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TAMING THE PERFECT POISON: A COMPARATIVE ANALYSIS OF THE EMEA'S EPAR SYSTEM AND THE FDA'S IMPROVED WARNING PROTOCOL

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Abstract: In Europe and the United States, regulatory agencies responsible for monitoring drug safety have struggled to address the health concerns raised by the burgeoning market for minimally invasive cosmetic procedures utilizing botulinum toxins, the active ingredients in Botox. A 2005 study published in the *Journal of the American Academy of Dermatology* drew attention to these shortcomings after an analysis of adverse event reports submitted to the Food and Drug Administration (FDA) linked twenty-eight patient deaths to Botox-induced respiratory arrest and myocardial infarction. After an independent review of adverse effects reports submitted to the European Medicines Agency (EMA) revealed similar findings in Europe, the FDA and EMA implemented bolstered product warnings aimed at increasing patient awareness of the drug's health risks. This Note compares the FDA and EMA's heightened warning protocols and argues that the agencies' recent efforts are unlikely to reduce the number of serious adverse events linked to botulinum toxins.

INTRODUCTION

The demand for minimally invasive cosmetic procedures utilizing botulinum toxins—the active ingredients in Botox—has exploded during the past decade in North America and Europe.¹ Nevertheless, at home and abroad, regulatory agencies charged with ensuring drug safety have struggled to address the health concerns associated with this

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¹ See MILLENNIUM RES. GROUP, EUROPEAN MARKETS FOR FACIAL AESTHETICS 2008 54–73 (2008); Press Release, Millennium Res. Group, Botox and Dermal Fillers Will Be Used by More than 6 Million Americans by 2011 (Feb. 7, 2007), available at <http://www.mrg.net/News-and-Events/Press-Releases/BOTOX-AND-DERMAL-FILLERS-WILL-BE-USED-BY-MORE-THAN.aspx>.

nascent area of medicine.² In 2005, a study published in the *Journal of the American Academy of Dermatology* (Coté Study) drew attention to these shortcomings after an analysis of adverse event reports submitted to the Food and Drug Administration (FDA) linked twenty-eight deaths to Botox-induced respiratory arrest and myocardial infarction.³ On the heels of this study, government watchdog groups petitioned the Agency to take stronger measures to protect patients.⁴ In 2009, the FDA responded by implementing a bolstered warning protocol mimicking the advisory system used by the European Medicines Agency (EMA), the FDA's European counterpart.⁵

It is unclear whether the FDA's recent efforts are sufficient to deal with the crisis currently facing the cosmetic medicine industry.⁶ Botulinum toxins are the deadliest naturally occurring substances in the world.⁷ Improperly injected, botulinum toxins can cause severe life-threatening complications.⁸ Nonetheless, regulations governing who may perform such injections are quite lax.⁹ In the United States, Botox

² See Bridget M. Kuehn, *Botox Risks Under Review*, 299 JAMA 1417, 1417 (2008); Constanze Löffler, *Die Heilsame Giftspritze*, FOCUS, Sept. 1, 2008, at 36; Lauran Neergaard, *Health Canada Reviews Safety of Botox After Deaths Reported*, TORONTO STAR, Feb. 9, 2008, at A02.

³ See Timothy R. Coté et al., *Botulinum Toxin A Injections: Adverse Events Reported to the US Food and Drug Administration in Therapeutic and Cosmetic Cases*, 53 J. AM. ACAD. DERMATOL. 407, 409 (2005).

⁴ See, e.g., Press Release, Pub. Citizen Health Res. Group, Petition to the FDA Requesting Regulatory Action Concerning the Possible Spread of Botulinum Toxin (Botox, Myobloc) from the Site of Injection to Other Parts of the Body (HRG Publication #1834) (Jan. 23, 2008), available at <http://www.citizen.org/publications/release.cfm?ID=7559>.

⁵ See *id.*; Bridget M. Kuehn, *FDA Requires Black Box Warnings on Labeling for Botulinum Toxin Products*, 301 JAMA 2316, 2316 (2009).

⁶ See generally Peter Conrad, *The Pursuit of Perfection: The Promise and Perils of Medical Enhancement*, 292 JAMA 867 (2004) (concluding that regulatory agencies have ignored health risks associated with the cosmetic medicine industry).

⁷ See Carl Lamanna, *The Most Poisonous Poison*, 130 SCI. 763, 766 (1969) (observing that "other protein poisons, such as diphtheria toxin and animal venoms, are hundreds and tens of thousands of times less poisonous" than botulinum toxins); Robert Schechter, *Extreme Potency of Botulinum Toxin*, 355 LANCET 237, 237 (2005).

⁸ See, e.g., Daniel S. Chertow et al., *Botulism in 4 Adults Following Cosmetic Injections with an Unlicensed, Highly Concentrated Botulinum Preparation*, 296 JAMA 2476, 2476, 2478 (2006).

⁹ See MED. BD. OF CAL., USE OF MID-LEVEL PRACTITIONERS FOR LASER, DERMABRATORS, BOTOX, AND OTHER TREATMENTS, ACTION REPORT 1, 9 (2006); Memorandum from the Meds. and Healthcare Regulatory Agency on the Supply and Admin. of Botox, Vistabel, Dysport and Other Injectable Medicines in Cosmetic Procedures (Jan. 10, 2008), available at <http://www.mhra.gov.uk/Howweregulate/index.htm> (follow "Medicines" hyperlink; then follow "Availability, Prescribing, Selling and Supplying of Medicines" hyperlink; then follow "Frequently Raised Issues" hyperlink; then follow "Botox, Vistabel, Dysport and Other Injectable Medicines in Cosmetic Procedures" hyperlink) [hereinafter MHRA Botox]; Memorandum from Mo. Bd. of Registration for the Healing Arts on Med. Spas, Lasers, and Botox

may be injected by non-physician practitioners in the absence of direct doctor supervision.¹⁰ In Great Britain, the Medicines and Healthcare Products Regulatory Agency even permits patients to perform self-administered injections.¹¹

This Note compares and evaluates the adequacy of safety regulations imposed by the FDA and EMEA on manufacturers of botulinum toxin products. In particular, this Note addresses the sufficiency of the FDA's improved warning protocol as a method of reducing the incidence of serious adverse events related to botulinum toxin type A (Botox). Part I traces the history of botulinum toxin use and its emergence as a drug for cosmetic indications. Part II discusses the Coté Study's independent review of adverse event reports submitted to the FDA in connection with botulinum toxin type A. This section also canvasses the EMEA's European Public Assessment Report (EPAR) advisory system and the EMEA's response to seventeen reported deaths in European Union (EU) member states linked to botulinum toxin products. Furthermore, Part II examines the FDA's new warning protocol vis-à-vis botulinum toxin products as a response to criticism that the FDA lagged behind its European counterpart. Part III compares the FDA's strengthened warning protocol to the advisory system employed by the EMEA and evaluates whether the improved protocol can reduce the number of serious adverse events in the United States. Finally, Part III proposes an alternative approach toward reducing the number of serious adverse events that relies on state-based regulatory action by medical licensing boards.

I. BACKGROUND

Nineteenth-century physician Justinus Kerner first examined the effects of botulinum toxin after he identified more than two hundred cases of botulism¹² attributed to the ingestion of inadequately pre-

(Jul. 1, 2009), available at <http://www.pr.mo.gov/boards/healingarts/Medical-Spas-Lasers-Botox.pdf> [hereinafter MBRHA Memo].

¹⁰ See MED. BD. OF CAL., *supra* note 9, at 1, 9; MBRHA Memo, *supra* note 9.

¹¹ See MHRA Botox, *supra* note 9.

¹² Botulism, "a paralytic disease caused by [the] potent neurotoxin . . . *Clostridium botulinum*," is separated into three distinct cases: (1) food-borne botulism, caused by the ingestion of food contaminated with *C. botulinum*; (2) wound botulism, which develops in wounds infected with the toxin; and (3) intestinal botulism, caused by "ingestion of spores and production of [the] toxin in the intestines" of infected individuals. Elias Abrutyn, *Botulism*, in HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 841, 842 (16th ed. 2005). All incidences of the disease "begin[] with cranial nerve involvement," with paralytic symptoms gradually spreading to the extremities. *Id.*

served blood sausages.¹³ In an 1817 monograph, Kerner suggested the toxin had potential therapeutic use in blocking abnormal motor movements and eliminating hypersecretion after observing its paralytic effect on the eye muscles and secretory glands.¹⁴ In the same monograph, however, Kerner expressed doubt over the tenability of such applications, hypothesizing that the toxin's extreme lethality would make it difficult to manage in a clinical setting.¹⁵

In 1989, the FDA approved botulinum toxin type A (BTX-A) for the treatment of adult strabismus (crossed eyes) and blepharospasm (eyelid tics) after a decade's worth of data demonstrated BTX-A's positive effect in eliminating eyelid and hemifacial spasms.¹⁶ Shortly thereafter, ophthalmologists noticed that blepharospasm patients injected with BTX-A around the eyes and upper face at intervals of three or four months demonstrated significant improvements in the appearance of glabellar rhytides (frown lines).¹⁷ In response, several clinical studies tested the efficacy and safety of this off-label cosmetic usage of BTX-A.¹⁸ In 2002, the FDA approved BTX-A "for the temporary improvement in the appearance of moderate to severe glabellar lines" (brow furrow) in adult patients.¹⁹

Clostridium Botulinum, the bacterium responsible for the foodborne botulism observed by Kerner, has "eight serotypes (A, B, C α , C β , D, E,

¹³ Frank J. Erbguth & Markus Naumann, *Historical Aspects of Botulinum Toxin: Justinus Kerner (1786–1862) and the "Sausage Poison,"* 52 NEUROLOGY 1850, 1850–51 (1999).

¹⁴ See Alan B. Scott, *Development of Botulinum Toxin Therapy*, 22 DERMATOLOGIC CLINICS 131, 131 (2004).

¹⁵ See Frank J. Erbguth, *Botulinum Toxin, a Historical Note*, 351 LANCET 1820, 1820 (1998) (citing JUSTINUS KERNER, DAS FETTGIFT ODER DIE FETTSÄURE UND IHRE WIRKUNG AUF DEN TIERISCHEN ORGANISMUS EIN BEYTRAG ZUR UNTERSUCHUNG DES IN VERDORBENEN WÜRSTEN GIFTIG WIRKENDEN STOFFES (F.R.G.) (Stuttgart-Tübingen, Cotta 1822)).

¹⁶ See Scott, *supra* note 14, at 132.

¹⁷ See *id.*

¹⁸ See J. Alastair Cartuthers et al., *A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Botulinum Toxin Type A in the Treatment of Glabellar Lines*, 46 J. AM. ACAD. DERMATOLOGY 840, 841 (2002); Monte S. Keen et al., *Botulinum Toxin A for Hyperkinetic Facial Lines: Results of a Double-Blind, Vehicle-Controlled Study*, 94 PLASTIC & RECONSTRUCTIVE SURGERY 94, 94–99 (1994); Nicholas J. Lowe et al., *Botulinum A Exotoxin for Glabellar Folds: A Double-Blind, Vehicle-Controlled Study with an Electromyographic Injection Technique*, 35 J. AM. ACAD. DERMATOLOGY 569, 572 (1996).

¹⁹ Press Release, Allergan Pharms., Allergan's Botox Cosmetic Receives Approval by the FDA for the Treatment of Glabellar Lines (Brow Furrow) (Apr. 15, 2002), *available at* <http://agn.client.shareholder.com/releasedetail.cfm?ReleaseID=82518>. Allergan manufactures and distributes BTX-A separately as Botox and Botox Cosmetic to distinguish between BTX-A's cosmetic and therapeutic indications. See *id.* Unless otherwise noted in this commentary, Botox will refer to BTX-A for cosmetic indications.

F, and G) that produce seven . . . distinct neurotoxins.”²⁰ Each serotype shares the ability to block acetylcholine from being released in striated muscles, which causes chemical denervation, temporary muscle paralysis at the site of injection, and “smooth[es] hyperkinetic lines [facial wrinkles].”²¹ Although botulinum toxin type B has been approved by the FDA for therapeutic (non-cosmetic) indications,²² BTX-A is the only serotype currently approved for cosmetic use in the United States.²³ Until April 2009, Botox was the only commercially available formulation of BTX-A.²⁴

Achieving the correct dosage of Botox is essential to safe and effective use, and depends on the proficiency of the medical practitioner who is performing the injection.²⁵ Botox is a sterile, freeze-dried form of BTX-A.²⁶ It is distributed in a concentrated crystalline form, and must be reconstituted with saline prior to use.²⁷ The dilution ratio of BTX-A to saline varies and depends on a range of factors that must be assessed by the injector prior to use.²⁸ Moreover, “incorrect dosages are

²⁰ Arnold W. Klein, *Complications, Adverse Reactions, and Insights with the Use of Botulinum Toxin*, 29 *DERMATOLOGIC SURGERY* 549, 549 (2003) [hereinafter Klein, *Complications, Adverse Reactions, and Insights*]; see Erbguth & Naumann, *supra* note 13, at 1850.

²¹ See J. Alastair Carruthers & Jean Carruthers, *Botulinum Toxin A in the Mid and Lower Face and Neck*, 22 *DERMATOLOGIC CLINICS* 151, 152 (2004) [hereinafter Carruthers & Carruthers, *Botulinum Toxin A in Face and Neck*]; Arnold W. Klein, *Contraindications and Complications with the Use of Botulinum Toxin*, 22 *CLINICS IN DERMATOLOGY* 66, 66, 68 (2002) [hereinafter Klein, *Contraindications*].

²² See Timothy C. Flynn, *Myobloc*, 22 *DERMATOLOGIC CLINICS* 207, 207 (2004); Press Release, Elan Pharms., FDA Approves Elan's Myobloc Botulinum Toxin Type B Injectable Solution (Dec. 11, 2000), available at <http://ir.elan.com/phoenix.zhtml?c=88326&p=ir-olnewsArticle&ID=137749&highlight=>. See generally Craig Zalvan et al., *Noncosmetic Uses of Botulinum Toxin*, 22 *DERMATOLOGIC CLINICS* 187 (2004).

²³ See Arnold W. Klein, *Complications with the Use of Botulinum Toxin*, 22 *DERMATOLOGIC CLINICS* 197, 198 (2004) [hereinafter Klein, *Complications with the Use of Botulinum Toxin*].

²⁴ See J. Alastair Carruthers & Jean Carruthers, *Use of Botulinum Toxin A for Facial Enhancement*, in *TISSUE AUGMENTATION IN CLINICAL PRACTICE: PROCEDURES AND TECHNIQUES* 117, 119 (Arnold W. Klein ed., 2005) [hereinafter Carruthers & Carruthers, *Botulinum Toxin A for Facial Enhancement*]; Press Release, Ipsen & Medicis Pharms., FDA approves Dysport™ for Therapeutic and Aesthetic Uses (Apr. 30, 2009), available at http://www.ipsen.com/articles/investorrelations/regulatedinformation/20090430_dysport_usa_10.pdf.

²⁵ See Coté et al., *supra* note 3, at 410–11 (finding that numerous AEs related to BTX-A were caused by improper dilution modifications); Alan M. Mantell, *Dilution, Storage, and Electromyographic Guidance in the Use of Botulinum Toxins*, 22 *DERMATOLOGIC CLINICS* 135, 135 (2004).

²⁶ See Carruthers & Carruthers, *Botulinum Toxin A for Facial Enhancement*, *supra* note 24, at 119.

²⁷ See Carruthers & Carruthers, *Botulinum Toxin A in Face and Neck*, *supra* note 21, at 151.

²⁸ See *id.* (concluding that adjustments should be made prior to performing injections in singers, musicians, and other patients who use their perioral muscles with intensity);

very likely to result in severe adverse effects.”²⁹ Researchers have concluded that improper dilution of BTX-A is a significant cause of unintended spread of the toxin away from the site of injection, and may “[produce] symptoms of botulism.”³⁰

In 2002, an estimated 1.1 to 1.6 million patients received Botox injections in the United States.³¹ By 2003, Botox injections were the second most commonly performed cosmetic procedure in North America.³² Contemporaneously, several prominent medical journal articles allayed lingering concerns over the drug’s toxicity and detrimental health effects.³³ Physicians urged that when “[p]roperly used, the incidence of complications [associated with the use of Botox] is low and their severity mild.”³⁴ Additionally, they insisted that “most complications [were] related to poor injection techniques”³⁵ and that there were no reported “long-term adverse effects or health hazards related to the use of Botox for any cosmetic indication.”³⁶

Klein, *Complications, Adverse Reactions, and Insights*, *supra* note 20, at 553; Mantell, *supra* note 25, at 135. Factors influencing the dilution ratio include the anatomy of the injection site, patient’s prior conditions, and the patient’s occupation. See Carruthers & Carruthers, *Botulinum Toxin A in Face and Neck*, *supra* note 21, at 156; Klein, *Complications, Adverse Reactions, and Insights*, *supra* note 20, at 553; Mantell, *supra* note 25, at 135.

²⁹ See Mantell, *supra* note 25, at 135.

³⁰ Coté et al., *supra* note 3, at 411; Bridget M. Kuehn, *Studies, Reports Say Botulinum Toxins May Have Effects Beyond Injection Site*, 299 JAMA 2261, 2262 (2008) [hereinafter Kuehn, *Reports*]. Botulism is characterized 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.” Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation and Research, FDA, to Sidney Wolfe et al., Dir., Pub. Citizen (Apr. 30, 2009), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/UCM143989.pdf> (citing Abrutyn, *supra* note 12, at 842-45).

³¹ See Coté et al., *supra* note 3, at 408 (citing the findings of the Am. Soc’y of Aesthetic Plastic Surgeons).

³² See J. Alastair Carruthers & Jean Carruthers, *Botulinum Toxin-A Development and Use for Upper Facial Lines*, in TEXTBOOK OF FACIAL REJUVENATION: THE ART OF MINIMALLY INVASIVE COMBINATION THERAPY 151, 151 (Nicholas J. Lowe ed., 2002).

³³ See Benjamin Ascher et al., *A Multicenter, Randomized, Double-Blind Placebo-Controlled Study of Efficacy and Safety of 3 Doses of Botulinum Toxin A in the Treatment of Glabellar Lines*, 51 J. AM. ACAD. DERMATOLOGY 223, 233 (2004) (concluding that BTX-A is an effective and safe treatment for glabellar lines); Arnold W. Klein, *Complications with the Use of Botulinum Toxins*, 45 INT’L OPHTHALMOLOGY CLINICS 163, 168 (2005).

³⁴ See Klein, *Complications with the Use of Botulinum Toxin*, *supra* note 23, at 197.

³⁵ See Alastair Carruthers & Jean Carruthers, *Botulinum Toxin Type A for the Treatment of Glabellar Rhytides*, 22 DERMATOLOGIC CLINICS 137, 141 (2004).

³⁶ See Klein, *Contraindications*, *supra* note 21, at 68 (citing Peter Hambleton & A. Peter Moore, *Botulinum Neurotoxins: Origin, Structure, Molecular Actions, and Antibody*, in HANDBOOK OF BOTULINUM TREATMENT 17, 17-27 (A. Peter Moore ed., 1995)).

II. DISCUSSION

A. Independent Review of Adverse Event Reports Submitted to the FDA

In 2005, data emerged that cast grave doubt on the safety of Botox.³⁷ A study published in the *Journal of the American Academy of Dermatology* (Coté Study) reviewed 1437 adverse events (AEs) reported to the FDA³⁸ in connection with both therapeutic and cosmetic uses of BTX-A.³⁹ Researchers of this study set out to independently tally the number of serious AEs linked to BTX-A.⁴⁰ They classified AEs according to the statutory definition outlined by Title 21 of the U.S. Code of Federal Regulations.⁴¹ According to this provision, an AE is defined as “[a]ny adverse experience occurring at any dose that results in [*inter alia*] . . . [d]eath, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization.”⁴²

The Coté Study found that 217 of the 406 AEs related to therapeutic use of BTX-A satisfied the statutory definition of “serious.”⁴³ Of these, BTX-A was causally linked to twenty-eight deaths and seventeen seizures.⁴⁴ Researchers also identified thirty-six serious AEs related to cosmetic use of BTX-A, including five instances of focal facial paralysis and dysphagia (difficulty swallowing).⁴⁵

In explaining why the number of serious AEs was significantly greater for therapeutic use as opposed to cosmetic use, researchers hig-

³⁷ See Kuehn, *supra* note 30, at 2261.

³⁸ Coté et al., *supra* note 3, at 407. See generally Timothy Brewer & Graham A. Colditz, *Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, 281 JAMA 824 (1999) (providing an overview of the FDA's adverse event reporting system). The FDA receives notice of all AEs through the MedWatch reporting system. Coté et al., *supra* note 3, at 407. Manufacturers are required to report all AEs within fifteen calendar days of discovery. Food, Drug, and Cosmetic Act, 21 C.F.R. § 310.305 (2009). Nevertheless, “reporting by clinicians and others . . . remains voluntary;” therefore, “AEs reported to MedWatch represent only a subset of the actual number [of AEs] that occur.” Coté et al., *supra* note 3, at 408.

³⁹ See Coté et al., *supra* note 3, at 407.

⁴⁰ *Id.* at 407.

⁴¹ *Id.* at 408 (citing 21 C.F.R. § 600.80 (2005)).

⁴² 21 C.F.R. § 600.80.

⁴³ Coté et al., *supra* note 3, at 409; see 21 C.F.R. § 600.80.

⁴⁴ Coté et al., *supra* note 3, at 409 (noting that “[a]mong the 28 deaths, 6 were attributed to respiratory arrest, 5 to myocardial infarction, 3 to cerebrovascular accident, 2 to pulmonary embolism, 2 to pneumonia . . . 5 to other known causes, and 5 to unknown causes of death”).

⁴⁵ *Id.* at 409, 412 tbl.II; see Raj K. Goyal, *Dysphagia*, in HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 217, 217 (16th ed. 2005) (defining dysphagia as “a sensation of ‘sticking’ or obstruction of the passage of food through the mouth, pharynx, or esophagus”).

highlighted the differences between the clinical characteristics of therapeutic and cosmetic cases.⁴⁶ Notably, for therapeutic cases, “doses were higher . . . and patients tended to have serious underlying diseases.”⁴⁷ By contrast, patients receiving cosmetic BTX-A injections “typically had no underlying disease reported, and [they] were injected with much smaller doses.”⁴⁸

More significantly, the Coté Study emphasized that many AEs tied to cosmetic injections were caused by a “lack of adherence to [basic] precepts” of BTX-A use: “[c]areful attention to drug dose, dilution, handling, storage, and site of injection.”⁴⁹ In more than a dozen cosmetic cases, patients were injected with five times the maximum labeled dosage of BTX-A.⁵⁰ Researchers also found that many cosmetic injections deviated from the labeled dilution procedure.⁵¹ In fact, “[d]rug dilution modifications were reported frequently with such diluent substitutions as bupivacaine, lidocaine, water, and previously reconstituted [BTX-A], rather than the recommended saline diluent.”⁵² In a similar vein, common handling errors included “injecting reconstituted product after the recommended 4-hour expiration, freezing or refrigerating reconstituted product for future use, [and] injecting multiple patients with [BTX-A] from a vial labeled for single-patient use.”⁵³

B. EMEA Warnings Regarding Adverse Reactions to BTX-A and BTX-B

The EMEA has implemented its own adverse reactions reporting system since 2004.⁵⁴ Medicines meeting the EMEA’s standards of quality, safety, and efficacy are granted Marketing Authorization after undergoing review by the Committee for Medicinal Products for Human Use (CHMP).⁵⁵ Once Marketing Authorization has been granted, the CHMP publishes a European Public Assessment Report (EPAR), which details “the reasons for its opinion in favour of granting authorisation.”⁵⁶ In

⁴⁶ See Coté et al., *supra* note 3, at 409.

⁴⁷ *Id.*

⁴⁸ *Id.*

⁴⁹ *Id.* at 410.

⁵⁰ See *id.* at 410–11.

⁵¹ *Id.* at 411.

⁵² See Coté et al., *supra* note 3, at 411.

⁵³ *Id.*

⁵⁴ See 2004 O.J. (L 136) 12; Pub. Citizen Health Res. Group, *supra* note 4 (recognizing the EMEA’s system as the counterpart to the FDA’s MedWatch reporting system).

⁵⁵ See 2004 O.J. (L 136) ¶¶ 13, 23.

⁵⁶ *Id.* ¶ 3.

addition, EPARs contain a Summary of Product Characteristics (SPC).⁵⁷ On botulinum toxin products, the SPC includes a “[s]pecial warnings and precautions for use” section that succinctly addresses all the major issues related to migration of [the] injected drug.⁵⁸ All EPARs are written “in a manner that is understandable to the public” and are published on the EMEA’s website.⁵⁹

In March of 2005, the CHMP updated its SPC for Neurobloc (BTX-B) after an interim analysis found that thirty percent of the total number of adverse reactions⁶⁰ reported to the EMEA between January 2001 and December 2003 satisfied the EMEA’s definition of “serious.”⁶¹ Mirroring the conclusion reached by the Coté Study with respect to BTX-A-related AEs reported to the FDA, the CHMP found that most adverse reactions associated with BTX-B were caused by spread of the toxin beyond the injection site.⁶²

Eight months later, the CHMP issued a second, more robust, advisory.⁶³ European health officials announced that they had discovered evidence linking BTX-B to the deaths of seventeen patients in Europe.⁶⁴ Furthermore, the CHMP clarified that the reported negative side effects were “not specific of [BTX-B] but of the whole class [of botulinum toxins].”⁶⁵ In connection with this finding, the updated EPAR warned patients of an “overall concern on the class of botulinum toxins regarding dysphagia and fatal outcomes.”⁶⁶ The EMEA further responded by requiring BTX-B manufacturers to package an updated set of warning leaflets along with every drug vial, explaining how patients should be

⁵⁷ See *id.*; Pub. Citizen Health Res. Group, *supra* note 4.

⁵⁸ See Pub. Citizen Health Res. Group, *supra* note 4.

⁵⁹ 2004 O.J. (L 136) ¶ 3; see, e.g., Eur. Meds. Agency, Procedural Steps Taken and Scientific Information After the Authorisation: Changes Made After 01/02/2004, 1, <http://www.emea.europa.eu/humandocs/PDFs/EPAR/neurobloc/H-301-en8b.pdf> (last visited Apr. 15, 2010) [hereinafter EMEA, Procedural Steps].

⁶⁰ EMEA, Procedural Steps, *supra* note 59, at 7, 8.

⁶¹ See 2001 O.J. (L 83) ¶ 12. European Community Regulations define “serious adverse reaction” as “a reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.” *Id.*

⁶² Compare Coté et al., *supra* note 3, at 410 (concluding that the majority of AEs reported to the FDA in connection with BTX-A were caused by distant spread of the toxin), with EMEA, Procedural Steps, *supra* note 59, at 4 (concluding that most adverse effects reported to the EMEA in connection with BTX-B were caused by distant spread of the toxin).

⁶³ See EMEA, Procedural Steps, *supra* note 59, at 5.

⁶⁴ *Id.*

⁶⁵ See *id.*

⁶⁶ See *id.* at 4–5.

given BTX-B, and warning against the possibility of serious adverse effects caused by the spread of the toxin from the site of injection.⁶⁷

C. *The FDA's Response to Calls for Stronger Patient Warnings*

Heeding the EMEA's call for an aggressive stance toward botulinum toxin products, regulatory agencies in the United Kingdom and Germany "amplified the EU[']s warning[s] [by requiring manufacturers to issue] 'Dear Doctor Letters'" that "alert[ed] physicians in its 27 member states about the need to monitor for signs of botulinum toxin adverse events."⁶⁸ Despite the Coté Study's somber findings, however, "no similar official warnings [were issued] by the FDA [in the United States]."⁶⁹ Responding to government inaction in the United States, in January 2008, Public Citizen Health Research Group (Public Citizen) sent a letter to FDA Commissioner Andrew von Eschenbach petitioning the Agency to take stronger measures to warn patients of the dangers associated with BTX-A and BTX-B.⁷⁰ Using the EMEA's EPAR advisory system as a model for reform, the petition set forth three basic recommendations for protocol change.⁷¹

First, the petition called for clearer, more stream-lined, physician-directed warnings.⁷² Unlike the warnings issued by the EMEA, in the United States, information for physicians was "scattered throughout the labels," or obliquely listed under an "Adverse Reactions" section.⁷³ In response, Public Citizen requested a concise description of "all major issues related to migration of the injected drug."⁷⁴ The petition also requested that the FDA clarify that "the phenomenon of distant spread is not restricted to patients [undergoing therapeutic BTX-A treatment]" but equally applies to cosmetic use of BTX-A.⁷⁵

Second, Public Citizen called for a clear and consistent set of patient-directed warnings.⁷⁶ In the United States, only a fraction of drugs possess patient-friendly labels that provide complete and accessible in-

⁶⁷ Public Citizen Health Res. Group, *supra* note 4.

⁶⁸ *See id.*

⁶⁹ *See id.*

⁷⁰ *See* Food, Drug, and Cosmetic Act, 21 C.F.R. § 10.30 (2009) (outlining the administrative procedure for citizen petitions to the FDA). *See generally* Pub. Citizen Health Res. Group, *supra* note 4.

⁷¹ *See generally* Pub. Citizen Health Res. Group, *supra* note 4.

⁷² *See id.*

⁷³ *See id.*

⁷⁴ *See id.*

⁷⁵ *See id.*

⁷⁶ *See id.*

formation regarding adverse effects.⁷⁷ For BTX-A products in particular, “the ‘Information for Patients’ section [was] very brief, and [did] not approach the five-page EU patient information in [terms of] comprehensiveness.”⁷⁸ For example, on the label then-existing for Botox, the only information provided “was that ‘[p]atients or caregivers should be advised to seek immediate medical attention if swallowing speech or respiratory disorders arise.’”⁷⁹ The labeling also failed to consistently advise patients of the health risks posed by distant spread of the toxin.⁸⁰

Third, the petition urged the FDA to require “detailed written information in the form of FDA-approved Medication Guides” to be dispensed by the physician at the time the drug is injected into the patient.⁸¹ In this respect, Public Citizen addressed the concern that “[e]ven if [the] . . . labeling [*was*] more complete, there [was] no evidence that physicians [would] actually discuss [the] information with their patients.”⁸²

In April of 2009, the FDA responded to Public Citizen’s petition by granting all three of its requests for protocol reform.⁸³ The Agency notified all Biologics License Application (BLA) holders for botulinum toxin products that “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).”⁸⁴ Additionally, the FDA sent notification letters to BLA holders advising that a “Risk Evaluation and Mitigation Strategy (REMS) . . . is necessary to ensure that the benefits of these products outweigh the risks.”⁸⁵ Lastly, it required that every REMS must include “a Medication Guide and Communication Plan, including a Dear Health Care Provider letter, and a timetable for submission of assessments.”⁸⁶

III. ANALYSIS

The FDA’s improved warning protocol vis-à-vis BTX-A represents a considered response to Public Citizen’s criticism that the Agency lagged

⁷⁷ See Pub. Citizen Health Res. Group, *supra* note 4.

⁷⁸ See *id.*

⁷⁹ *Id.*

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² *Id.*

⁸³ See generally Woodcock, *supra* note 30 (providing the FDA’s response to Public Citizen’s petition).

⁸⁴ *Id.* at 1.

⁸⁵ *Id.*

⁸⁶ *Id.*

behind its European counterpart.⁸⁷ Like the Summary of Product Characteristics accompanying every EPAR, the FDA's new BTX-A labeling requirements include a strengthened "Warnings and Precautions" section that provides a stream-lined advisory regarding the spread of botulinum toxin effects beyond the site of injection.⁸⁸ The FDA-required physician-distributed Medication Guides mimic the "Package Leaflet: Information for the User" pamphlets accompanying botulinum toxin products distributed in the EU.⁸⁹ Both publications are "additional method[s] of communicating the signs and symptoms of the spread of botulinum toxin effects" and "can help ensure that the patient or caregiver is aware of and can self-monitor for serious risks."⁹⁰ Finally, the FDA-mandated "Dear Health Care Professional" letters—considered a minimum component of the FDA's REMS communication program—are functionally similar to the "Dear Doctor Letters" required by regulatory agencies in the United Kingdom and Germany.⁹¹

The FDA's bolstered warning protocol may raise public awareness of the health risks posed by botulinum toxins.⁹² Nevertheless, it is unclear whether this protocol will reduce the number of serious AEs linked to BTX-A.⁹³ Despite reports by mainstream media of BTX-A related deaths, the number of Botox injections performed in the United States rose by eight percent in 2008.⁹⁴ This statistic offers compelling

⁸⁷ See Pub. Citizen Health Res. Group, *supra* note 4. See generally Woodcock, *supra* note 30 (outlining the FDA's improved warning protocol vis-à-vis botulinum toxins).

⁸⁸ See EUR. MEDS. AGENCY, NEUROBLOC: SUMMARY OF PRODUCT CHARACTERISTICS 3, 5, <http://www.emea.europa.eu/humandocs/PDFs/EPAR/neurobloc/emea-combined-h301en.pdf> (last visited Apr. 15, 2010) [hereinafter EMEA, BTX-B SPC]; Woodcock *supra* note 30, at 14, 15.

⁸⁹ See EMEA, BTX-B SPC, *supra* note 88; Woodcock, *supra* note 30.

⁹⁰ Woodcock, *supra* note 30, at 17; see EMEA, BTX-B SPC, *supra* note 88, at 26–28.

⁹¹ See Woodcock, *supra* note 30, at 17–18; Letter from Bundesinstitut für Arzneimittel und Medizinprodukte to Prescribing Physicians (June 2007), *available at* <http://www.bfarm.de/SharedDocs/Publikationen/DE/Pharmakovigilanz/roteHandBriefe/2007/botulinumtoxin,templateId=raw,property=publicationFile.pdf/botulinumtoxin.pdf>; Letter from Meds. and Healthcare Prods. Reg. Agency to Prescribing Physicians (June 2007), *available at* <http://www.mhra.gov.uk/home/groups/es-era/documents/websiteresources/con2031672.pdf>.

⁹² See Pub. Citizen Health Res. Group, *supra* note 4 (concluding that "failure to immediately [implement the strengthened warning protocol] is likely to result in more preventable serious adverse reactions and deaths from [botulinum toxin] products").

⁹³ See AM. SOC'Y OF PLASTIC SURGEONS (ASPS), 2009 REPORT OF THE 2008 STATISTICS 5 (2009), *available at* <http://www.plasticsurgery.org/Media/stats/2008-US-cosmetic-reconstructive-plastic-surgery-minimally-invasive-statistics.pdf> (last visited Apr. 15, 2010).

⁹⁴ *Id.*; see, e.g., Gardiner Harris, *Group Seeks New Warning About Botox*, N.Y. TIMES, Jan. 25, 2008, at A19.

evidence that the U.S. Botox market may be unwilling to part with the drug's wrinkle-reducing effects.⁹⁵

For a stalwart population of U.S. patients receiving Botox injections, a heightened warning protocol alone may not provide a practical strategy for minimizing the incidence of complications.⁹⁶ Although the new warning protocol obligates BTX-A manufacturers to provide patients with a clearer list of complications caused by the distant spread of the toxin, the FDA has not required manufacturers to educate patients or caregivers about *why* distant spread occurs or ways to prevent it.⁹⁷ FDA Director Janet Woodcock conceded this point in her response to Public Citizen's petition: "[a]lthough we do not currently have recommendations for how to prevent these events, it is essential that the potential for distant spread of toxin effects be considered in assessing the risks and benefits of using botulinum toxin products."⁹⁸

In order to reduce the number of serious AEs linked to BTX-A, it may be necessary for officials to identify the cause of distant spread, and require manufacturers to educate caregivers and patients about ways to prevent it.⁹⁹ The Coté Study made substantial contributions to the first step of this proposal.¹⁰⁰ In that study, researchers concluded that distant spread of botulinum toxins frequently occurred when practitioners ignored fundamental precepts of BTX-A usage: proper handling, storage, dilution, and injection of BTX-A.¹⁰¹ If this conclusion is correct, minimum training requirements and additional guidelines with respect to BTX-A injection practices may be necessary in order to reduce the number of AEs related to BTX-A.¹⁰²

The power to regulate medical practices, however, falls squarely outside of the FDA's authority.¹⁰³ In the United States, the FDA's drug approval power is governed by the Food, Drug, and Cosmetic Act.¹⁰⁴

⁹⁵ See ASPS, *supra* note 93, at 5.

⁹⁶ See *id.*

⁹⁷ Woodcock, *supra* note 30, at 14–15; see Pub. Citizen Health Res. Group, *supra* note 4.

⁹⁸ Woodcock, *supra* note 30, at 14–15.

⁹⁹ See Coté et al., *supra* note 3, at 410.

¹⁰⁰ See *id.*

¹⁰¹ See *id.* at 410–11.

¹⁰² See *id.*

¹⁰³ *Id.* at 408 (concluding that "[t]he FDA does not have authority to control decisions made by qualified health care practitioners . . . or to otherwise regulate medical or surgical practice").

¹⁰⁴ 21 U.S.C. § 355 (2006); Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J. L. MED. & ETHICS 476, 477 (2009) (citing R.A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753 (1996)).

Once the FDA approves a drug for a particular use, it issues a “specific label [that] includes information about approved indications for product use, as well as the approved dosage, method of administration and patient population.”¹⁰⁵ Nevertheless, “[o]nce a drug . . . has been approved or cleared . . . health-care professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product’s approved labeling.”¹⁰⁶ The FDA’s refusal to monitor and restrict such “off-label” uses has been interpreted by the U.S. Supreme Court as “a necessary corollary of the FDA’s mission to regulate [medicine] without directly interfering with the practice of medicine.”¹⁰⁷

In contrast, states retain broad latitude to define and regulate the practice of medicine.¹⁰⁸ Many states have medical boards that are responsible for overseeing medical practices, and are authorized to promulgate rules, license practitioners and conduct disciplinary proceedings.¹⁰⁹ Despite this fact, states have similarly struggled to arrive at an adequate solution to the problem of improper BTX-A medical practices.¹¹⁰

Physicians representing national boards of plastic surgeons and dermatologists have disagreed over what training physicians should be required to undergo in order to perform minimally invasive cosmetic

¹⁰⁵ Dresser & Frader, *supra* note 104, at 477.

¹⁰⁶ FOOD AND DRUG ADMIN., GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES 3 (Jan. 2009), available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf>; see also 21 U.S.C. § 396 (2006) (providing that the FDCA shall not be interpreted “as limiting or interfering with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship”).

¹⁰⁷ *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001).

¹⁰⁸ See 243 MASS. CODE REGS. 2.01 (2009) (defining the practice of medicine as the “maintenance of human health by the prevention, alleviation, or cure of disease [through] . . . diagnosis, treatment, use of instruments or other devices, or the prescription or administration of drugs for the relief of diseases or adverse physical or mental conditions”). Other states, however, have opted not to provide a statutory definition of medical practice. See, e.g., *Johnson v. Missouri*, 58 S.W.3d 496, 499 (Mo. 2001) (holding that “the phrase ‘the practice of medicine,’ is not legislatively defined [in Missouri], but has been construed by the courts to include the diagnosis and treatment of the sick”).

¹⁰⁹ See, e.g., CAL. BUS. & PROF. CODE §§ 2050, 2330–34 (West 2009); MASS. GEN. LAWS. ch. 13, § 10 (2002).

¹¹⁰ See, e.g., Paul Harasim, *Proposed Rules Clarify What Medical Assistants Can, Can’t Do*, LAS VEGAS REV.-J., Sept. 18, 2009, at B1; Cy Ryan, *Medical Board Adopts Emergency Botox Regulation*, LAS VEGAS SUN, Sept. 18, 2009, <http://www.lasvegassun.com/news/2009/sep/18/medical-board-adopts-emergency-botox-regulation>.

procedures such as Botox injections.¹¹¹ State medical boards, however, have grappled with an even more basic issue: whether licensed *non-physician* practitioners, such as nurses and physicians assistants, should be allowed to perform Botox injections.¹¹² Among those states that do permit licensed non-physician practitioners to perform Botox injections, there is wide disagreement about the level of oversight that must be invested by supervising physicians.¹¹³ In other states, there remains a lingering debate about whether *unlicensed* non-physician practitioners, such as medical assistants, should be allowed to administer Botox.¹¹⁴

CONCLUSION

Justinus Kerner first warned that harnessing the benefits of botulinum toxins would require future practitioners to overcome the inherent difficulties of handling the toxins in a clinical setting. Kerner's prognostic commentary from over a century ago offers surprising insight into a dilemma that currently grips the cosmetic medicine industry.

The FDA's strengthened labeling requirements and Risk Evaluation and Mitigation Strategy, which mirrors the European Medicines Agen-

¹¹¹ See generally Matthew C. Camp, Mapping the Future of Plastic Surgery: Demographic and Geographic Analysis of Providers of Cosmetic Services in the Greater Los Angeles Area, Presentation Before the 88th Annual Meeting of the Am. Ass'n of Plastic Surgeons 1, 14 (March 23, 2009) (unpublished monograph, on file with the Am. Ass'n of Plastic Surgeons) (concluding that consumers have sought minimally invasive cosmetic procedures from practitioners with a more limited skill set than surgeons, in part because such procedures are not legally required to be performed by plastic surgeons).

¹¹² See, e.g., MED. BD. OF CAL., *supra* note 9, at 1 (providing that "[p]hysicians . . . may inject Botox, or they may direct registered nurses, licensed vocational nurses, or physician assistants to perform the injection under their supervision").

¹¹³ See MBRHA Memo, *supra* note 9. The Missouri Board of Registration for the Healing Arts recommends "direct supervision," entailing that the supervising physician is located in the same facility as the practitioner administering BTX-A. *Id.* The Board only *requires* "indirect supervision," meaning that the physician is located within twenty miles or thirty minutes of the treatment facility. *Id.* In contrast, the Medical Board of California only requires supervising physicians to be "immediately available by electronic communications." See Memoranda from the MED. BD. OF CAL., Supervision of Physicians Assistants (May 18, 2008), available at http://www.pac.ca.gov/forms_pubs/sup_of_pa.pdf.

¹¹⁴ See Harasim, *supra* note 110, at B1. In September 2009, the Nevada Medical Board promulgated a rule that would have prevented medical assistants from performing shots of any kind, including Botox injections. *Id.* As an effect of that rule, medical assistants were temporarily prohibited from administering influenza vaccinations, including vaccinations for the H1N1 virus. See Edward Vogel, *Nevada Medical Board Director Ling Resigns*, LAS VEGAS REV.-J., Oct. 10, 2009, at B1. After a district judge granted a temporary injunction blocking that rule, the Board overturned its earlier decision, prompting the Director of the Medical Board to resign. See Michael Blasky, *Judge Blocks Rules for Medical Assistants*, LAS VEGAS REV.-J., Sept. 30, 2009, at A1.

cy's European Public Assessment Report system, represents a positive step toward raising public awareness of the health risks related to botulinum toxins. Nonetheless, for a U.S. cosmetic medicine market that appears unwilling to part with the aesthetic benefits offered by products such as Botox, it is doubtful that this improved protocol, *tout court*, will reduce the number of serious adverse events linked to BTX-A.

Following Kerner's advice, a reduction in the number of adverse events requires that practitioners surmount the dangers attendant to clinical BTX-A use. As the Coté Study suggests, this means practitioners must follow well-established precepts of BTX-A use, including proper handling, storage, dilution, and injection. Although regulatory action to that effect falls outside of the FDA's authority, it remains available to the states and their respective medical boards.