

Evaluation of epinephrine's expiration date: A US Food and Drug Administration's perspective



To the Editor:

Kassel et al¹ report results for epinephrine drug degradation in 46 random epinephrine autoinjectors (EAI) from 1 to 168 months (median of 24 months) after the labeled expiration date. They found that EAI up to 30 months beyond labeled expiration dates showed 90% epinephrine concentration. Because of the high percentage of epinephrine beyond the expiration date, they question the true expiration dates of these EAI.¹

We agree with the authors that the expiry of EAI is an important issue as it is recommended for patients who are at risk for anaphylaxis to carry an epinephrine product.² US Food and Drug Administration (FDA) is aware of the implications of the expiry of EAI, given the price the manufacturers charge and epinephrine shortage issues. However, we are concerned that the report from Kassel et al may encourage the use of EAI beyond the expiration date. We believe it is important to provide some additional perspective from FDA on determination of expiry dates for EAI.

FDA regulations require drug applicants to provide stability testing data with a proposed expiration date and storage conditions when they submit an application for FDA approval of their drug.³ This testing is designed to provide confidence that the product will meet the applicable standards of strength, quality, and purity throughout its shelf-life. The FDA verifies that the proposed expiration date is supported by the submitted data. FDA and manufacturers evaluate multiple parameters to ensure that the quality of the drug product is maintained throughout its shelf-life. For EAI, the concentration of the active ingredient (epinephrine) is important, but it is not the only parameter of concern for these products. Epinephrine is a chiral molecule with the L-(−)-enantiomer having greater activity than the D-(+)-enantiomer. Epinephrine is readily oxidized, and this oxidation process leads to impurities or degradants, including change from the L to D enantiomer.⁴ Change from the L to D enantiomer over time could impact the efficacy of the product. Measurement of total epinephrine concentration may not reflect the concentration of the active L-(−)-enantiomer. Storage conditions can impact oxidation and degradation. In the case of epinephrine products, impurities and antioxidant content can limit the shelf-life because we need to ensure the safety of these impurities and degradants. Given the stability and oxidation issues with epinephrine, extending the shelf-life of EAI has been a challenge.

FDA sets an expiry date based on the data provided by the manufacturer. Manufacturers can support an extension in the expiry date by submitting additional stability data, so the current shelf-life of EAI could be updated in the future.

We appreciate the efforts of Kessel et al to raise awareness of this issue and raise questions regarding the expiry of EAI. We hope our perspective provides some insights into the challenges of extending the shelf-life of EAI. However, we caution against the

use of EAI beyond the expiry date because we cannot ensure the pharmaceutical quality of the product.

For additional information regarding pharmaceutical quality and expiration dates, visit: <https://www.fda.gov/drugs/pharmaceutical-quality-resources/expiration-dates-questions-and-answers>.

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Reply



To the Editor:

Lan et al¹ raise interesting and important points regarding our study.² Our study analyzed epinephrine autoinjectors (EAI) in a laboratory setting, and thus our findings are not able to comment on the clinical ability of the expired EAI to blunt an anaphylactic response. Lan et al bring this further to light in encouraging patients to continue to carry in-date EAI, and we concur, based on current labeling and expiration dating done by the Food and Drug Administration (FDA) in collaboration with drug manufacturers. We believe that the FDA's standards and processes for assigning expiration dates are well explained by Lan et al.

Secondly, epinephrine's degradation into the inactive D-(+)-enantiomer raises additional questions to be studied. In conjunction to our previously published method, we are currently collecting and studying additional expired EAI with the intent to study epinephrine enantiomer levels using a chiral column to determine which enantiomer (and in what amount) is present in each expired device. The risks of conversion of epinephrine enantiomers should not be overlooked, as a suboptimal balance of active and inactive enantiomers could be life threatening.