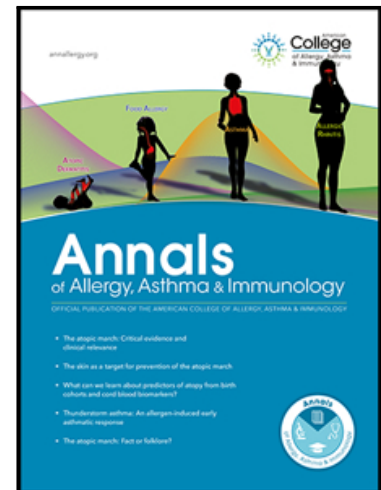


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Retained strength of expired albuterol and montelukast pharmaceuticals

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Abbreviations:

COPD: Chronic obstructive pulmonary disease; FDA: U.S. Food & Drug Administration;

GMFC: Greater Milwaukee free clinic; HPLC: high-performance liquid chromatography; SLEP:

Shelf-Life Extension Program; UV: ultraviolet

Expiration dates are integral components of pharmaceutical product labels. These dates are based on stability studies conducted by manufacturers up to the stated dates.¹ This implies that medications no longer retain their potency and should be appropriately discarded once expiration date is reached when, in fact, the post-expiration residual drug strength is usually undetermined. The financial, environmental and societal burdens resulting from expired medication disposal is significant.² An added variable to this equation is the possibility that many ‘expired’ medications still retain enough strength to make them therapeutically beneficial.³ In our ongoing research to investigate post-expiration drug strength, we developed validated reversed-phase high-performance liquid chromatography (HPLC) methods with UV detection to determine potency of pharmaceutical products with expiration dates up to 20 years ago. Our goal was (i) to investigate if the levels of active constituents were within 90-110% of manufacturer label strength, which is the acceptable quality control range for pharmaceutical products, and (ii) to support the notion that expired medications may be therapeutically utilized instead of being wasted. For this study, we chose albuterol and montelukast, two medications commonly used for the treatment of asthma and COPD.^{4,5}

Expired batches of albuterol and montelukast products were donated by the Greater Milwaukee Free Clinic (no longer operational) in May 2019. The HPLC methods were

developed on a Prominence LC-2030 system (Shimadzu, Japan) and were validated for selectivity, accuracy and precision using standard albuterol and montelukast (Sigma-Aldrich, St. Louis, MO) according to FDA guidelines.⁶ Analysis was performed on C18 columns with gradient elution of acetonitrile in 0.1% aqueous formic acid at 1 mL/min flow rate. Albuterol and montelukast peaks were detected at 277 and 280 nm, respectively. Tablet, granule, and liquid dosage forms were quantitatively extracted with methanol, while albuterol inhaler puffs were captured in a balloon and extracted with 50% aqueous methanol before injection. All samples were diluted per procedure, filtered into HPLC vials, and analyzed in triplicates of 10 μ L injections.

A total of 17 albuterol (11 solution and 6 inhaler) and 5 montelukast (4 tablet and 1 granule) samples were analyzed. Expiration dates ranged from March 2001 to January 2021 including an in-date product control for each drug. As shown in Figure 1, all montelukast samples were within quality control range ($95.2 \pm 1.4\%$; Figure 1, top panel). Albuterol solutions showed similar quality ($98.1 \pm 4.0\%$; Figure 1, top panel) except for two samples which showed 85% and 88% of label strength (Figure 1, middle panel). One plausible explanation is the fact that these two products were formulated as multiple-dose bottles not as single-dose sealed vials like the rest of the analyzed products. Albuterol inhalers displayed lowest strengths and significant variability ($86.8 \pm 10.4\%$; Figure 1, bottom panel) which may be attributed to challenges in consistent recovery attributed to the complexity of the actuator mechanism of dispensing puffs as well as the use of an intermediate capturing device (balloon).

Based on the obtained results, it is apparent that solid dosage forms and most liquid dosage forms of montelukast and albuterol, respectively, retain their strength over extended periods of up to 20 years. Similar results for other drugs were reported in earlier studies.^{3,7,8} The

financial burden of disposal of effective pharmaceuticals triggered the Shelf-Life Extension Program (SLEP) to address this issue. Through a partnership between the FDA and the US military, 122 medications of the national were analyzed and their expiration dates extended for 5 years based on analytical strength determination. This resulted in a significant reduction in replacement cost for these drugs.⁹ From a healthcare practice perspective, the financial burden of medication access on economically challenged patients may be equally significant especially when these individuals suffer from chronic conditions, such as asthma and COPD. These patients are frequent visitors to free clinics where healthcare disparities may be reduced, in part, through the use of donated medication. This situation brings us to the core argument of our findings: should expired medications be utilized at free clinics as a viable solution to those who cannot afford the price of new medications? Although there is no general consensus on what may constitute future guidelines for this practice, we recommend the following as relevant points of consideration. First, expired medications need to be stored at normal conditions of temperature, light and humidity. The fact that most samples in this study retained analytical strength despite occasional sub-optimal storage conditions makes our first recommendation easy to apply. Second, solid dosage forms are usually most stable and are least affected when stored at normal shelf conditions. Third, individual classes of drugs may be relatively unstable based on their molecular structure, e.g. aspirin. Thus, caution needs to be exercised if no published post-expiration data is available. Fourth, biological products, e.g. peptide hormones and vaccines, are outside the scope of this work and need to be investigated as a different class of pharmaceuticals.

In conclusion, we hope that this work adds to the growing body of evidence that many pharmaceutical products retain their strength long after their stated expiration dates. This knowledge may allow healthcare professionals to engage in a broader discussion to drive drug

manufacturing policies and to guide the decision-making process when non-traditional solutions are sought to address healthcare disparities in underserved communities.

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Figure 1

Current analytical strength of albuterol and montelukast pharmaceutical products as percent of label strength at manufacturing time (x-axis expiration dates begin in March 2001 and end in January 2021)

Figure 1

