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

NICHOLAS R. KENNEDY *

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 (EMEA) revealed similar findings in Europe, the FDA and EMEA implemented bolstered product warnings aimed at increasing patient awareness of the drug’s health risks. This Note compares the FDA and EMEA’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.  

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nascent area of medicine. 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. On the heels of this study, government watchdog groups petitioned the Agency to take stronger measures to protect patients. In 2009, the FDA responded by implementing a bolstered warning protocol mimicking the advisory system used by the European Medicines Agency (EMEA), the FDA's European counterpart.

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

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

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 botulism attributed to the ingestion of inadequately pre-

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. 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. 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.

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. 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). In response, several clinical studies tested the efficacy and safety of this off-label cosmetic usage of BTX-A. 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.

Clostridium Botulinum, the bacterium responsible for the foodborne botulism observed by Kerner, has “eight serotypes (A, B, Cα, Cβ, D, E, etc.).

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.
F, and G) that produce seven . . . distinct neurotoxins.” 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].” Although botulinum toxin type B has been approved by the FDA for therapeutic (non-cosmetic) indications, BTX-A is the only serotype currently approved for cosmetic use in the United States. Until April 2009, Botox was the only commercially available formulation of BTX-A.

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. Botox is a sterile, freeze-dried form of BTX-A. It is distributed in a concentrated crystalline form, and must be reconstituted with saline prior to use. 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. 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.


24 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 in Face and Neck, supra note 21, at 151.

27 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. 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.”

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

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.

See Mantell, supra note 25, at 135.

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).

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


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


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* (Côté Study) reviewed 1437 adverse events (AEs) reported to the FDA in connection with both therapeutic and cosmetic uses of BTX-A.38 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 Côté 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 hi-

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37 See Kuehn, supra note 30, at 2261.
39 See Côté 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 Côté et al., supra note 3, at 409; see 21 C.F.R. § 600.80.
44 Côté 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.\footnote{See Coté et al., supra note 3, at 409.} Notably, for therapeutic cases, “doses were higher . . . and patients tended to have serious underlying diseases.”\footnote{Id.} By contrast, patients receiving cosmetic BTX-A injections “typically had no underlying disease reported, and [they] were injected with much smaller doses.”\footnote{Id. at 410.}

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.”\footnote{Id. at 410–11.} In more than a dozen cosmetic cases, patients were injected with five times the maximum labeled dosage of BTX-A.\footnote{See id. at 410–11.} Researchers also found that many cosmetic injections deviated from the labeled dilution procedure.\footnote{See Coté et al., supra note 3, at 411.} 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.”\footnote{Id.} 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.”\footnote{Id.}

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

The EMEA has implemented its own adverse reactions reporting system since 2004.\footnote{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).} 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).\footnote{See 2004 O.J. (L 136) ¶¶ 13, 28.} 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.”\footnote{Id. ¶ 3.} In
addition, EPARs contain a Summary of Product Characteristics (SPC). On botulinum toxin products, the SPC includes a “special warnings and precautions for use” section that succinctly addresses all the major issues related to migration of the injected drug. All EPARs are written “in a manner that is understandable to the public” and are published on the EMEA’s website.

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 reactions reported to the EMEA between January 2001 and December 2003 satisfied the EMEA’s definition of “serious.” 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.

Eight months later, the CHMP issued a second, more robust, advisory. European health officials announced that they had discovered evidence linking BTX-B to the deaths of seventeen patients in Europe. Furthermore, the CHMP clarified that the reported negative side effects were “not specific of [BTX-B] but of the whole class [of botulinum toxins].” 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.” 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

60 EMEA, Procedural Steps, supra note 59, at 7, 8.
61 Id.
62 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.
63 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).
64 See EMEA, Procedural Steps, supra note 59, at 5.
65 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.  

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-

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68 See id.
69 See id.
72 See id.
73 See id.
74 See id.
75 See id.
76 See id.
formation regarding adverse effects. 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.” 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.’” The labeling also failed to consistently advise patients of the health risks posed by distant spread of the toxin.

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. 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.”

In April of 2009, the FDA responded to Public Citizen’s petition by granting all three of its requests for protocol reform. 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).” 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.” 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.”

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

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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.”\textsuperscript{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.\textsuperscript{91}

The FDA’s bolstered warning protocol may raise public awareness of the health risks posed by botulinum toxins.\textsuperscript{92} Nevertheless, it is unclear whether this protocol will reduce the number of serious AEs linked to BTX-A.\textsuperscript{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.\textsuperscript{94} This statistic offers compelling

\textsuperscript{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).


\textsuperscript{89} See EMEA, BTX-B SPC, supra note 88; Woodcock, supra note 30.

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


\textsuperscript{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”).


\textsuperscript{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.
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”).
Once the FDA approves a drug for a particular use, it issues a “specific
label [that] includes information about approved indications for prod-
uct use, as well as the approved dosage, method of administration and
patient population.” Nevertheless, “[o]nce a drug . . . has been
approved or cleared . . . health-care professionals may lawfully use or pre-
scribe that product for uses or treatment regimens that are not in-
cluded in the product’s approved labeling.” 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.”

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

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

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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 De-
vices 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 in-
terpreted “as limiting or interfering with the authority of a health care practitioner to pre-
scribe or administer any legally marketed device to a patient for any condition or disease
within a legitimate health care practitioner-patient relationship”).
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 ad-
ministration 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 Regu-
medical-board-adopts-emergency-botox-regulation.
procedures such as Botox injections.\textsuperscript{111} State medical boards, however, have grappled with an even more basic issue: whether licensed \textit{non-physician} practitioners, such as nurses and physicians assistants, should be allowed to perform Botox injections.\textsuperscript{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.\textsuperscript{113} In other states, there remains a lingering debate about whether \textit{unlicensed} non-physician practitioners, such as medical assistants, should be allowed to administer Botox.\textsuperscript{114}

\textbf{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-

\begin{itemize}
\item \textsuperscript{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).
\item \textsuperscript{112} See, e.g., Med. Bd. of Cal., \textit{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”).
\item \textsuperscript{113} See MBRHA Memo, \textit{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. \textit{Id.} The Board only requires “indirect supervision,” meaning that the physician is located within twenty miles or thirty minutes of the treatment facility. \textit{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.
\item \textsuperscript{114} See Harasim, \textit{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. \textit{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, \textit{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, \textit{Judge Blocks Rules for Medical Assistants}, LAS VEGAS REV.-J., Sept. 30, 2009, at A1.
\end{itemize}
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.