was listed as the primary suspect medication, including 87 cases with an outcome of hospitalization and 16 cases with an outcome of death (Petition at 8 to 9). In Table 2 of the Petition, you provide partial information regarding 16 deaths reported to the AERS database, and you note that one of these cases was associated with use of Botox for “skin wrinkling”<sup>24</sup> (see Petition at 8 to 9). You acknowledge certain limitations to your analysis of AERS reports for purposes of evaluating adverse events related to distant spread of the botulinum toxin effects from the site of injection, including the inability to prove causality of the reported adverse event, underreporting, and nonexhaustive search criteria (see Petition at 9).

### *FDA Response*

Although you have identified several adverse event reports that we consider suggestive of distant spread of botulinum toxin effects (see discussion below), we note that the search criteria that you used to identify serious adverse event reports in the AERS database representing distant spread of botulinum toxin effects lack adequate sensitivity (because other symptoms of distant spread of botulinum toxin effects such as weakness, dysarthria, ptosis, and diplopia are not included) and specificity (because aspiration, dysphagia and pneumonia can occur without distant spread of botulinum toxin effects). As discussed in sections I.B and II.A.1 of this response, dysphagia is a common, labeled, and well-recognized local adverse effect of injection of botulinum toxin for treatment of cervical dystonia. Stratification of adverse event reports by indication and/or site of injection would be needed to evaluate distant spread of toxin effects. In addition, aspiration and pneumonia are common complications of the underlying neurologic diseases that comprise a substantial subpopulation of the patients who are treated with botulinum toxin. Review of the details of each spontaneous case report is necessary to evaluate whether the report may suggest distant spread of botulinum toxin effects and assess whether the AERS search has identified a safety signal that may warrant further investigation.

#### *a. FDA review of adverse event reports and published literature*

We have conducted several searches of the AERS database to identify serious adverse event reports suggestive of distant spread of the toxin effects from the site of injection, including a search (discussed below) that predates submission of your Petition. As a preliminary matter, it should be noted that there are inherent limitations to a voluntary reporting system for adverse events associated with the use of a drug or biological product, including but not limited to, underreporting, duplicate reporting, and reporting biases. Further, for any given report, the reported adverse event(s) may not be causally related to the product(s) reported to have been taken. The event may have been related, for example, to the underlying disease being treated, to other medical conditions, or to another product taken at the same time.

In response to two serious case reports of botulism in pediatric patients administered botulinum toxin to treat muscle spasticity associated with cerebral palsy, an unapproved use, we performed a search of the AERS database from December 1989 (date of approval of the first licensed botulinum toxin product (Botox)), through July 13, 2007, for reports coded with the MedDRA

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<sup>24</sup> The AERS report described this case more specifically as involving use of botulinum toxin for glabellar lines, an approved use, and forehead area lines and “crow’s feet” (lateral canthal lines), both of which are unapproved uses.

Preferred Term of *botulism* in adult patients and pediatric patients (age 16 years or younger) and for reports of all adverse events in pediatric patients. From the 13 reports of *botulism* in adults, we excluded the following 6 cases from our analysis: 1 foreign case that was described as attributable to food poisoning, 1 case in which the symptoms resembled chronic neurologic events rather than an acute case of botulism, and 4 cases of misuse of a highly concentrated, unlicensed preparation of botulinum toxin type A.<sup>25</sup> This resulted in 7 reports (6 United States (U.S.), 1 Foreign) for further evaluation.<sup>26</sup> Six of the seven reports involved patients who were being treated for neurologic indications, including two that were treated for unapproved uses. Five of the seven patients had underlying neurologic conditions, which may have been related to the reported adverse event. Patients who had received botulinum toxin injections in the head, neck and shoulder areas described dysphagia, speech problems, ptosis, and difficulty holding their heads up. These events could reflect regional diffusion of the toxin, which is consistent with current product labeling. There were two patients who were administered botulinum toxin in the cervical areas who described symptoms of weakness and numbness in the lower extremities, which suggests a systemic effect. There was one adult case report describing potential systemic symptoms of “botulism” one day after administration of 20 units of the toxin for temporary improvement in the appearance of glabellar lines, an approved use, and periorbital lines (lines around the eye), an unapproved use; however, this case was potentially confounded by a concurrent viral illness.

There were 8 reports (7 U.S., 1 Foreign) of botulism in pediatric patients administered botulinum toxin, all of whom had cerebral palsy and were treated for muscle spasticity (an unapproved use).<sup>27</sup> Seven of the eight cases<sup>28</sup> reported serious outcomes (requiring interventions such as mechanical ventilation, tracheostomy, gastric tube feeding, and pyridostigmine), including one foreign report of botulism resulting in death that also is reported in the literature.<sup>29</sup> The AERS search of all adverse event reports in pediatric patients (range: 18 months to 16 years of age) identified 9 other cases (6 U.S., 3 Foreign) with an outcome of death (including the pediatric cases described in Table 2 of the Petition) and 66 reports of hospitalization. All of the pediatric patients who died had underlying neuromuscular disorders, including several patients who had swallowing difficulties prior to starting treatment with

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<sup>25</sup> See Chertow DS, Tan ET, Maslanka SE, et al. Botulism in 4 Adults Following Cosmetic Injections With an Unlicensed, Highly Concentrated Botulinum Preparation. *JAMA* 2006;296(20):2476-2479.

<sup>26</sup> We note that the number of cases reported to FDA’s AERS database cannot be used to calculate incidence rates, to estimate drug risk for a particular product, or to compare risks between products. Due to limitations of available product utilization data, FDA did not calculate an estimated reporting rate for adverse events associated with botulinum toxin use.

<sup>27</sup> See also Crouner BE, Brunstrom JE, Racette BA. Iatrogenic botulism due to therapeutic botulinum toxin A injection in a pediatric patient. *Clin Neuropharmacol* 2007;30(5):310-313; Howell K, Selber P, Graham HK, Reddihough D. Botulinum neurotoxin A: an unusual systemic effect. *J Paediatr Child Health* 2007;43(6):499-501. These articles described case reports that were not available in AERS at the time of FDA’s database search and were identified by FDA in a subsequent review of the literature.

<sup>28</sup> See Partikian A, Mitchell WG. Iatrogenic botulism in a child with spastic quadriplegia. *J Child Neurol* 2007;22(10):1235-1237; Goldstein EM. Safety of high-dose botulinum toxin type A therapy for the treatment of pediatric spasticity. *J Child Neurol* 2006;21(3):189-192.

<sup>29</sup> See Beseler-Soto B, Sánchez-Palomares M, Santos-Serrano L, et al. [Iatrogenic botulism: a complication to be taken into account in the treatment of child spasticity.] *Rev Neurol* 2003;37(5):444-446 [Article in Spanish].

botulinum toxin and two patients with underlying seizure disorders. The reported causes of death were cardiorespiratory arrest (4 cases, 2 of which included suspected aspiration), seizures (2 cases), fatal arrhythmia (1 case), pneumonia (1 case), and stroke (1 case).

We also performed a separate search of the AERS database from December 1989 (date of approval of the first licensed botulinum toxin product (Botox)), through March 20, 2008, for reports with an outcome of death to identify cases of potential iatrogenic botulism associated with administration of botulinum toxin in adults. This search identified 58 unduplicated cases of death from any cause, of which 17 (9 U.S., 8 Foreign) reports were suggestive of potential iatrogenic botulism. The AERS reports for adults listed in Table 2 of the Petition were among the 58 cases of death from any cause that we reviewed. We note that certain adult patient reports listed in Table 2 of the Petition were not suggestive of potential iatrogenic botulism and were excluded from subsequent analysis. Although most of the 17 reports in our case series described underlying neuromuscular disorders with preexisting dysphagia, choking, and/or pneumopathies (pulmonary disorders), a potential association between use of botulinum toxin and symptoms consistent with iatrogenic botulism could not be excluded. These cases reported a temporal relationship between administration of botulinum toxin and one or more symptoms (e.g., muscle paralysis with dysphagia and secondary fatal respiratory failure) that is consistent with the pharmacologic mechanism of action (chemical denervation) of the toxin. However, given that the patients suffered from complications of other conditions, we cannot determine whether the administration of botulinum toxin was a causal factor in the outcome of death. The doses reported in these cases ranged from 22 units to 500 units for Botox and 2,500 U to 30,000 U (overdose) for Myobloc. Although two (1 U.S., 1 Foreign) of the 17 reports described use of botulinum toxin for dermatologic uses, neither report clearly suggested an adverse event attributable to the toxin. In the first report, the course of the patient's flu-like symptoms (beginning more than 3 weeks after botulinum toxin administration, with respiratory distress and staphylococcal pneumonia several weeks later) did not clearly suggest aspiration due to spread of botulinum toxin. In the second report, the patient had a diagnosis of Guillain-Barré syndrome with cytomegalovirus (CMV) infection. These two cases were included in our case series because they met our threshold search criteria, and our review was intended to encompass all cases that reported symptoms consistent with potential iatrogenic botulism.

To identify and evaluate reports of serious adverse events that may have reflected symptoms consistent with potential iatrogenic botulism but were not reported using the Preferred Term *botulism* or described in patients with an outcome of death, we performed a separate search of the AERS database from December 1989 (date of approval of the first licensed botulinum toxin product (Botox)) through December 22, 2008, for reports with an outcome of hospitalization or a life-threatening event that included other higher level Preferred Terms reflecting symptoms of botulism. This search identified 33 unduplicated cases (21 U.S., 11 Foreign, 1 source not reported) in patients treated for neurologic (22 cases) and dermatologic (10 cases) conditions.<sup>30</sup> These cases reported dysphagia, difficulty breathing, muscle weakness, generalized weakness, or other symptoms preceding a diagnosis of Guillain-Barré syndrome (7 cases) and spread of botulinum toxin effects (26 cases). Of the latter, 13 patients experienced respiratory disorders, including seven patients who required ventilator support.

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<sup>30</sup> The indication for use of botulinum toxin was unreported for one case.



In addition, we reviewed submissions by the BLA holders of the botulinum toxin products licensed at that time (Botox, Botox Cosmetic, and Myobloc) in response to our request for serious and nonserious adverse event reports coded with sentinel terms for spread of toxin effects and meeting prespecified criteria.<sup>31</sup> These submissions included information from clinical trials, observational studies, published literature, and postmarketing data for pediatric and adult patients. FDA's review of the submissions from Allergan and Solstice and FDA's literature review and searches of the AERS database through March 20, 2008, (described earlier in this section of the response), identified 225 case reports that described signs and symptoms consistent with the pharmacologic effects of botulinum toxin at sites noncontiguous and distant from the site of injection.

### 3. *FDA Safety-related Labeling Actions*

Based on our analysis of reports in the AERS database, relevant clinical trial data, and published literature, we have notified the holders of the BLAs for botulinum toxin products that we believe that new safety information regarding spread of botulinum toxin effects from the site of injection (including a boxed warning) should be included in the labeling of the products (see section 505(o)(4) of the Act). At this time, we consider the addition of a boxed warning and a strengthened WARNINGS AND PRECAUTIONS section of product labeling, development of a Medication Guide (see section II.B of this response), and submission of a REMS that includes the Medication Guide and a Communication Plan (see section II.C of this response) to be the necessary steps to communicate with the health care community and with the public regarding the potential for clinically significant spread of botulinum toxin effects.

The Warnings Draft Guidance provides examples of situations in which a boxed warning may be needed to highlight important prescribing information. For example, a boxed warning may be used to highlight an "adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug" (see Warnings Draft Guidance at 9). Based on our current analysis of the data, we have concluded that a boxed warning under § 201.57(c)(1) or § 201.80(a), as applicable, is necessary for botulinum toxin products to highlight the potential severity of distant spread of toxin effects (including reports of death) and emphasize that symptoms consistent with systemic botulism can occur with treatment for a range of labeled and unlabeled conditions of use. Botulinum toxin effects may be observed beyond the site of local injection, resulting in symptoms (which may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties) in areas noncontiguous with the injection site that are consistent with the mechanism of action of botulinum toxin. Although we do not currently have recommendations for how to prevent these events, it is essential that the potential

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<sup>31</sup> We note that the Petition also described information provided by the European Medicines Agency (EMA) regarding adverse event reports for botulinum toxin products (see Petition at 2 to 3). The summary of the EMA findings describes a higher number of adverse events than those identified in the AERS database. This may reflect, in part, different search strategies or the approval of an additional botulinum toxin product in the European Union at the time of the search. However, the type of serious adverse events (including those attributed to *distant spread*) and nature of the serious cases are consistent across the EMA and FDA databases.



for distant spread of toxin effects be considered in assessing the risks and benefits of using botulinum toxin products (see Warnings Draft Guidance at 9).

The risk of clinically significant systemic adverse effects (including severe dysphagia and respiratory compromise from typical doses of botulinum toxin) in patients with preexisting neuromuscular disorders is described in current product labeling for botulinum toxin products. We have notified licensees that we believe that additional information about the spread of botulinum toxin effects beyond the site of local injection should be included in the WARNINGS or WARNINGS AND PRECAUTIONS section of product labeling, as applicable, to identify patients that may be at increased risk of clinically significant adverse events and for whom close monitoring may be required. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms.<sup>32</sup>

We note that product labeling is easier for health care professionals to access, read, and use in the updated format described by the Physician's Labeling Rule (PLR),<sup>33</sup> although conversion to PLR format is not required for Botox, Botox Cosmetic, and Myobloc at this time (see 21 CFR 201.56(c)).

The Petition suggests that the risk/benefit balance may differ between the dermatologic and neurologic indications. For the approved dermatologic use of temporary improvement in the appearance of glabellar lines (frown lines between the eyebrows), we have not identified any definitive serious adverse event reports of a distant spread of toxin effect producing symptoms consistent with botulism when the botulinum toxin products are used in accordance with the FDA-approved labeling. However, we note that there have been serious adverse events reported in association with the administration of botulinum toxin for dermatologic use that is not in accordance with approved product labeling. Based on our review of the data, it appears that the overall risk of serious adverse effects for the approved dermatologic indication of temporary improvement in the appearance of glabellar lines is lower than the risk of such adverse effects when botulinum toxin is used to treat its approved neurologic indications. This may be due to the site of injection (away from anatomical structures associated with swallowing and breathing) and the lower doses of toxin used. However, we caution that there is insufficient information to fully characterize the safety profile and potential risk factors for spread of botulinum toxin at this time, given that the mechanism by which spread may occur has not been confirmed. The serious adverse events associated with spread of the toxin are generally extensions of the known pharmacological effect of botulinum toxin. Based on available information, it is not possible to precisely predict the role of injection site, injection technique, or dose in the spread of toxin or severity of the event. Therefore, we are seeking safety labeling changes for the both the dermatologic and neurologic indications.

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<sup>32</sup> There are no botulinum toxin products approved in the United States for the treatment of spasticity in children or adults, although FDA is aware of the body of literature describing this unapproved use.

<sup>33</sup> See "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule" (71 FR 3922, January 24, 2006).

We recognize that botulinum toxin products have been used to treat a number of conditions not identified in current labeling. The overall safety and efficacy of the botulinum toxin products has not been established with respect to these unapproved uses and the maximum safe dose has not been determined. In light of the reports received by the Agency describing serious adverse events associated with the unapproved use of botulinum toxin to treat spasticity associated with cerebral palsy, we are requiring postmarketing clinical trials by all BLA holders of botulinum toxin products to assess the signal of serious risk regarding the distant spread of the toxin effects. Section 901 of FDAAA added authority for FDA to require, under certain circumstances, postmarketing studies and clinical trials.<sup>34</sup> FDA may require a postapproval study or postapproval clinical trial of an approved drug or biological product if FDA becomes aware of new safety information.<sup>35</sup> Pursuant to section 505(o)(3) of the Act, we are requiring all BLA holders of botulinum toxin products to collect safety data in a specified number of pediatric and adult patients treated for spasticity to assess the signal of serious risk regarding distant spread of toxin effects and signals of serious risks related to the effects on blood glucose and alkaline phosphatase as a marker of bone metabolism. We will continue to carefully monitor relevant data related to spread of the toxin effects, including data generated by the requested postmarketing trial and the BLA holders' periodic REMS assessments, which should include, among other things, a summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection, and may take additional regulatory action, if warranted.

## **B. Medication Guide**

Your Petition requests that FDA require the BLA holders of botulinum toxin products to provide mandatory FDA-approved Medication Guides to be dispensed by physicians at the time the product is injected. You have suggested that patient information is particularly important in the context of "cosmetic" use, given the different risk/benefit calculus as compared to a neurologic indication (see Petition at 10). You further note that "improved warnings to doctors and patients would increase the likelihood of earlier medical intervention when symptoms of adverse reactions to botulinum toxin first appear and could prevent more serious complications, including death" (Petition at 1).

### *FDA Response*

Based on our analysis of reports in the AERS database, relevant clinical trial data, and published literature, we have notified the BLA holders for licensed botulinum toxin products of the need to develop a Medication Guide for distribution by physicians to patients at the time the product is

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<sup>34</sup> Under section 505(o)(3)(D)(i) of the Act, before requiring a postmarketing study, FDA must find that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) will not be sufficient to meet the purposes described in section 505(o)(3)(B). In addition, under section 505(o)(3)(D)(ii), before requiring a postmarketing clinical trial, FDA must find that a postmarketing study will not be sufficient to meet the purposes described in section 505(o)(3)(B).

<sup>35</sup> Under section 505(o)(3)(A) through (B) of the Act, the requirement must be based on scientific data and is limited to the following purposes:

- (i) To assess a known serious risk related to the use of the drug involved.
- (ii) To assess signals of serious risk related to the use of the drug.
- (iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk.

injected. This reflects our determination that a REMS is necessary for these products in accordance with section 505-1(a)(1) and (2) of the Act, as applicable, to help ensure that the benefits of these products outweigh their risks, and that a Medication Guide should be an element of the REMS under section 505-1(e)(2)(A) of the Act. In accordance with 21 CFR 208.1(c)(1) and (c)(2), we have determined that botulinum toxin products pose serious and significant public health concerns requiring the distribution of a Medication Guide, and that these products have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, these products. The Agency also has determined that patient labeling for botulinum toxin products could help prevent the consequences of serious adverse events. We consider this Medication Guide to be part of the labeling for which safety labeling changes are necessary under section 505(o)(4) of the Act, as well as an element of a REMS under section 505-1(e)(2)(A) of the Act.

We have determined that a Medication Guide is an appropriate additional method of communicating the signs and symptoms of the spread of botulinum toxin effects to the patient or the caregiver. A Medication Guide can help ensure that the patient or caregiver is aware of and can self-monitor for serious risks that have been reported hours to weeks following the injection, and may increase the likelihood of earlier medical intervention (appropriate monitoring and treatment) if needed. Patients may require immediate medical attention if they develop problems with swallowing, speaking, or breathing, or if they have other symptoms of botulism such as loss of strength and muscle weakness, double vision, blurred vision and drooping eyelids; symptoms of dysphonia (hoarseness, change, or loss of voice) or dysarthria; or loss of bladder control. We have determined that patients' awareness of these risks may affect their decisions on whether to use or continue use of a botulinum toxin product. Issuance of a Medication Guide increases the likelihood that patients will receive the appropriate educational material and be aware of the risks associated with botulinum toxin products.

The PATIENT COUNSELING INFORMATION section of botulinum toxin product labeling will be revised to state that the physician should provide a copy of the FDA-approved Medication Guide and review the contents with the patient. In addition, this section of product labeling will be revised to summarize the most important adverse event information about the botulinum toxin product.

### **C. Issuance of a Dear Health Care Professional Letter**

Your Petition requests that FDA direct the BLA holders of botulinum toxin products to send a "warning letter" to physicians regarding all formulations of botulinum toxin products that would "alert physicians to serious problems, including hospitalizations and deaths, resulting from the spread of the toxin from the site of injection to other parts of the body" (Petition at 1).

#### *FDA Response*

Based on our analysis, we have determined that a REMS is necessary for botulinum toxin products in accordance with section 505-1(a)(2) of the Act to help ensure that the benefits of these products outweigh their risks, and that a Communication Plan should be one of the elements of the REMS under section 505-1(e)(3) of the Act. The Communication Plan would

include distribution of Dear Health Care Professional letters that describe the risks of potential distant spread of botulinum toxin effects after local injection and the lack of interchangeability of botulinum toxin products. The Dear Health Care Professional letters will be sent to neurologists, dermatologists, and other specialists and health care professional staff who prescribe or inject botulinum toxin products.

We also note that on April 30, 2009, we provided an Update to the Early Communication on FDA's Web site that informs health care professionals, patients, and other interested persons about serious adverse events related to distant spread of the toxin effects from the site of injection. This Update to the Early Communication also is distributed to an estimated 120,000 stakeholders through the Medwatch Partners program and the Medwatch listserve.

#### **D. Next Steps for Safety Labeling Changes and REMS Under FDAAA**

Our letters notifying BLA holders that we believe that the labeling for the botulinum toxin products should be modified to provide additional warnings and develop a Medication Guide were issued on April 29, 2009, based on our new authority with respect to safety labeling changes under section 505(o)(4) of the Act. As discussed in sections II.C and II.D of this response, based on the new safety information regarding distant spread of botulinum toxin effects from the site of injection (and lack of interchangeability of botulinum toxin products), the notification letters also informed the BLA holders for botulinum toxin products that a REMS is necessary for their products in accordance with section 505-1(a)(2) of the Act to help ensure that the benefits of these products outweigh their risks. The proposed REMS that each botulinum toxin BLA holder will submit must include a Medication Guide, Communication Plan (including, at a minimum, Dear Health Care Provider letters), and a timetable for submission of assessments of the REMS.

In accordance with section 505(o)(4) of the Act, the botulinum toxin BLA holders are required to submit by May 29, 2009, prior approval supplements containing the proposed labeling changes (including additional warnings, other labeling revisions, and the Medication Guide), or notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons why changes are not warranted. The botulinum toxin BLA holders also must submit a prior approval supplement containing a proposed REMS within 30 days of the notification letter.

If the botulinum toxin BLA holders do not submit proposed safety labeling changes, or if we disagree with the language that the companies propose, the Act provides strict timelines under section 505(o)(4) for discussions regarding the labeling changes. At the conclusion of these discussions, section 505(o)(4) also allows us to issue an order directing labeling changes as deemed appropriate to address the new safety information. We are awaiting the response of the botulinum toxin BLA holders, under these FDAAA procedures, to our notification that additional warnings, other revisions to product labeling, and a Medication Guide are necessary. The specific language we have recommended is subject to change depending on what language the BLA holders propose and their reasoning. Thus, we have not required specific labeling changes at this stage of the process under section 505(o)(4) of the Act. However, we have taken all the necessary steps that are required under the carefully prescribed procedures of FDAAA to pursue

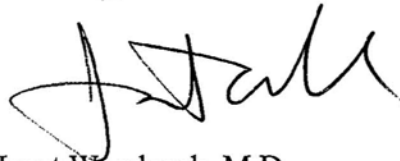
the necessary changes. In this manner, we are granting in part the requests for additional warnings and a Medication Guide.

### **III. CONCLUSION**

Based on our review and analysis of the data, your Petition is granted in part with respect to your request that we require the BLA holders of botulinum toxin products to provide additional warnings (including a boxed warning) in product labeling regarding the risk of distant spread of the toxin effects from the site of injection. Your request that we require a Medication Guide and Dear Health Care Professional letter are granted in part.

We will work with the BLA holders of botulinum toxin products through the FDAAA procedures to promptly implement the safety labeling changes that we have requested, including the Medication Guide and the REMS, to ensure that the benefits of these products outweigh their risks. We will continue to carefully monitor relevant safety data related to spread of the toxin effects, including data generated by the required postmarketing trial and periodic REMS assessments, and if necessary, we will take further action to address this concern.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', is written over a faint, larger signature that appears to read 'Janet Woodcock'.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research