

Epinephrine drug degradation in autoinjector products

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Clinical Implications

- Expiration dating of epinephrine autoinjectors may be too short, as many retained a percentage above the Food and Drug Administration's minimum requirements. Extending the expiration dating may allow patients experiencing anaphylaxis access to some medication, particularly during a drug shortage.

TO THE EDITOR:

Epinephrine (adrenaline) is the key ingredient of autoinjectors that are used in the case of anaphylaxis to blunt the effects of anaphylactic shock.¹ Because of the quick onset of anaphylaxis, patients at risk for anaphylaxis must always carry at least 1 epinephrine autoinjector (EAI), as its use can treat anaphylaxis until medical care is reached. However, in recent years, there has been a sharp increase in the price of EAI due to manufacturer prices, a shortage of epinephrine, or both.² Coupled with the high cost, the short shelf-life poses a problem for patients who cannot afford to purchase multiple autoinjectors per year. Access to EAIs in each location pertinent to the patient furthers the cost to acquire the devices. Understanding the point at which the percentage of remaining epinephrine falls below 90%, as deemed by the Food and Drug Administration (FDA) as the point of expiration, may help to extend the life of these valuable devices.

This study assessed epinephrine concentrations from EAIs via reversed-phase high-performance liquid chromatography (RP-HPLC) to determine the time point at which epinephrine concentrations fall below 90%, as a longer shelf-life would benefit patients requiring EAIs. The EAIs were collected from friends, relatives, and colleagues. Although the proper storage of all collected EAIs is uncertain, we felt that this represents the treatment of EAIs by their broad population of users. A total of 46 autoinjectors were collected and represented multiple brands: EpiPen and its authorized generic, the authorized generic of Adrenaclick, and Auvi-Q autoinjectors. The analyzed EAIs contained either 0.15 or 0.3 mg epinephrine, for pediatric and adult dosing, respectively, at the time of manufacture. In total, 46 EAIs were collected and analyzed.

The EAIs were injected directly into HPLC vials, simulating injection by maintaining pressure for 10 seconds, to be analyzed immediately, avoiding oxidation or disruption of the epinephrine stability by the local environment. All 46 EAIs ejected contents into the HPLC vials, demonstrating a working firing mechanism in each EAI beyond the expiration dating. Percent remaining in

each EAI and categorizing of time from expiration dating are shown in [Tables I and II](#), respectively.

The United States Pharmacopeia RP-HPLC method for the assessment of epinephrine has been validated with regard to specificity and ability to separate the degradation products within the autoinjectors.^{3,4} Chromatogram peak areas were used to calculate epinephrine concentrations. A 5-point calibration curve was constructed using epinephrine standard solutions, and the regression parameters were calculated. Hoellein and Holzgrabe⁵ had described the various epinephrine degradation pathways and the degradation products, including those responsible for color changes as the solution degrades.

The 46 studied EAIs had expiration dates from 1 to 168 months after the labeled expiration date (from June 2004 to August 2018). The median duration of months between labeled expiration date and testing was 24 months, with an interquartile range (IQR) of 28.8 months. Approximately 80% ($n = 37$) of the EAIs had retained more than 90% of epinephrine remaining, whereas only 9 had fallen below the FDA's requirement of 90%. The median amount of drug remaining in all tested autoinjectors was 97.2%, with an IQR of 8.1%. Each manufacturer was represented at least once within the 37 autoinjectors retaining more than 90% of epinephrine.

As shown in [Table II](#), EAIs with up to 6 months past labeled expiration date ($n = 4$) maintained 100% of the drug. EAIs 1 year ($n = 10$) after labeled expiration date showed at least 95% drug content. All EAIs ($n = 27$) up to 30 months beyond their labeled expiration dates have shown 90% drug content. Similar results have been reported by Rachid et al⁶; epinephrine solutions in EAIs with up to 24 months past their expiry date retained at least 90% of the labeled dose. According to our results, the expiration date of EAIs was set considerably short of the point at which epinephrine in the EAI drops below the FDA's required 90%.

Although we analyzed a relatively small number of EAIs in this project, our data corroborate previously published data by Parish et al,⁷ which indicated that epinephrine may be more robust and stable than the current prescribing information storage recommendations suggest. Previous works outline that epinephrine might not degrade with exposure to extreme conditions and that most epinephrine products were effective after their labeled expiry dates.⁷ Rachid et al⁶ reported that epinephrine solutions in EAIs with up to 24 months past their expiry date retained at least 90% of the labeled dose. A report by Simons et al⁸ described that patients who cannot afford a timely replacement had kept their outdated EAIs for backup or emergency use. Acknowledging an extended expiration date of EAIs would allow patients who otherwise could not obtain a replacement EAI to continue use of ones currently in their possession.

This was an *in vitro* study; thus, no anaphylactic reactions were blunted using expired EAIs. The collection of donated EAIs resulted in a small sample size tested thus far, but the results are likely generalizable to how the broad population stores EAIs. Many EAIs were donated by colleagues with a health care background and may represent ideal storage conditions; however,

TABLE I. Epinephrine percent remaining in autoinjectors

EAI number	Manufacturer's expiration date	Manufacturer	Percent epinephrine remaining via RP-HPLC	Time tested (months from expiration)
1	June 2004	EpiPen	43.8	168
2	December 2010	EpiPen	74.3	87
3	January 2012	EpiPen	79.8	74
4	September 2012	EpiPen	92.2	73
5	January 2013	EpiPen	87.4	62
6	October 2013	EpiPen	93.2	60
7	October 2013	EpiPen	88.4	53
8	September 2014	EpiPen	90.4	49
9	September 2014	EpiPen	93.7	44
10	October 2014	EpiPen	87.3	49
11	October 2014	EpiPen	88.5	41
12	November 2014	EpiPen	90.8	42
13	January 2015	EpiPen	88.5	46
14	May 2015	EpiPen	95.1	42
15	May 2015	Auvi-Q	93.9	41
16	May 2015	EpiPen	87.1	34
17	June 2015	EpiPen	94.9	41
18	June 2015	Auvi-Q	92.1	40
19	August 2015	Auvi-Q	98.5	33
20	September 2015	EpiPen	97.3	29
21	January 2016	EpiPen	90.2	26
22	September 2016	Auvi-Q	98.1	25
23	September 2016	Auvi-Q	99.5	20
24	October 2016	EpiPen	109.9	24
25	October 2016	EpiPen	91.6	25
26	December 2016	EpiPen	100	23
27	December 2016	EpiPen	99.9	23
28	December 2016	EpiPen	97.1	22
29	January 2017	Adrenaclick generic	97.5	21
30	January 2017	EpiPen	98.9	21
31	January 2017	EpiPen	95.0	14
32	January 2017	EpiPen	98.4	16
33	February 2017	EpiPen	96.6	20
34	March 2017	EpiPen	98.7	14
35	April 2017	Adrenaclick generic	101	11
36	June 2017	Adrenaclick generic	102	9
37	September 2017	EpiPen	93.1	14
38	October 2017	EpiPen	99.6	13
39	November 2017	EpiPen	100	6
40	November 2017	EpiPen	100	6
41	January 2018	EpiPen	99.1	9
42	January 2018	EpiPen	100	5
43	March 2018	EpiPen	99.4	7
44	May 2018	EpiPen generic	106	5
45	June 2018	EpiPen	102.3	3
46	August 2018	Adrenaclick generic	103.5	1

EAI, Epinephrine autoinjector; RP-HPLC, reverse-phase high-performance liquid chromatography.

not all EAIs may have been stored appropriately. A minimum sample size was not calculated; however, because of reliance on donations, obtaining a large enough sample to sway manufacturers to alter expiration dating practices could take years.

In summary, most of the expired EAIs studied here retained a high enough percentage of epinephrine, above the requirements by the FDA, to question their true expiration dating.

TABLE II. Epinephrine autoinjectors by months from expiration dating and percentage of drug remaining

Time of device testing (months past the expiration date)	No. of EAI's	Percent drug remaining*			
		100% or above	99%-95%	94%-90%	Less than 90%
0-2.9	1	1			
3.0-5.9	3	3			
6.0-8.9	3	2	1		
9.0-11.9	3	2	1		
12.0-14.9	4		3	1	
15.0-17.9	1		1		
18.0-20.9	2		2		
21.0-23.9	5	1	4		
24.0-29.9	5	1	2	2	
30.0-35.6	2		1		1
36.0-41.9	4			3	1
42.0-47.8	4		1	2	1
48.0-59.9	3			1	2
60.0-71.9	2			1	1
>72	4			1	3
Total	46	10	16	11	9

EAI, Epinephrine autoinjector.

*Numbers in the table indicate the number of EAI's within each percentage range.

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