



# HANDBOOK OF BOTULINUM TOXINS FOR AESTHETIC INDICATIONS

THEORY AND PRACTICE



Kenneth Beer

# Contents

|                     |                                                                                            |           |
|---------------------|--------------------------------------------------------------------------------------------|-----------|
| <b>Preface</b>      |                                                                                            | <b>v</b>  |
| <b>Contributors</b> |                                                                                            | <b>x</b>  |
| <b>Chapter 1</b>    | <b>Structure and function of different neurotoxin types</b>                                | <b>1</b>  |
|                     | <i>Jacob I. Beer, Stephanie Bayers</i>                                                     |           |
| <b>Chapter 2</b>    | <b>Safety and liability issues</b>                                                         | <b>9</b>  |
|                     | <i>Kenneth R. Beer</i>                                                                     |           |
| <b>Chapter 3</b>    | <b>Injection techniques: forehead and eyebrow shaping</b>                                  | <b>15</b> |
|                     | <i>Joely Kaufman, Jeremy B. Green</i>                                                      |           |
| <b>Chapter 4</b>    | <b>Injection techniques: periorbital, crow's feet and eyelids</b>                          | <b>23</b> |
|                     | <i>Carolee M. Cutler Peck, Talmage J. Broadbent, Brian S. Biesman</i>                      |           |
| <b>Chapter 5</b>    | <b>Injection techniques: midface, perioral, DAO, gummy smile, chin and masseters</b>       | <b>35</b> |
|                     | <i>Emily Catherine Keller, Michael S. Kaminer</i>                                          |           |
| <b>Chapter 6</b>    | <b>Injection techniques: neck, chest, and jawline</b>                                      | <b>47</b> |
|                     | <i>Anthony P. Sclafani, Gregory Dibelius</i>                                               |           |
| <b>Chapter 7</b>    | <b>Injection techniques: hyperhidrosis of the axilla, hands, feet and other body areas</b> | <b>61</b> |
|                     | <i>Dee Anna Glaser</i>                                                                     |           |
| <b>Chapter 8</b>    | <b>Reshaping of the lower face: concept and technique</b>                                  | <b>73</b> |
|                     | <i>Steven C.C. Liew</i>                                                                    |           |

|                   |                                                                         |     |
|-------------------|-------------------------------------------------------------------------|-----|
| <b>Chapter 9</b>  | <b>The combination of neurotoxins<br/>with lasers and light sources</b> | 87  |
|                   | <i>Marnie B. Nussbaum</i>                                               |     |
| <b>Chapter 10</b> | <b>Combinations of neurotoxins with fillers</b>                         | 97  |
|                   | <i>Frederick C. Sailes, Julius Few</i>                                  |     |
| <b>Chapter 11</b> | <b>Topical botulinum toxin</b>                                          | 115 |
|                   | <i>Timothy Corcoran Flynn</i>                                           |     |
| <b>Index</b>      |                                                                         | 123 |

*Kenneth R. Beer*

## Introduction

In 2012, the *Wall Street Journal* highlighted some of the dangers surrounding illegally imported and improperly sourced drugs.<sup>1</sup> This problem was especially dangerous for patients receiving illegally obtained chemotherapy drugs. However, the lack of standardization and increasing commoditization of injected cosmetic devices and drugs has created a situation in which injectors of botulinum toxins (BTXs) and various cosmetic fillers have resorted to purchasing these at discounts without concern for the purity or activity of the products. Frequently, the products purchased through these illegal channels contain research grade materials or contaminants. The increasing popularity of injections of type A botulinum toxins (BTXs-A), as well as the increasing pressure on pricing, creates a 'perfect storm' for physicians and patients alike.

---

## A brief history of the problem

The US Food and Drug Administration (FDA) notified the public of this problem in April 2013 after previously notifying the public when a rogue distributor began to sell research grade toxin to physicians suggesting that they dilute the toxin and inject it into patients instead of paying the 'high prices' charged by Allergan. In the warning from 2013, the FDA declared that the product was a counterfeit version of Botox that was provided in a counterfeit box. Although it was purported to be a version of the material approved for use outside of the USA, this was not the case. However, the agency said that they could not verify the source or contents of the counterfeit product and the warning advised practitioners and patients to avoid these products.

Counterfeit products mentioned in this warning included products available from 'Onlinebotox' and 'Onlinebotox.com.' According to this press release, 'Onlinebotox.com' was using a US-based return address to project the image of being a legitimate business, while in reality they operated outside the United States.

This most recent FDA initiative follows a similar one in 2004, when research grade BTXs were advertised and sold to physicians across the United States. Despite the fact that those that purchased the research toxin knew or should have known that it was not approved by the FDA for human use, many physicians purchased this product and several injected it into patients. The medical consequence of this action was the development of botulism among four people injected with the product. Legal consequences included fines, jail, and other penalties for several

people involved. However, many of those that purchased this research grade toxin were not penalized and they remain in practice to this day.

---

## **Rationale for purchasing counterfeit and illegally sourced products**

There are many reasons why counterfeit and illegally sourced products (CISPs) continue to be an issue in the United States and other markets. Some physicians will say that they resent the constant price increases demanded by the companies that sell these products. Others will say that they want to deliver a more cost-effective solution for their patients who are not able to afford the real product. Despite all of the reasons why people import counterfeit or illegal product, the most compelling reason is profit. Physicians risk penalties and harm to their patients in order to save money and compete in a marketplace that only understands price. Since there is no national initiative or coalition by the makers of these products to educate patients about the dangers of CISPs, the patients frequently decide where to go based on price.

The high price of the botulinum type A products as well as their popularity make them easy targets to counterfeit. There are many prominent features that help set counterfeit products apart from real ones but as the counterfeiters gain access to better printers and fabrication as well as better use of the internet, the differences in appearance of real and counterfeit BTXs become harder to discern.

There are many different reasons that injectors look to find alternate sources of toxin, but they all distill down to cost savings. As physicians are faced with annual cost increases from manufacturers and the ongoing siege of patients seeking \$99 'Botox' the physicians are faced with a dilemma not of their making. Since the patient has no idea what they are being injected with, the physician may elect to dilute the toxin to decrease the dose administered (while the patient remains happy that he/she obtained a 'syringe' of product). The physician can pass the cost increases onto the patients and hope they will understand that they always obtain what they pay for. Alternatively, injectors may choose to go their own route and import product from offshore.

Perhaps the easiest way to avoid using counterfeit products is also the most obvious: purchase products directly from the manufacturer or their authorized distributor. In most instances, each of the companies has a sales representative that will be happy to assist with your order and to make sure that it is being registered by the correct company.

---

## **Combating the problem**

The producers of all toxins have improved their anticounterfeit strategies. The box and the bottles now have holograms and physicians have been instructed to look for both. Packing slips are also an opportunity to verify the source of product received. In some of the counterfeit products seized by investigators, although the bottles

appeared to be legitimate, the serial numbers on the bottle and the box did not match.

Each of the companies that market type A toxins in the United States has a strong desire to maintain the integrity of their distribution channel. However, there is no national legislative initiative that seeks to make this an enforcement priority and as such, the FDA is limited in what they are able to do. Manufacturers have tried to educate physicians on the dangers and potential liability of purchasing illegal or counterfeit products, but because the risks of these actions are perceived as trivial there is little to dissuade a physician that can potentially save 25–50% cost on each bottle of material ordered.

---

## The size of the problem

It has been estimated that the size of the problem stemming from counterfeit drugs is about \$75 billion annually.<sup>2</sup> However, the actual size of the problem as it relates to counterfeit and illegally sourced BTXs is hard to quantify. It is likely to be several million dollars a year dependent on supply and demand for the product.

According to Katona, there were seven approved manufacturing facilities in the world for medical grade toxin and three more that are licensed to make reagent grade product not suitable for human use. Since the publication of his article, there are more manufacturers that have become capable of producing toxin. With several different sources of product, the ability to produce counterfeit product has increased.

Counterfeit BTXs have been found in the United States, Brazil, Iran, Canada, Spain, Russia, China, and Hong Kong. The various names they are offered under include Spain Tox, ProSigne, Quick Star, EsteTox A, Refinex, Novotox, Canitox, Linurase, and more.<sup>3</sup>

Internet sites offering illegal toxins have proliferated, and in 2011 there were at least 34 of them scattered across the globe.<sup>4</sup>

---

## Where does the unauthorized botulinum toxin come from?

According to the FDA, there are many sources of illegitimate BTX. In a recent warning to physicians and patients, the FDA warned that 'Online Botox Pharmacy,' 'Onlinebotox.com,' and 'Onlinebotox' were targeting users by using blast faxes rather than online solicitations.<sup>5</sup> These companies advertise discounted Botox and have return addresses in the United States but they operate outside US borders. The 'Onlinebotox' material uses a counterfeit box and the material inside is purported to be foreign Botox. However, the FDA reports that there is no way to know what the material or its source is. Potentially, the products might be a harmless white powder, but there is no certainty that it will not be toxic material. The FDA warns physicians to look for boxes where the carton expiration does not match the bottle expiration and to monitor any signs indicating that the material is foreign. Another potential

indication that a product is not legal is that it may say 'botulinum toxin type A'(BTX-A) instead of onabotulinum toxin A.

The illegal products enter the United States from a variety of countries. In some instances, physicians may purchase product in other countries and ship them to the United States. These may be toxin that is manufactured in approved facilities but not approved for importation. While these products are safe to inject, they run the risk of violating customs and FDA law. Other sources are not as reliable. For instance, there are several sources of counterfeit products that purport to be toxin that is approved but in reality these are manufactured by suppliers that are not approved for the production of any biologic material.

---

## What are the dangers of counterfeit or illegally sourced product?

One potential problem with counterfeit or illegally sourced product is that the potency is not known. In one sample of illegal, counterfeit product, the potency of a Chinese made BTXA was 243 units despite being labeled as being 55 units.<sup>6</sup> Obviously, for a patient receiving this toxin instead of one of the approved US toxins, the dose will be drastically different from what is expected. Symptoms of dysphagia, diplopia, and ptosis are all within the scope of likely outcomes from a dose that is 4.4 times as potent as Botox. For patients that are receiving treatment with multiple injections for multiple locations, it is possible that the Chinese toxin will deliver systemic symptoms.

There are many sources of CISPs. These range from foreign companies engaged in counterfeit manufacturing of BTXs and other biologic agents for profit to rogue countries making BTXs for bioweapon use to small businesses located in the United States and near the United States that copy materials. All have several things in common: they have no accountability, no quality control, and no reporting mechanism in the event of a problem. Each is in the business for cash and all seek to improve their margins by any means.

The authors of a *Scientific American* article, Ken Coleman and Raymond A. Zilinskas, highlight the problem created by demand for counterfeit BTXs and believe that it has created a secondary market for this drug and with that secondary market there are now secondary suppliers. The authors believe that 'the counterfeits contain real toxin, meaning that basement brewers may already be cultivating lethal toxin-making bacteria to satisfy avid consumer demand.'<sup>7</sup> These authors also point out another problem posed by the counterfeit BTXs: the regulatory agencies set up to deal with these problems are fragmented, with some oversight carried out by the FDA and some by the Centers for Disease Control and Prevention (CDC), but no comprehensive plan or agency that deals with this issue in a systematic manner.



---

## Conclusion

Counterfeit and illegally sourced BTXs have been an issue since soon after approval of these products for cosmetic use. Despite statutory penalties and the risk of malpractice suits as well as criminal prosecution, the problem continues to grow. The advent of new facilities that can make type A toxins as well as improvements by counterfeiters now make the problem one that seems likely to grow. In this environment, technologic improvements such as radiofrequency tagging devices as well as consumer education and vigorous enforcement by the FDA seem to be the most promising opportunities to protect patients.

---

## References

1. Weaver C. Illicit Botox sparks alert. *Wall St Journal*. Dec 23, 2012.
2. Katona P. Botulinum toxin: therapeutic agent to cosmetic enhancement to lethal biothreat. *Anaerobe* 2012; 18:240–243.
3. Pickett A, Mewies M. Serious issues relating to the clinical use of unlicensed botulinum toxin products. *J Am Acad Dermatol* 2009; 61:149–150.
4. Pickett A. Serious issues relating to counterfeit dermal fillers available from Internet sources. *J Am Acad Dermatol* 2011; 65:642–643.
5. US Food and Drug Administration (FDA). Fraudulent versions of Botox found in the United States. [www.fda.gov/drugs/drugsafety/ucm349503.htm](http://www.fda.gov/drugs/drugsafety/ucm349503.htm). Silver Spring, MD: FDA; 2013. (last accessed 21 July 2015)
6. Hunt T, Clarke K. Potency of the botulinum toxin product CNBTX-A significantly exceeds labeled units in standard potency test. *J Am Acad Dermatol* 2008; 58:517–518.
7. Coleman K, Zilinskas RA. Fake botox, real threat. *Sci Am* 2010; 302:84–89.



# HANDBOOK OF BOTULINUM TOXINS FOR AESTHETIC INDICATIONS THEORY AND PRACTICE

*Handbook of Botulinum Toxins for Aesthetic Indications: Theory and Practice* offers practical guidance on securing the best possible aesthetic results for different indications and in different patient types.

Introductory chapters on the structure and function of neurotoxin types and clinical safety are followed by chapters devoted to injection techniques in different regions of the face and body. Each of these techniques is clearly described in a step-by-step fashion, with illustrations showing injection sites and 'before and after' photographs.

Written by highly experienced practitioners and edited by a renowned educator in the field, *Handbook of Botulinum Toxins for Aesthetic Indications* is the ideal reference source for all clinicians seeking to expand their knowledge about the use of botulinum toxins in clinical practice.

- Provides a comprehensive, current review of new and existing neurotoxins and how best to combine with other treatments for optimal outcomes for patients
- Explains clearly how to treat different regions of the face, neck and chest, as well as hyperhidrosis in other body areas
- Includes chapters on the latest topical treatments and combining neurotoxins with lasers and fillers



[www.jpmedpub.com](http://www.jpmedpub.com)

