BOTULINUM TOXIN: FROM THE MOST POISONOUS TOXIN TO A VALUABLE PHARMACEUTICAL

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Introduction. Botulinum neurotoxin type A (BoNT/A) is the most poisonous substance known to humankind. Since its approval by the FDA in 1989 for three dystonic disorders, BoNT/A has emerged as an extremely valuable pharmaceutical for treatment of a myriad of neurological disorders and for cosmesis.
This paper will summarize the early development of BoNT/A as a biological, and describe recent key developments, particularly chemistry and manufacturing controls (CMC), and a non-animal assay based on induced pluripotent stem cells (iPSC). Future developments in progress for improved BoNT/A as a drug are also described.

Methods. The overall strategy of this work is to describe key developments in the elaboration of BoNT/A as an approved drug. This includes aspects of manufacturing, CMC, and non-animal testing methods. The methods include challenges and solutions in FDA and worldwide approval of BoNT/A.

Results. After 20 years of investigation in nonhuman primates and human volunteers, BoNT/A was approved by the FDA in the USA for limited use of three neurological disorders of the face and neck. The use has expanded to include inflammatory and pain disorders, including cerebral palsy, spasticity following stroke, and migraine headaches.
The key technologies include production using special strains of *Clostridium botulinum*, purification methods, CMC, and animal and non-animal assays.

Conclusions. The key characteristics of BoNT/A as an approved pharmaceutical are its purity, specific activity (toxicity), safety measures, and potency testing. Although currently limited to treatment of approximately 10 neurological disorders, off-label trials indicate that BoNT/A can be used in approximately 100 neurological disorders.

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