

Regulations and Bureaucracy Boosted EpiPen Prices

Statement of

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Reviewing the Rising Price of EpiPens

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Chairman Chaffetz and Members of the Committee, I am Devon Herrick, a health economist and senior fellow at the National Center for Policy Analysis, a nonprofit, nonpartisan public policy research organization dedicated to empowering Americans by advancing liberty through free market solutions. Thank you for allowing me the opportunity to share my views.

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

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 As health plan deductibles steadily rose over the past 10 years, families increasingly had to bear more of the cost out of pocket. Higher cost-sharing made it more difficult for Mylan to mask its price increases.⁴ This is an example of 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

Epinephrine auto-injectors worth more than \$1 billion expire annually, unused. Or maybe it's more accurate to say that Americans waste more than \$1 billion annually on \$80 million worth of epinephrine auto-injectors that are discarded unused. Mechanical engineers have been working on auto-injectors for 50 years and the technology is not particularly complicated at this point. The devices should only cost less than \$20 apiece. That's probably about how much they 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 save lives by making epinephrine more widely available.

History of the EpiPen. An early version of the EpiPen epinephrine auto-injector was patented in 1977 by Sheldon Kaplan and four colleagues. Kaplan was a mechanical engineer trained at Northwestern, who worked for Survival Technologies, Inc. The Pentagon needed an auto-injector that could administer anti-nerve agents quickly while keeping them stable in the field.⁵ Kaplan's design could also inject epinephrine and became the EpiPen around 1980. Kaplan's auto-injector was an improvement over an earlier one invented by two colleagues, Calkins and

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 National Inventors Hall of Fame. Patent 4,031,893, issued on June 28, 1977.

Sarnoff, who also worked with Kaplan on the later design. Calkins and Sarnoff's design improved upon earlier versions designed by others.⁶

Survival Technologies Inc. patented numerous improvements over the years. The firm later merged with another company to become Meridian Medical Technologies, Inc.⁷ Sheldon Kaplan died in 2009.⁸ However, in 2004 he invented the auto-injector that became the current version of the EpiPen.⁹ The patent will not expire until 2025.

Regulations Limit Competition. Why is a 40-year old product used to administer a generic drug still so expensive? Like many costly drugs, much of the blame is due to the way drugs are regulated in the United States and the U.S. Food and Drug Administration (FDA).

Although the initial patent on the EpiPen expired in the 1997, safety improvements made to the design of the auto-injector over the years extended the patent. A new patent was issued in 2004 updating various aspects of the EpiPen.¹⁰ Once the firm that licensed the technology to Mylan identified potential problems and developed a newer design with features that boost efficacy or safety, the FDA is unlikely to approve a generic version based on the earlier 1977 design. The newer EpiPen auto-injector has features that guard against accidental needle sticks once the cannula (needle) has been extended and lowers the probability of premature cannula deployment.

Unnecessary FDA Roadblocks. 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).¹¹ A talking epinephrine auto-injector made by French drug maker Sanofi was recalled because 26 of its units supposedly administered inaccurate doses.¹² Sanofi ended its licensing agreement to sell the Auvi-Q and is not expected to return the product to market.¹³ A generic EpiPen that was to be made by Israeli drug maker Teva suffered design setbacks when the FDA declined to approve its version until Teva

⁶ U.S. patent 3,882,863, issued May 13, 1975.

⁷ Meridian Medical Technologies Inc. is a subsidiary of drug maker Pfizer.

⁸ "Sheldon Kaplan Obituary, *Tampa Bay Times*, September 23, 2009. Available at <http://www.legacy.com/obituaries/sptimes/obituary.aspx?n=sheldon-kaplan&pid=133335366>.

⁹ U.S. patent 6,767,336, issued July 27, 2004.

¹⁰ Among other improvements, U.S. patent 6,767,336 has a means to shield the exposed needle once the cannula has been deployed and the dose injected.

¹¹ 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.

¹² "UPDATED: Sanofi US Issues Voluntary Nationwide Recall of All Auvi-Q® Due to Potential Inaccurate Dosage Delivery," Sanofi US, October 30, 2016. Available at <http://www.fda.gov/Safety/Recalls/ucm469980.htm>.

¹³ David Mills, "Sanofi Ending Its Licensing Agreement for Auvi-Q Auto-Injectors," Healthline, February 25, 2016.

addresses some of the FDA's concerns. As a result, the launch of Teva's epinephrine auto-injector has been delayed until 2018.¹⁴

Adrenaline was synthesized more than 100 years ago.¹⁵ Epinephrine — a synthetic form of adrenaline — has long since lost patent protection. The epinephrine injected by the EpiPen is available in ampules, with doses costing less than \$1. One firm sought FDA approval to sell syringes pre-filled with epinephrine. The FDA rejected the application — requiring the firm conducted more usability studies to assess whether patients are capable of self-injecting.¹⁶ The FDA has twice rejected applications to market syringes prefilled with epinephrine.¹⁷

Auto-injector syringes are a mature technology, with well over 100 patents registered.¹⁸ Arguments that patient safety requires auto-injectors to be expensive and doses extremely precise 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. The 0.3 EpiPen and the 0.15 EpiPen Jr. Regardless of their size, all patients suffering an anaphylaxis emergency must take either a 0.15 or 0.3 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 principle method of action of the combination product determines whether the FDA's Center for Drug Evaluation and Research takes the lead on approval or the FDA's Center for Devices and Radiological Health coordinates 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. The generic drug, epinephrine, is already made by several firms and sold inexpensively in ampules. It makes little sense to require each new epinephrine auto-injector to be approved as 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

¹⁴ Ransdell Pierson and Deena Beasley, "Teva Says Aims to Launch EpiPen-Like Device by 2018 in U.S.," Reuters, Health News, September 9, 2016.

¹⁵ Max R. Bennett, "One Hundred Years of Adrenaline: The Discovery of Autoreceptors," *Clinical Autonomic Research*, Vol. 9, No. 3, June 1999, pages 145–159.

¹⁶ "Adamis Pharmaceuticals Receives Complete Response Letter from FDA for Its Epinephrine Pre-Filled Syringe NDA," Adamis Pharmaceuticals Corporation, News Release, June 6, 2016.

¹⁷ "Adamis Pharmaceuticals Announces FDA Acceptance of Resubmission of Its Epinephrine Pre-Filled Syringe NDA," Adamis Pharmaceuticals Corporation, News Release, January 14, 2016.

¹⁸ See U.S. patent 6,767,336 for the current EpiPen. Notice patents cited and referenced by: Available at <http://www.google.com/patents/US6767336>. 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, hospital patient could be injected different doses using a syringe and ampule.

number nearly 4,000.²⁰ Approving a competing product could take several years — even if the FDA was willing to approve a generic based on the older design, which it is unlikely do to.

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 identify a similar device already on the market and submit a 510(k) Premarket Notification. To be eligible for the abbreviated clearance process known as 510(k), a device maker merely has to prove the new device is “substantially equivalent” both in effectiveness and safety to a predicate device. Indeed, a quick search of the FDA’s 510(k) Premarket Notification database identified 10 different auto-injector devices that are registered and legal to market.²¹ These devices all claimed substantial equivalence to earlier devices on the market. In theory, a person at risk of anaphylaxis could preload one of these with epinephrine.²² Yet, the 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 Pharmaceutical’s 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

Significant lobbying and savvy marketing 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 are not performed merely as 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. 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 Mylan is expected to sell more than 8 million EpiPens this year.²⁴

Background on Anaphylaxis. Severe allergies can result in anaphylaxis, where a person’s windpipe begins to swell closed. On very rare occasions anaphylaxis can result in death, but the

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, p. 29. Available at: <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM434884.pdf>.

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 Pierson and Beasley, “How Marketing Turned the EpiPen into a Billion-Dollar Business,”

²⁴ Mark Maremont, “Mylan’s EpiPen Pretax Profits 60% Higher than Number Told to Congress,” *Wall Street Journal*, September 26, 2016.

mortality rate is only a small fraction of 1 percent.²⁵ 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.²⁶ Yet the likelihood of a child suffering anaphylaxis is very low. Estimates vary, but a study from Minnesota back 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.²⁷ The difference was due to differing definitions of anaphylaxis.

Researchers in the U.K. found that in any given year, the chance of a child *with* a food allergy dying of anaphylaxis is just under 1 in 300,000.²⁸ Another study put the number in Britain at 1 in 800,000.²⁹ 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.³⁰ A study published in the *Journal of Allergy and Clinical Immunology* counted 2,458 fatal anaphylaxis deaths in the United States from 1999 to 2010. Most of those are adults — more than 95 percent.³¹ The most common known causes were allergic reactions to medications (59 percent) and venom (15 percent). Food allergies accounted for slightly less than 7 percent, although 19 percent of deaths had no known cause.³² Most deaths were in a hospital or an inpatient setting.

²⁵ 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 from anaphylaxis is far less than 1 per million population. See “Case Fatality and Population Mortality Associated with Anaphylaxis in the United States.” In the general population, approximately 200 people die for every 200,000 anaphylactic reactions.

²⁶ 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. Available at <https://www.cdc.gov/nchs/data/databriefs/db10.pdf>.

²⁷ 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.

²⁸ 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.

²⁹ 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. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1719140/pdf/v086p00236.pdf>.

³⁰ 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.

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. Available at: [http://www.jacionline.org/article/S0091-6749\(14\)01190-7/pdf](http://www.jacionline.org/article/S0091-6749(14)01190-7/pdf).

³² *Ibid.* The most common drugs were antibiotics, radio contrast agents and chemotherapy.

Treatment of Anaphylaxis. The treatment of choice for anaphylaxis is epinephrine — a 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.³³ One study estimates that 84 percent of those prescribed an epinephrine auto-injector do not know how to use it properly.³⁴ 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 that 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 begin selling EpiPens only in twin-packs. This move was unnecessary and largely designed to boost sales. A recent study found that when a second dose of epinephrine is needed, a medical professional administers the second dose more than 80 percent of the time.³⁵

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 for 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 only 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.

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 aggressive price increases and rent-seeking by its owner. 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.

³³ 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.

³⁴ 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.

³⁵ 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.