SPECIAL ARTICLE

Creation and Development of the Public Service Orphan Drug Human Botulism Immune Globulin

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The author has indicated he has no financial relationships relevant to this article to disclose.

ABSTRACT

The public service orphan drug Human Botulism Immune Globulin for the treatment of infant botulism would not have come into existence without the federal Orphan Drug Act and the funding mechanism that it provided to conduct pivotal clinical trials. Nonetheless, creating, developing, and achieving licensure of Human Botulism Immune Globulin took approximately 15 years and approximately $10.6 million (2005 dollars) to accomplish. Use of Human Botulism Immune Globulin to treat patients with infant botulism has resulted thus far in more than 30 years of avoided hospital stay and more than $50 million (2005 dollars) of avoided hospital costs. To provide a possible paradigm for others, the circumstances that enabled a state public health department to create, test, license, and distribute an orphan drug are described here.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-0646

doi:10.1542/peds.2006-0646

This work was presented in part at the Scientific Symposium of the 25th reunion class, Harvard Medical School; June 5, 1997; Boston, MA.

Key Words
infant botulism, botulism immune globulin, BabyBIG, botulinum toxin, botulism, orphan drugs, orphan diseases, drug development

Abbreviations
FDA—US Food and Drug Administration
BIG—Botulism Immune Globulin
BIG-IV—Botulism Immune Globulin Intravenous (Human)
CDHS—California Department of Health Services
IND—investigational new drug
OOPD—Office of Orphan Products Development
IRB—institutional review board
CDC—Centers for Disease Control and Prevention

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275); published in the public domain by the American Academy of Pediatrics

INFANT BOTULISM IS the intestinal toxemia form of human botulism that occurs when swallowed spores of *Clostridium botulinum* (or, rarely, *Clostridium butyricum* or *Clostridium baratii*) germinate, temporarily colonize the large intestine, and produce botulinum toxin in it. Botulinum toxin blocks neuromuscular transmission, and the illness usually presents as weakness and hypotonia of bulbar and skeletal musculature. Seven toxin types (A through G) of botulinum toxin exist that are distinguished from each other by the inability of neutralizing antitoxin against 1 toxin type to neutralize any of the other 6 types. Almost all infant botulism in the United States results from either botulinum toxin type A or B.

ORPHAN DISEASES AND ORPHAN DRUGS

Infant botulism causes the hospitalization of ~80 to 110 children in the United States each year and thereby qualifies as an orphan disease, which, by definition, is an illness or condition that affects fewer than 200 000 persons in the United States.[1] This definition was chosen in part because this disease prevalence had historically provided insufficient market incentives to stimulate development of new therapeutics by the pharmaceutical industry.[2] However, ~6000 such orphan diseases are believed to exist that collectively affect ~25 million US residents.[3] Thus, the large population of patients with orphan disease (~8% of the US population) who had been left without medicines constituted a major societal lapse and public health problem that was remedied partially by passage of the Orphan Drug Act in 1982. The act (Pub L No. 97-414, as amended) enabled the US Food and Drug Administration (FDA) to support pivotal (phase III) clinical trials, as this requirement had been identified as the major obstacle to licensure of potential products for orphan diseases. The act also provided financial incentives (research credits and a period of market exclusivity) to orphan-drug sponsors. From 1995 to 2005, Congress provided between $11.3 and $14.4 million annually to the FDA for pivotal orphan-drug and -device trials.[4] In the 22 years 1983–2005, a total of 256 orphan drugs and devices have been licensed, in contrast to fewer than 10 in the 10 years preceding 1982.[2] The Orphan Drug Act also authorized academic, governmental, and other not-for-profit institutions to sponsor the development of orphan drugs.

THE PRODUCT

Botulism Immune Globulin Intravenous (Human) (BIG-IV) was created by the California Department of Health Services (CDHS) in 1991 to treat infant botulism caused by type A or B botulinum toxin.[5] BIG-IV was produced from high-titer immune plasma that was donated by CDHS volunteers and others who had been immunized with pentavalent (A–E) botulinum toxoid for occupational safety and then boosted before plasmapheresis. The product was made and licensed in accord with all FDA requirements, which included careful screening of donors and testing of plasma for viral (eg, HIV) and other illnesses. BIG-IV is a lyophilized, 5% immunoglobulin G powder that is stabilized with 1% human albumin and 5% sucrose and contains ≥15 IU of anti-A and ≥4 IU of anti-B neutralizing antibody per 50 mg.

BIG-IV was evaluated for safety and efficacy in a randomized, controlled pivotal trial in California in 1992–1997 and in a subsequent nationwide open-label study in 1998–2003. The primary efficacy end point of the pivotal trial was a significant reduction of mean hospital stay, while the safety evaluation was a comparison of the occurrence of adverse events in the treatment and placebo (commercial normal human immune globulin) arms of the study.

In brief, in the pivotal statewide clinical trial, treatment with BIG-IV shortened the mean hospital stay from 5.7 to 2.6 weeks ($P < .001$) and reduced mean hospital charges by $88 600 (2004 dollars) per patient ($P < .001$). The mean duration of intensive care was shortened by 3.2 weeks ($P < .001$), mean duration of mechanical ventilation was reduced by 2.6 weeks ($P = .01$), and mean duration of tube or intravenous feeding was shortened by 6.4 weeks ($P < .001$). All these primary and secondary outcome measures were also reduced significantly when stratified by toxin type (A or B) of illness. There were no serious adverse events attributable to treatment. In the nationwide open-label study, the mean hospital stay was further reduced to 2.2 weeks, and early treatment with BIG-IV shortened hospital stay significantly more than did later treatment.[5] Since introduction of BIG-IV, its use to treat patients with infant botulism has resulted thus far in more than 30 years of avoided hospital stay and more than $50 million (2005 dollars) of avoided hospital costs.

CHRONOLOGY

The need for a human botulism immune globulin to treat patients with infant botulism became evident with initial recognition of the disease in California in 1976. The existing equine botulism antitoxin was known to have substantial serious adverse effects (eg, allergic reactions, serum sickness, anaphylaxis)[6] and a short 5- to 7-day half-life.[7] Efforts in 1977–1978 by the CDHS and the University of Wisconsin to initiate civilian development of a human botulism immune globulin to be sponsored by the US Department of Health, Education, and Welfare (predecessor to the Department of Health and Human Services) were unsuccessful. However, in 1978 the US Army began to collect hyperimmune botulism immune plasma,[8] from which it eventually made a BIG investigational new drug (IND) product.[9]

The request of the CDHS in 1982 for a small amount of the IND Army BIG with which to treat patients with infant botulism was fulfilled some years later after passage of the 1986 Federal Technology Transfer Act pro-

vided the Army with needed authority to make its research products available to the civilian sector. The now-available Army product enabled the CDHS in December 1988 to apply to the FDA Office of Orphan Products Development (OOPD) for funds with which to carry out a pivotal clinical trial of BIG for the treatment of infant botulism. At the time, California was the only locale in the world that could conduct such a trial because its high endemic incidence of this rare disease provided an adequate number of patients and its established state health department infant botulism program provided disease expertise and statewide laboratory diagnostic services. The OOPD officially designated BIG an orphan drug in early 1989.

With OOPD approval of its randomized, placebo-controlled, double-masked, pivotal clinical trial design and funding application, the CDHS proceeded to organize the study by recruiting participating physicians and hospitals and obtaining institutional review board (IRB) approval from each one. California's large size, together with the rarity of the disease and the unpredictability of its occurrence, necessitated recruitment of all hospitals that had treated at least 1 patient with infant botulism in the previous 5 years. Organizational efforts, arranging hospital and local investigator participation, and obtaining the needed 59 hospital IRB approvals took ~1 year to complete. IRB approval times for the identical protocol ranged from 2.5 weeks to 10.5 months.

In August 1990, as the pivotal-trial organizational efforts neared completion, Iraq invaded Kuwait. In consequence, the US Army redirected its entire supply of BIG to anticipated military needs in the Persian Gulf. Although the CDHS and the California pediatric community were ready to begin the pivotal clinical trial, there was no product to evaluate.

This setback was overcome by creating a new product that the FDA formally named Botulism Immune Globulin Intravenous (Human) (BIG-IV). Because of its ongoing botulism research and diagnostic activities, the CDHS had in 1990 a relatively large number of individuals who had been immunized for occupational safety with a still-investigational (after 30 years) botulinum toxoid product that was distributed by the Centers for Disease Control and Prevention (CDC). These people, together with others similarly immunized, volunteered to donate their immune plasma so that the antibotulinum toxin antibodies in it could be used to make the new BIG-IV to replace the Army's diverted product. The FDA Orphan Drug Office provided supplementary funding for collection of plasma, and a licensed manufacturer of human immune globulin products (the Massachusetts Public Health Biologic Laboratories) fractionated the immune plasma into BIG-IV lot 1 at no charge because the prospect of a public service orphan drug harmonized with its institutional activities and goals. Approvals from the IRBs of the 59 participating hospitals then had to be obtained to substitute BIG-IV lot 1 for the original Army BIG product.

The pivotal clinical trial of BIG-IV finally opened for patient enrollment in February 1992. Five years later, the planned 120th patient with laboratory-confirmed infant botulism was entered into the study. In the interim, at the urging of parents of patients with infant botulism, the California legislature and governor had approved a measure that aligned the CDHS activities with the requirements of the federal Orphan Drug Act. The unanimously passed legislation provided for ongoing production and national distribution of BIG-IV as a not-for-profit, self-supporting state activity if the pivotal clinical trial demonstrated safety and efficacy of the product.

In May 1997, after obtaining the advance approval of FDA statisticians and regulators with whom the study statisticians had previously and privately reviewed the results, a semipublic data-unveiling meeting was held in Berkeley, California. At this meeting, the study investigators and representatives of the FDA, the CDC, CHDS administrative leadership, parents of patients, donors of BIG-IV source plasma, and interested colleagues all learned for the first time that the pivotal clinical trial had succeeded in meeting its primary and secondary end points. A few days later, the FDA authorized open-label distribution of BIG-IV in California under compassionate use and emergency IND status because hospital IRB approval of the product already existed here.

In June 1998, while licensure efforts continued, the FDA authorized nationwide open-label distribution of BIG-IV under treatment IND status because the pivotal clinical trial had been completed and the product treated a life-threatening condition for which no alternative therapy existed.[10] Open-label treatment IND distribution of BIG-IV enabled confirmation and extension of the safety and efficacy results of the pivotal clinical trial with a much larger number of treated patients; such follow-up confirmation was later recommended generally for orphan-drug studies.[11] Open-label treatment IND distribution also permitted limited ($1.8 million [2005 dollars]) recovery of the prelicensure CDHS developmental expenses for BIG-IV that are specified in federal regulations as not to exceed "the costs of manufacture, research, development and handling of the investigational drug."[12] The FDA recently proposed new regulations that further limit cost recovery for investigational drugs.[13]

A principal remaining licensure requirement was the production of a second lot of BIG-IV, an ~3-year endeavor that was completed in 2000. Because plasma donors were then being boosted with the investigational (ie, unlicensed) botulinum toxoid for nonoccupational safety reasons, additional IRB (CDHS and CDC) and FDA approvals were required. Later in 2000, the CDHS and the FDA met for prelicensure application discussions, and in 2001 the CDHS submitted the biologics license

application for BIG-IV as a preapproved "fast-track" submission. In June 2002, the FDA returned a comprehensive review of the biologics license application that conveyed additional licensure requirements, to which the CDHS was able to respond in April 2003. The responses were satisfactory, and exactly 6 months later on October 23, 2003, in accord with fast-track procedures, the FDA licensed BIG-IV to the CDHS as BabyBIG for the treatment of infant botulism types A and B.

COMPARATIVE COSTS AND REGULATORY APPROVAL TIMES

Creating, testing, and obtaining licensure for BIG-IV cost approximately $10.6 million (2005 dollars) in cash expenditures. The FDA OOPD provided approximately $1.9 million (17.9%), FDA-approved prelicensure cost-recovery fees provided $1.8 million (17.0%), and the State of California provided $6.9 million (65.1%) through "in-kind" contributions and interest-bearing loans from the state's general fund (a not-uncommon method of launching eventually self-supporting "at-cost" public health programs) (all in 2005 dollars). In comparison, as determined by the Tufts Center for the Study of Drug Development, the median "out-of-pocket" developmental costs (comparing only phase II and III costs because BIG-IV had negligible phase I costs) for 24 newly approved (1983–1994) small-molecule and biological products were $110.2 million (2000 dollars).[14] Although the Tufts Center methodology has been questioned,[15] it determined that the total out-of-pocket developmental costs for these and other products averaged $403 million (2000 dollars).[14]

The mean time from initiation of clinical testing to licensure for the 24 products analyzed by the Tufts Center was 14.0 years (a duration that includes the "interphase" times between phase I–III studies and submission of the license application[14]). The equivalent interval for BIG-IV was 11.7 years. Total development time for BIG-IV from submission of the study protocol and initial funding application to licensure was 14.8 years.

Recent calls for improvement in the drug-approval process reflect in part the shortcomings of the present pathway in expeditiously providing new medicines, particularly new molecular entities, to patients.[16,17] This deficiency is highlighted by the fact that in the mean interval between the start of clinical testing and new product licensure (14.0 years[14]), Marco Polo in the 13th century could have traveled over land and sea from Venice, Italy, to Beijing, China, and back to Venice approximately twice (2 × 7.8 years). Other comparative multiples of noteworthy feats of exploration and discovery accomplished under similarly arduous circumstances during the ensuing 700 years are substantially higher (Table 1).

CONCLUSION

BIG-IV came into existence through a variety of special circumstances. The high incidence of this rare illness in California enabled a randomized, controlled, pivotal treatment trial to be conducted here. The federal Orphan Drug Act provided a mechanism for funding the trial. The availability in northern California of potential donors immunized with investigational botulinum toxoid permitted collection of the botulism immune plasma that was needed to make sufficient BIG-IV to carry out the clinical trials. The California legislature and governor supported the project with legislation and loans, which enabled the medicine eventually to become licensed. The developmental costs of BIG-IV were substantially lower than those of most new pharmaceutical products, and its time to licensure was less than average. The humanitarian and societal benefits of BIG-IV have been established by the more than 30 years of avoided hospital stay and by the more than $50 million of avoided hospital costs that have been achieved thus far through use of the medicine. In 2004 the National Museum of American History (a part of the Smithsonian Institution) requested and received an exemplary vial of BabyBIG for its permanent medicines collection.

TABLE 1 **Comparative Times of Terrestrial Exploration Achievements and Modern Drug Licensure**

Explorer/Leader	Destination	Departure Date, Location	Arrival Date, Location	Elapsed Time, y
Marco Polo[18]	China	Spring 1271, Venice, Italy	Summer 1275, Beijing, China	4.3
		Spring 1292, Zayton, China	Winter 1295, Venice	3.5
Columbus[19]	East Indian islands	August 1492, Palos, Spain	March 1493, Palos	0.6
Magellan[20]	Philippine and "Spice" Islands (circumnavigation of the globe)	August 1519, Seville, Spain	September 1522, Seville	3.1
Cook[21]	"Great South Land" (Antarctica) and Pacific Ocean exploration	July 1772, Plymouth, UK	July 1775, Plymouth	3.0
Lewis and Clark[22]	Pacific Ocean overland	May 1804, St Louis, MO	September 1806, St Louis	2.4
Burton[23]	Headwaters of the Nile	October 1856, London, UK	May 1859, London	2.6
Amundsen[24]	South Pole	June 1910, Norway	March 1912, Tasmania, Australia	1.8[a]
Hunt[25]	First ascent of Mt Everest	February 1953, London	July 1953, London	0.4
New drug sponsor[14]	US licensure	1983–1994 survey period	FDA, Rockville, MD	14.0[b]

[a] In Antarctica January 1911 to January 1912; Amundsen did not immediately return to Norway but instead proceeded to a lecture tour in Australia.
[b] Mean time from start of phase I clinical testing to licensure, including mean interphase times (data are from Table 3 in ref 14).

ACKNOWLEDGMENTS

This work was supported by Cooperative Agreement FD-U-000476 between the FDA OOPD and the CDHS and by the CDHS.

I thank Marlene Haffner and the late William Silverman for many years of wise counsel and support and Robert Schechter for exceptional contributions to the success of the clinical trials of BIG-IV.

REFERENCES

1. Orphan Drug Act, US Pub L No. 97-414 (1984, as amended); 21 USC §360aa et seq
2. Haffner ME. Adopting orphan drugs: two dozen years of treating rare diseases. *N Engl J Med.* 2006;354:445–447
3. National Organization for Rare Disorders. *NORD Guide to Rare Disorders*. Philadelphia, PA: Lippincott Williams & Wilkins; 2003
4. National Organization for Rare Disorders. Public policy priorities: update from NORD's Washington office. *Orphan Dis Update.* 2005;23:16
5. Arnon SS, Schechter R, Maslanka SE, Jewell NP, Hatheway CL. Human Botulism Immune Globulin for the treatment of infant botulism. *N Engl J Med.* 2006;354:462–471
6. Black RE, Gunn RA. Hypersensitivity reactions associated with botulinal antitoxin. *Am J Med.* 1980;69:567–580
7. Hatheway CL, Snyder JD, Seals JE, Edell TA, Lewis GE Jr. Antitoxin levels in botulism patients treated with trivalent equine botulism antitoxin to toxin types A, B, and E. *J Infect Dis.* 1984;150:407–412
8. Lewis GE Jr, Metzger JF. Botulism immune plasma (human). *Lancet.* 1978;2(8090):634–635
9. Lewis GE Jr. Approaches to the prophylaxis, immunotherapy, and chemotherapy of botulism. In: Lewis GE Jr, ed. *Biomedical Aspects of Botulism*. New York, NY: Academic Press; 1981: 261–270
10. 21 CFR §312.34
11. Lagakos SW. Clinical trials and rare diseases. *N Engl J Med.* 2003;348:2455–2456
12. 21 CFR §312.7(d)(3)
13. US Food and Drug Administration. Charging for investigational drugs under 21 CFR part 312. *Fed Regist.* 2006;71:75168–75181
14. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ.* 2003;22:151–185
15. Love J. How much does it cost to develop a new drug? Available at: www.cptech.org/ip/health/econ/howmuch.html. Accessed February 15, 2007
16. Wood AJJ. A proposal for radical changes in the drug-approval process [published correction appears in *N Engl J Med*. 2006; 355:2712]. *N Engl J Med.* 2006;355:618–623
17. Curfman GD, Morrissey S, Drazen JM. Blueprint for a strong Food and Drug Administration. *N Engl J Med*. 355:1821
18. Polo M. *The Travels of Marco Polo*. New York, NY: Orion Press; 1958
19. Morison SE. *Admiral of the Ocean Sea: A Life of Christopher Columbus*. Boston, MA: Little Brown; 1942
20. Cameron I. *Magellan and the First Circumnavigation of the World*. New York, NY: Saturday Review Press; 1973
21. Villiers A. *Captain James Cook*. New York, NY: Scribner; 1967
22. Ambrose SE. *Undaunted Courage*. New York, NY: Simon & Schuster; 1996
23. Rice E. *Captain Sir Richard Francis Burton*. New York, NY: Scribner; 1990
24. Huntford R. *The Last Place on Earth*. New York, NY: Atheneum; 1985
25. Hunt J. *The Conquest of Everest*. New York, NY: Dutton; 1954