

# BOTOX Overview

## What is BOTOX®?

BOTOX® is a drug known most widely for its ability to temporarily smooth out facial wrinkles, though it also has several medical applications. Both its cosmetic and medical applications relate to Botox's ability to block muscle contractions.

Botox is manufactured by Allergan, based in Irvine, CA (see also our overview of Allergan). Its key ingredient is the same toxin responsible for Botulism food poisoning.<sup>1</sup> Botulinum toxin is "the most poisonous substance known," with the capacity to cause muscle paralysis and death in humans and other animals.<sup>2</sup> The toxin is produced by the bacteria Clostridium botulinum and has seven different forms known as serotypes (labeled A through G). Botox is a purified form of Botulinum Toxin Type A (BTA).<sup>3,4</sup>

## How Does Botox Work?

The active ingredient in Botox, BTA, blocks nerve impulses to muscles by interfering with the release of a key chemical involved in nerve signal transmission. Specifically, BTA binds to sites at the tips of nerves, enters these nerve "terminals" and inhibits the release of acetylcholine.<sup>5</sup> As a consequence, the nerve's signal to contract fails to reach the muscle. Over time, however, the nerve can grow new connections to the muscle, which is why, for example, Botox's effect on smoothing out facial wrinkles is only temporary (3-6 months).

## What is Botox Used For?

Botox is approved by the U.S. Food and Drug Administration (FDA) to treat several medical conditions (its "therapeutic" applications):<sup>6</sup>

- Cervical Dystonia – involuntary movement and prolonged muscle contraction of the neck
- Blepharospasm – involuntary forcible closure of the eyelids
- Strabismus – crossed eyes
- Hyperhidrosis – excessive sweating
- Dynamic muscle contracture in pediatric cerebral palsy patients (approved as an orphan drug\*) – an abnormality of motor function usually acquired at a young age

Botox is sometimes used for other medical conditions without specific FDA approval (so-called "off-label" applications which the company cannot advertise).<sup>7</sup> (See Appendix.)

In April 2002, Allergan gained FDA approval to market Botox to smooth out frown lines on the forehead (so-called glabellar lines between the eyes). It is sometimes used to treat wrinkles in other facial areas "off-label".<sup>8</sup> Botox designated for wrinkle smoothing is marketed as BOTOX® Cosmetic, whereas the product destined for medical applications is simply called Botox or Botox Therapeutic.

Botox has been approved for cosmetic applications in the following countries<sup>9,10</sup>: Canada (2001), New Zealand (2001), United States (2002), Australia (2002), Switzerland (2002), Taiwan (2002), Singapore (2002), and France (2003 as VISTABEL®).

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\* Technically speaking, FDA uses the term "designate" instead of "approval" when referring to orphan drugs, or those drugs that treat diseases/conditions that affect less than 200,000 Americans. (Office of Rare Diseases: [http://rarediseases.info.nih.gov/html/resources/about\\_ord.html](http://rarediseases.info.nih.gov/html/resources/about_ord.html) and FDA: <http://www.fda.gov/orphan/designat/index.htm>)

No cosmetic license has been approved for BTA or similar products in the United Kingdom. Any such licenses would be controversial given the prohibition on animal use for cosmetic purposes. However, BTA and similar products have been used for cosmetic purposes “off-license” in the UK.<sup>11</sup>

According to the American Society for Aesthetic Plastic Surgery (ASAPS), nearly 2.3 million cosmetic Botox procedures were performed in 2003, a 37% increase from 2002.<sup>12</sup> A single vial of Botox reportedly costs physicians \$400. Physicians on average charged \$443 per treatment in 2003. Each vial can treat up to approximately 5 patients with the physician potentially making around \$2,200 per vial.<sup>5, 13, 14</sup> However, product labeling states a vial should be used to treat only a single person. Once a vial of Botox powder has been mixed with saline, it has a life-span of 4 hours. This has led to the craze of Botox parties in which several people gather for Botox treatments in an effort to eliminate wasting the product.<sup>5, 11, 15</sup>

### **How is Botox Tested for Potency** (see also our overview on the LD<sub>50</sub> Test)

Botox belongs to a class of products known as biologics—physiologically active substances produced naturally by organisms (in this case bacteria) or synthetically in the laboratory. Examples include hormones, vaccines, antitoxins, and toxins themselves. The processes for producing most biologics are relatively crude, so the potency of these substances tends to vary from batch to batch. In the case of Botox, this means that each manufactured batch of the product is tested for potency, as a means of standardization.<sup>11</sup>

The procedure for assessing Botox potency is the LD<sub>50</sub> Test. This test involves injecting Botox into the abdominal cavity of mice and observing them for 3-4 days.<sup>4, 11</sup> The aim of the test is to estimate the dose that kills 50% of the animals (the “lethal dose 50%”), which is taken to be a measure of potency.<sup>11</sup> Approximately 100 mice have conventionally been used to test *each* batch of botulinum toxins products,<sup>11</sup> though Allergan has claimed to The HSUS that the company has significantly reduced this number.

Depending on the dose and potency of the batch being assessed, the test animals experience differing levels of muscular paralysis and impaired vision. The end point of the LD<sub>50</sub> Test is death, usually by suffocation after the respiratory muscles become paralyzed.<sup>11</sup>

### **How is Botox Manufactured?**

The steps in the manufacturing process of Botox are as follows:<sup>11</sup>

- Cultures of *Clostridium botulinum* are grown in a fermenter.
- Acid is added to precipitate the toxin produced by the bacteria.
- The toxin is harvested by centrifugation, then solubilized and purified.
- The solution is tested for contamination, *potency*, and protein content.
- The toxin is diluted in a solution containing human serum albumin and placed in storage vials, after which it is freeze-dried and the vials sealed.
- The vials are tested for integrity, sterility, moisture content and *potency*.
- Further confirmatory *potency* tests will be carried out by one or more control laboratories in the countries in which the batch will be used.

### **Are There Any Other Botulinum Toxin Products?**

Botox is the only BTA product approved to be marketed in the US (for both cosmetic and therapeutic purposes).<sup>16</sup> Dysport, a BTA product manufactured in the UK by Ipsen Ltd, is pending FDA

approval for cosmetic use in the United States.<sup>17</sup> Solstice Neurosciences, Inc (San Diego, CA) markets a Botulinum Toxin Type B (BTB) product known as MYOBLOC<sup>®</sup>, which is approved by the FDA for the treatment of cervical dystonia, a muscle disorder of the neck. It is marketed in the UK under the name Neurobloc<sup>®</sup>.<sup>18</sup> BTB has a different manufacturing process than BTA. Compared to BTA products, BTB products take effect more quickly but also wear off more quickly.<sup>11, 19</sup>

### **How is Botox Regulated?**

Botox is the only botulinum toxin product approved for cosmetic use in the United States. Little information is available publicly about the types of potency testing, if any, that the FDA requires Allergan to conduct on Botox. Repeated requests by The HSUS to the FDA have yielded little pertinent information. However, given that the LD<sub>50</sub> Test is the international standard for assessing potency of botulinum toxin products, there is little doubt that the FDA holds Allergan to this standard. In light of the technical and humane problems associated with the LD<sub>50</sub> Test, European authorities have identified potential alternative tests that, once validated, would be acceptable as substitutes in assessing botulinum products. These potential alternatives include the endopeptidase assay and a mouse assay using paralysis as the endpoint, such as the hind limb assay.

## Appendix

### “Off-Label” Uses of Botox

Multiple sclerosis	a neurodegenerative disease characterized by the gradual accumulation of focal plaques of demyelination particularly in the periventricular areas of the brain. Onset usually occurs in 3rd or 4th decade.
Schilder’s disease	at least two separate disorders described by Schilder: 1) Diffuse sclerosis or encephalitis periaxialis diffusa; a non-familial disorder affecting primarily children and young adults and characterized by progressive dementia, visual disturbances, deafness, pseudobulbar palsy, and hemiplegia or quadriplegia. 2) The leukodystrophies - cause damage to the myelin sheath of the nerve fibers in the brain. The myelin sheath is a fatty covering which acts as an electrical insulator
Central demyelinating of corpus callosum	disease in which the myelin sheath of nerves in the great commissure (connection) between the two cerebral hemispheres is destroyed.
Hereditary spastic paraplegia	a hereditary condition that causes paresis of the lower extremities with increased muscle tone and spasmodic contraction of the muscles.
Anal fissures	tears or superficial lacerations that can occur in the mucosa that lines the anal canal.
Migraines	periodic attacks of severe headaches on one or both sides of the head.
Achalasia/Cardiospasm	constriction of the lower portion of the food pipe (oesophagus) due to inability of the sphincter muscles to relax.
Tourette syndrome	a neurologic disease of unknown cause that presents with multiple tics (uncontrolled behavior), associated with snorting, sniffing and involuntary vocalizations.
Low back pain	
Piriformis syndrome	entrapment of the sciatic nerve by the piriformis muscle.
Diabetic Gastrointestinal Disorder	caused by spasms in the pylorus, the small opening between the stomach and the small intestine

<sup>1</sup> eMedicine (<http://www.emedicine.com/pmr/topic216.htm>)

<sup>2</sup> FDA ([http://www.fda.gov/fdac/features/095\\_bot.html](http://www.fda.gov/fdac/features/095_bot.html))

<sup>3</sup> FDA (<http://www.fda.gov/cder/foi/label/2002/botuall041202LB.pdf>)

<sup>4</sup> Pearce, L.B., et. al. 1994. Measurement of Botulinum Toxin Activity: Evaluation of the Lethality Assay. *Toxicology and Applied Pharmacology* 128, 69-77.

<sup>5</sup> Allergan (<http://www.botoxcosmetic.com/pi/pi/pdf>)

<sup>6</sup> Allergan ([http://www.botox.com/site/professionals/approved\\_uses/home.asp](http://www.botox.com/site/professionals/approved_uses/home.asp))

<sup>7</sup> The Regence Group (<http://www.regence.com/trgmedpol/drugs/dru006.html>)

<sup>8</sup> FDA (<http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01147.html>)

<sup>9</sup> Allergan (<http://www.shareholder.com/AGN/downloads/2003AnnualReport.pdf>)

<sup>10</sup> Allergan (<http://www.shareholder.com/agn/ReleaseDetail.cfm?ReleaseID=102530>)

<sup>11</sup> FRAME (ATLA, Vol 31, No 4, pg 381-391)

<sup>12</sup> PR Newswire ([http://biz.yahoo.com/prnews/040218/nyw030\\_1.html](http://biz.yahoo.com/prnews/040218/nyw030_1.html))

<sup>13</sup> American Academy of Facial Plastic and Reconstructive Surgery ([http://www.facial-plastic-surgery.org/media/stats\\_polls/AAFPRS%20MEDIA%202004%20-%20Final.pdf](http://www.facial-plastic-surgery.org/media/stats_polls/AAFPRS%20MEDIA%202004%20-%20Final.pdf))

<sup>14</sup> Los Angeles Times (<http://www.latimes.com/features/health/la-he-botox22sep22-20.7604567.story?coll=la-features-health>)

<sup>15</sup> FDA ([http://www.fda.gov/fdac/features/2002/402\\_botox.html](http://www.fda.gov/fdac/features/2002/402_botox.html))

<sup>16</sup> FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

<sup>17</sup> BioSpace ([http://www.biospace.com/news\\_story.cfm?StoryID=15087820&full=1](http://www.biospace.com/news_story.cfm?StoryID=15087820&full=1))

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<sup>18</sup> Solstice Neurosciences (<http://www.solsticeneuro.com>)

<sup>19</sup> Brin, M.F. 1997. Botulinum Toxin: Chemistry, Pharmacology, Toxicity, and Immunology. *Muscle & Nerve* 20, Suppl. 6, S146-S168.