

How Federal Regulations Hiked EpiPen Prices

Backgrounder No. 186

by Devon Herrick

October 24, 2016

People with severe allergies and asthma often carry an epinephrine auto-injector or have one readily available at all times. The most common model by far is the EpiPen, which enjoys an 85 percent market share.¹ The price of the EpiPen, preloaded with the generic drug epinephrine, has increased by more than 400 percent in less than a decade.



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The drug maker Mylan bought the rights to the nearly 30-year-old EpiPen in 2007. At the time, one EpiPen sold for about \$57.² By August 2016, Mylan had raised the price of each EpiPen to more than \$304.³ Due to rising health plan deductibles over the past 10 years, families have increasingly borne more of the cost of health care out of pocket. Higher cost-sharing made it more difficult for Mylan to mask its price increases.⁴ A public outcry at Mylan's price hikes ensued. The case of EpiPens shows why it important to use cost-sharing to enlist consumers in the battle to control drug spending. Without consumers complaining about their share of the cost, there would be little public outcry to stop many of the more egregious price hikes.

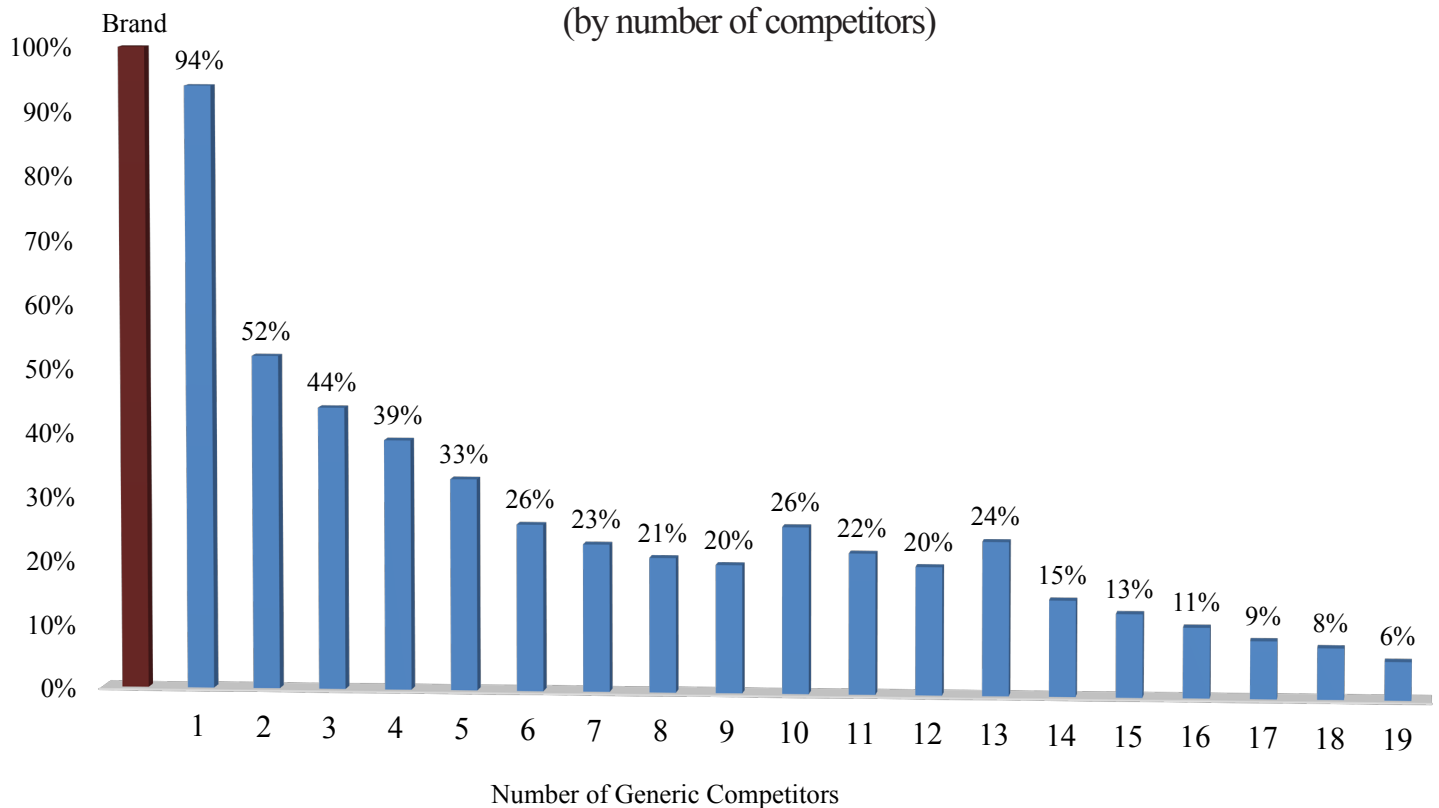
Costly Regulations

Mechanical engineers have been working on auto-injectors for 50 years and the technology is not particularly complicated. The devices should be sold for less than \$20 apiece, based on production costs. That is probably about how much they would cost if the Food and Drug Administration (FDA) approved an over-the-counter version or a "behind the counter" version pharmacists could dispense without a doctor's prescription. The price of a generic drug is much lower than the original when there are several competitors. [See Figure I.] Moreover, over-the-counter drugs often cost 95 percent less than when sold only by prescription. Greater access could save lives by making epinephrine more easily accessible.

Instead, Epinephrine auto-injectors worth more than \$1 billion expire annually, unused; or, more accurately, Americans waste more than \$1 billion annually on \$80 million dollars' worth of epinephrine

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Figure I
Generic Drugs Prices as a percentage of Branded Drug Prices
 (by number of competitors)



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective (™), 1999-2004, extracted February 2005. Cited in Office of the Assistant Secretary for Planning and Evaluation, "Expanding the Use of Generic Drugs," ASPE Issue Brief, Office of Science and Data Policy, U.S. Department of Health and Human Services, December 1, 2010. Available at <http://aspe.hhs.gov/sp/reports/2010/genericdrugs/ib.pdf>.

auto-injectors that are discarded unused.

History of the EpiPen. Sheldon Kaplan, a mechanical engineer, and four colleagues patented an auto-injector in 1977. Kaplan, who was trained at Northwestern University, worked for Survival Technologies, Inc., a Pentagon contractor, on an auto-injector that could administer antinerve-gas agents quickly, while keeping the agents stable in the field.⁶ Kaplan's design could also inject epinephrine and became the EpiPen around 1980. Kaplan's auto-injector was an improvement over an earlier invention by two colleagues, Calkins and Sarnoff, who also worked with Kaplan on the later design. Calkins and Sarnoff improved upon earlier versions designed by others.⁷

Survival Technologies Inc. patented numerous improvements over the years. The firm later merged with another company to become Meridian Medical

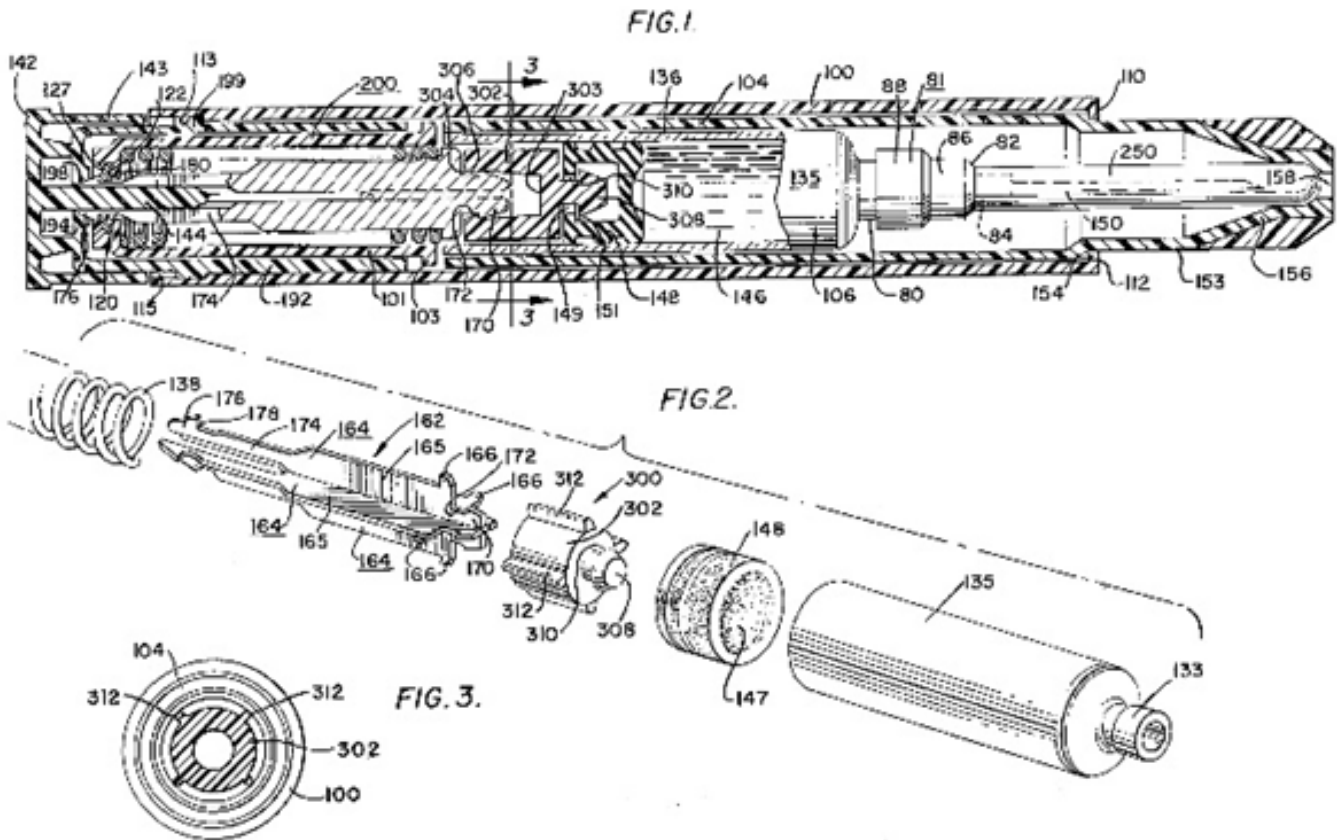
Technologies, Inc.⁸ In 2004, Kaplan invented the auto-injector that became the current version of the EpiPen.⁹ The patent will not expire until 2025. [See Figure II.]

Regulations Limit Competition. Why is a 40-year-old product used to administer a generic drug so expensive? Like many costly drugs, much of the blame is due to the way drugs are regulated in the United States by the FDA.

Adrenaline was synthesized more than 100 years ago.¹⁰ Epinephrine — a synthetic form of adrenaline — has long since lost patent protection. The epinephrine injected by the EpiPen is available in ampules costing less than \$1. One firm sought FDA approval to sell syringes prefilled with epinephrine. The FDA rejected the application — requiring the firm conducted more usability studies to assess whether patients are capable of self-injecting.¹¹

Figure II

U.S. Patent 4,031,893 June 28, 1977



Source: Sheldon Kaplan et al., "Hypodermic Injection Device Having Means for Varying the Medicament Capacity Thereof," U.S. patent 4031893 A, June 28, 1977. Available at: <http://www.google.com/patents/US4031893>.

The FDA has twice rejected applications to market syringes prefilled with epinephrine.¹²

Unnecessary FDA Roadblocks. The initial patent for the EpiPen expired in 1997, but safety improvements over the years led to patent extensions. A new patent was issued in 2004 for various updates to the EpiPen.¹³ The firm that licensed the technology to Mylan identified potential problems and developed a newer design with features to boost efficacy and safety. The newer EpiPen auto-injector has features that guard against accidental needle sticks after the cannula (needle) has been extended and lowers the probability of premature cannula deployment. Because newer versions are available, the FDA is unlikely to

approve a generic version based on the 1977 design.

There are currently nine competing epinephrine auto-injectors selling in various countries throughout Europe — only two of which have been approved for sale in the United States (EpiPen and AdrenaClick).¹⁴ A talking epinephrine auto-injector made by French drug maker Sanofi was recalled because 26 of its units supposedly administered inaccurate doses.¹⁵ Sanofi ended its licensing agreement to sell the Auvi-Q and is not expected to return the product to market.¹⁶

A generic EpiPen from the Israeli drug maker Teva suffered a setback when the FDA declined to approve it until Teva addresses some of the

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FDA's concerns. As a result, the launch of Teva's epinephrine auto-injector has been delayed until 2018.¹⁷

Auto-injector syringes are a mature technology, with well over 100 patents granted.¹⁸ Arguments that patient safety requires expensive auto-injectors are not grounded in logic. Patients potentially going into anaphylactic shock could be either male or female, young or old, heavy or slender, and have a high metabolism or a low one. Yet, there are only two FDA-approved doses for the auto-injector market — 0.3mg and 0.15mg. Regardless of their size, all patients suffering an anaphylaxis emergency must take either a 0.15 or 0.30 epinephrine dose, one (\$300 shot) at a time.¹⁹

From the FDA's perspective, an epinephrine auto-injector is a combination product; composed of both a drug and a medical device. The principal method of action of the combination product determines whether the FDA's Center for Drug Evaluation and Research or the FDA's Center for Devices and Radiological Health takes the lead on the approval process.

Since the method of action is epinephrine, an epinephrine auto-injector is considered a drug and must go through a new drug application (NDA) process. Once the patent expires, competing drug makers can, at least in theory, apply for an abbreviated new drug approval (ANDA) for a generic drug. Generic epinephrine is made by several firms and sold inexpensively in ampules. Yet, the FDA requires each new epinephrine auto-injector to be approved as if it were a new drug.

Even if firms were allowed to apply for the right to sell a generic using the older EpiPen design, the backlog of ANDAs awaiting the FDA's approval number nearly 4,000.²⁰ Approving a competing product could take several years — even if the FDA were willing to approve a generic based on the older design, which is unlikely.

By contrast, FDA marketing clearance for a medical device is much simpler when there are already similar devices on the market. All that is required is to submit a 510(k) Premarket Notification. To be eligible, the maker merely

has to prove the new device is “substantially equivalent” in effectiveness and safety to a preexisting device.

Indeed, a quick search of the FDA's 510(k) Premarket Notification database identified 10 different auto-injectors that are registered and legal to market.²¹ These devices all claimed substantial equivalence to earlier ones. In theory, a person at risk of anaphylaxis could preload one of these with epinephrine.²² Yet, manufacturers cannot sell them to patients preloaded without FDA approval as a new drug.

Currently, firms wishing to compete in the epinephrine auto-injector market face an impossible task. As we have seen in the case of Teva's generic EpiPen, Sanofi's Auvi-Q and Adamis Pharmaceuticals epinephrine-filled syringe, the FDA is hesitant to allow too much variation in competing products. The agency apparently believes one very costly standard is preferable to minor variations in design that cost a fraction of an EpiPen.

The Market for Epinephrine Auto-injectors

Lobbying and savvy marketing has raised awareness of anaphylaxis and severe allergic reactions to food and insect stings. Like any marketing campaign, raising the awareness of a medical condition and touting commercial remedies is not merely a public service. An aggressive public awareness campaign likely over-hyped the prevalence and severity of anaphylaxis — and was designed to boost sales of the EpiPen. [See the sidebar, “How Common Is Anaphylaxis?”] It worked very well. Mylan's marketing — and lobbying for public schools to stock EpiPens — increased the number of patients who use its product by two-thirds.²³ Indeed, Mylan lobbied to influence the U.S. Preventive Services Task Force to deem the EpiPen a preventive medicine, which would force health plans to cover it with no cost-sharing.²⁴ Mylan is expected to sell more than 8 million EpiPens this year.²⁵

Treatment of Anaphylaxis. The treatment of choice for anaphylaxis is epinephrine — a

How Common Is Anaphylaxis?

Severe allergies can result in anaphylaxis, where a person's windpipe begins to swell shut. On rare occasions anaphylaxis can result in death, but the mortality rate is only a fraction of 1 percent.²⁶ Anaphylaxis is especially worrisome for the parents of young children allergic to peanuts or tree nuts, because parents cannot be with their kids every moment of the day. By some estimates 4 percent of children have some type a food allergy.²⁷ Yet the likelihood of a child suffering anaphylaxis is very low. Estimates vary, but a study from Minnesota in the 1990s found the rate of children suffering an anaphylactic reaction was one in 1,400. A similar study from Washington State found only 1 child in 9,524 had an episode in any given year.²⁸ (Differing definitions of anaphylaxis were used.)

- Researchers in the United Kingdom found that in any given year the chance of a child with a food allergy dying of anaphylaxis is just under 1 in 300,000.²⁹
- Another study put the number in Britain at 1 in 800,000.³⁰
- A survey of the reported anaphylaxis deaths through the United States over 12 years only identified 37 people under the age of 20 confirmed to have died from food allergies.³¹

That is not to suggest the risk is trivial; it is estimated that just over 200 people die annually in the United States from anaphylaxis. A study in the *Journal of Allergy and Clinical Immunology* counted 2,458 fatal anaphylaxis deaths in the United States from 1999 to 2010, most were in a hospital or inpatient setting. More than 95 percent of them were adults.

Among the most common known causes were: allergic reactions to medications (59 percent); reactions to venom (15 percent); food (slightly less than 7 percent); 19 percent, had no known cause.

vasoconstrictor. When fatal anaphylaxis reactions do occur, they are most commonly associated with failure to use epinephrine or not using it in a timely manner.³⁵ One study estimates that 84 percent of those prescribed an epinephrine auto-injector do not know how to use it properly.³⁶ Yet I could find no studies in the academic literature where someone died from a malfunctioning epinephrine auto-injector or died from using one incorrectly.

One dose of epinephrine is not enough for about 10 percent of anaphylaxis patients. In 2010, the FDA issued new guidelines recommending people with serious allergies have two EpiPens on hand. Mylan took advantage of the new guidelines and began selling EpiPens only in twin-packs. This unnecessary move was largely to boost sales. A recent study found that when a second dose is needed, it is administered by a medical professional more than 80 percent of the time.³⁷

Families with adults or children who have severe allergies or asthma are often expected to have two EpiPens at work (or school) and two more at home in case of emergencies. To make matters worse, epinephrine is unstable when exposed to heat and light and EpiPens have an expiration date of about 12 months after purchase. Most are never needed and expire unused. Thus, many people with severe allergies are expected discard \$1,200 worth of EpiPen's annually and purchase new ones.

What Are Consumers' Options?

Mylan dismissed charges that it is price gouging by saying it offers a \$100 coupon to help cover copays so most families pay nothing for the pens. Mylan later upped the discount to \$300 cost-sharing coupons to reduce some patients' out-of-pocket costs, but stood firm on price.³⁸ Even with this discount, insurers, employers and individuals are still paying \$300 to \$1,000 per set.

In September 2016, the firm announced it would come out with its own half-priced generic.³⁹ Members of Congress questioned the announcement as disingenuous. Mylan could have easily lowered its price on the EpiPen rather than applying for a generic ANDA that could take several years to approve.⁴⁰ It is just speculation, but the move may be an attempt to discourage further investments in competing products by Teva and Sanofi, while buying Mylan several more years of high profits.

Doctors like to only prescribe what they trust. Many may not even know about the competing epinephrine auto-injector, Adrenaclick. According to *Consumer Reports*, an Adrenaclick twin-pack can be purchased at Walmart for \$145 with a GoodRx coupon. Unfortunately, regulations in most states prevent pharmacists from substituting the cheaper Adrenaclick for the \$608 EpiPen.⁴¹ Schools may not want parents to send their kids to class with an Adrenaclick because teachers

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and school nurses are used to the EpiPen. To get the cheaper version, patients must ask their doctors to prescribe the Adrenaclick or a “generic epinephrine auto-injector.”

Another option is to ask one’s physician to prescribe an ampule or vial, along with a syringe or even an auto-injector like one made by Owen Mumford, Inc. That may not always be the best option for children at school. But for adults and as a safety measure at home a vial and syringe would work fine.

Another option many people use is to keep using their EpiPens long after the expiration date. One study tested old EpiPens and found they lost about 0.63 percent of their potency for every month they were out of date — losing only 8 percent potency per year.⁴² A later study estimated EpiPens retained more than 90 percent of their dose up to two years after expiration.⁴³ Prior to 2002, the shelf life of an EpiPen was 27 months. It was later “reformulated” and lowered to 18 months.⁴⁴ The expiration is typically considered 12 months after filling the prescription, since time can lapse between manufacture and dispensing a prescription.

For the vast majority of people, the risk of keeping their own EpiPens for a year or two longer is very, very low even if they are among the unlucky few who need to administer an injection.

Conclusion

The EpiPen is a relatively simple auto-injector that administers epinephrine, a form of adrenaline that was synthesized over 100 years ago. The reason an EpiPen has a list price of more than \$300 is partly due to ill-conceived regulations and bureaucratic red tape that inhibits competition. Other reasons include rent-seeking by its owner and aggressive price increases designed to take advantage of the regulatory environment.

The FDA should allow drug makers to use the 510(k) premarket notification process to market

generic auto-injectors pre-filled with epinephrine. For that matter, there is little reason to limit epinephrine auto-injectors — used for potentially fatal emergencies — to the prescription-only market.

Twenty dollars is probably about how much a generic EpiPen would cost if the FDA approved an over-the-counter version or a version pharmacists could dispense to patients without a doctor’s prescription. Greater access could potentially save lives by making epinephrine more widely available. An OTC version would also save Americans nearly \$1 billion a year.

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Notes

1. Cynthia Koons and Robert Langreth, “How Marketing Turned the EpiPen into a Billion-Dollar Business,” *BloombergBusinessweek*, September 23, 2015.
2. Ibid. An EpiPen twin-pack was \$96.92 in 2004; a single auto-injector was \$52.38. See *Red Book, Pharmacy’s Fundamental Reference, 2004 Edition* (Montvale, NJ: Thomson PDR, 2004).
3. After 2010, EpiPens were only available in twin-packs.
4. Jayne O’Donnell, Patti Singer and Shari Rudavsky, “EpiPen’s Steady Price Increases Masked Until Deductibles Rose,” *USA Today*, August 25, 2016.
5. See the sidebar, “Cost Savings for OTC Claritin,” in Devon M. Herrick, “Patient, Heal Thyself: Why Congress Should Repeal the Medicine Cabinet Tax on Over-the-Counter Drugs,” National Center for Policy Analysis, NCPA Policy Report No. 362, November 2014.
6. National Inventors Hall of Fame; Patent 4,031,893, issued on June 28, 1977.
7. U.S. patent 3,882,863, issued May 13, 1975.
8. Meridian Medical Technologies Inc. is a subsidiary of drug maker Pfizer.
9. U.S. patent 6,767,336, issued July 27, 2004.
10. Max R. Bennett, “One Hundred Years of Adrenaline: The Discovery of Autoreceptors,” *Clinical Autonomic Research*, Vol. 9, No. 3, June 1999, pages 145–159.
11. “Adamis Pharmaceuticals Receives Complete Response Letter from FDA for Its Epinephrine Pre-Filled Syringe NDA,” Adamis Pharmaceuticals Corporation, News Release, June 6, 2016.
12. “Adamis Pharmaceuticals Announces FDA Acceptance of Resubmission of Its Epinephrine Pre-Filled Syringe NDA,” Adamis Pharmaceuticals Corporation, News Release, January 14, 2016.
13. Among other improvements, U.S. patent 6,767,336 shields the exposed needle once the cannula has been deployed and the dose injected.
14. Adrenalina WZF, adrenaline premixed for generic auto-injector, Altellus, Anapen, Emerade, Fastjekt, FastPen, Jext. See Annex I, “List of the names, pharmaceutical form(s), strength(s) of the medicinal product(s), route(s) of administration, marketing authorisation holder(s) in the Member States,” European Medicines Agency, August 26, 2015.
15. “UPDATED: Sanofi US Issues Voluntary Nationwide Recall of All Auvi-Q® Due to Potential Inaccurate Dosage Delivery,” Sanofi US, October 30, 2016.
16. David Mills, “Sanofi Ending Its Licensing Agreement for Auvi-Q Auto-Injectors,” *Healthline*, February 25, 2016.
17. Ransdell Pierson and Deena Beasley, “Teva Says Aims to Launch EpiPen-Like Device by 2018 in U.S.,” *Reuters, Health News*, September 9, 2016.
18. See U.S. patent 6,767,336 for the current EpiPen. An exhaustive search of all auto-injector and self-injector patents would likely discover many times this number.
19. F. Estelle R. Simons (World Allergy Organization), “Epinephrine Auto-Injectors: First-Aid Treatment Still out of Reach for Many at Risk of Anaphylaxis in the Community,” *Annals of Allergy, Asthma & Immunology*, Vol. 102, 2009, pages 403–409. Note that hospital patients could be injected with different doses using a syringe and ampule.
20. Kathleen Uhl (Director, Office of Generic Drugs), “Creating the Path to Success with GDUFA,” FDA Office of Generic Drugs Keynote Address, Generic Pharmaceutical Association, Annual Meeting, February 2015, page 29.
21. A quick search of the 510(k) premarket notification database found the following: K141384, K050434, K124026, K111467, K060389, K042557, K032425, K981266, K974678 and K860284. However, there are likely many more that fall under the device classification name “Introducer, Syringe Needle.”
22. The method that seems to work the best is intramuscular injection into the thigh. See “Epinephrine Injection, Route of Administration for the Treatment of Anaphylaxis,” *American Academy of Allergy Asthma & Immunology*, April 14, 2012.
23. Cynthia Koons and Robert Langreth, “How Marketing Turned the EpiPen into a Billion-Dollar Business.”
24. Robert King, “Doctors: Mylan Lobbying Feds to Require EpiPen Insurance Coverage,” *Washington Examiner*, October 12, 2016.
25. Mark Maremont, “Mylan’s EpiPen Pretax Profits 60% Higher than Number Told to Congress,” *Wall Street Journal*, September 26, 2016.
26. The fatality rate of anaphylaxis patients who present to the emergency department or are hospitalized is thought to be 0.3 percent. The overall death rate

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- from anaphylaxis is far less than 1 per million population. See Liyuan Ma, Theodore M. Danoff and Larry Borish, "Case Fatality and Population Mortality Associated with Anaphylaxis in the United States," *Journal of Allergy and Clinical Immunology*, Vol. 133, No. 4, April 2014, pages 1,075-1,083. In the general population, approximately 200 people die for every 200,000 anaphylactic reactions.
27. Amy M. Branum and Susan L. Lukacs, "Food Allergy Among U.S. Children: Trends in Prevalence and Hospitalizations," National Center for Health Statistics, U.S. Centers for Disease Control and Prevention, NCHS Data Brief, 2008, Vol. 10, pages 1-8.
 28. Anaphylaxis rates were 75.1 for children 0-9; 65.2 for children 10-19 years per 100,000 in Rochester, Minnesota. In Washington State, the rates were 10.5 per 100,000. See Chitra Dinakar, "Anaphylaxis in Children: Current Understanding and Key Issues in Diagnosis and Treatment," *Current Allergy and Asthma Reports*, Vol. 12, No. 6, December 2012, pages 641-649.
 29. Thisanayagam Umasunthar et al., "Incidence of Fatal Food Anaphylaxis in People with Food Allergy: a Systematic Review and Meta-analysis," *Clinical & Experimental Allergy*, Vol. 43, No. 12, December 2013, pages 1,333-1,341.
 30. Ratio is based on the assumption that 5 percent of English and Irish children have food allergies. See Colin Macdougall, Andrew Cant and Allan F. Colver, "How Dangerous is Food Allergy in Childhood? The Incidence of Severe and Fatal Allergic Reactions across the UK and Ireland," *Archives of Disease in Childhood*, Vol. 86, No. 4, April 2002, pages 236-239.
 31. Elina Jerschow, Robert Y. Lin, Moira M. Scaperotti and Aileen P. McGinn, "Fatal Anaphylaxis in the United States, 1999-2010: Temporal Patterns and Demographic Associations," *Journal of Allergy and Clinical Immunology*, Vol. 134, No. 6, December 2014, pages 1,318-1,328.e7.
 32. Annual deaths are estimated at between 186 and 225 people per year. See Liyuan Ma, Theodore M. Danoff and Larry Borish, "Case Fatality and Population Mortality Associated with Anaphylaxis in the United States," *Journal of Allergy and Clinical Immunology*, Vol. 133, No. 4, April 2014, pages 1,075-1,083.
 33. Elina Jerschow, Robert Y. Lin, Moira M. Scaperotti and Aileen P. McGinn, "Fatal Anaphylaxis in the United States, 1999-2010: Temporal Patterns and Demographic Associations," *Journal of Allergy and Clinical Immunology*, Vol. 134, No. 6, December 2014, pages 1,318-1,328.e7.
 34. Ibid. The most common drugs were antibiotics, radio contrast agents and chemotherapy.
 35. Hugh A. Sampson, Louis Mendelson and James P. Rosen, "Fatal and Near-Fatal Anaphylactic Reactions to Food in Children and Adolescents," *New England Journal of Medicine*, Vol. 327, No. 6, August 6, 1992, pages 380-384.
 36. Rana S. Bonds, Ashish Asawa and Aasia I. Ghazi, "Misuse of Medical Devices: a Persistent Problem in Self-Management of Asthma and Allergic Disease," *Annals of Allergy, Asthma & Immunology*, Vol. 114, No. 1, January 2015, pages 74-76.
 37. Antonella Muraro et al., "Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology," *Allergy*, Vol. 69, 8, August 2014, page 1,026-1,045.
 38. Nathan Bomey, "EpiPen Maker to Offer Discounts After Price Hike Firestorm," *USA Today*, August 26, 2016.
 39. Matt Egan, "Generic EpiPen Coming for \$300, as Mylan Responds to Outrage," *CNN Money*, August 29, 2016.
 40. Brett Norman and Sarah Karlin-Smith, "EpiPen Hearing Comes Up Empty," *Politico*, September 26, 2016.
 41. Ginger Skinner, "Can You Get a Cheaper EpiPen?" *Consumer Reports*, August 11, 2016.
 42. F. Estelle R. Simons, Xiaochen Gu and Keith J. Simons, "Outdated EpiPen and EpiPen Jr Autoinjectors: Past Their Prime?" *Journal of Allergy and Clinical Immunology*, Vol. 105, No. 5, May 2000, pages 1,025-1,030.
 43. Ousama Rachid, F. Estelle R. Simons, Michael B. Wein, Mutasem M. Rawas-Qalaji and Keith J. Simons, "Epinephrine Doses Contained in Outdated Epinephrine Auto-injectors collected in a Florida Allergy Practice," *Journal of Allergy and Clinical Immunology*, Vol. 114, No. 4, April 2015, pages 354-356.e1.
 44. Carolyn Y. Johnson, "Why EpiPens Expire So Quickly," *Washington Post*, September 27, 2016.