Debate exists regarding the relative potency of medications beyond their labeled expiration dates. Expired medications have not necessarily lost potency, since the expiration date is only an assurance that the labeled potency will last at least until that time. Clinical situations may arise in which expired drugs might be considered owing to lack of viable alternatives or financial concerns. Ongoing studies show that many medications retain their potency years after their initially labeled expiration dates. We sought to characterize the potency of some prescription medications that had expired decades ago.

**Methods.** Eight long-expired medications with 15 different active ingredients were discovered in a retail pharmacy in their original, unopened containers. All had expired 28 to 40 years prior to analysis. Three tablets or capsules of each medication were analyzed, with each sample tested 3 times for each labeled active ingredient. No analytical standard for homatropine could be found, so that ingredient was not tested.

Tablets or capsule contents were dissolved and sonicated in methanol, reconstituted in analysis buffer (10% methanol) and analyzed with Liquid Chromatograph (Agilent Technologies) Time-of-Flight Mass Spectrometer (Agilent) using electrospray ionization in negative and positive polarities. Chromatography was run with gradient elution using Eclipse Plus C18 column (Agilent). Data analysis was performed using Mass Hunter Qualitative and Quantitative Analysis (Agilent). Quantification was performed by isotope dilution method with a 6-point calibration curve.

**Results.** Twelve of the 14 drug compounds tested (86%) were present in concentrations at least 90% of the labeled amounts, the generally recognized minimum acceptable potency. Three of these compounds were present at greater than 110% of the labeled content. Two compounds (aspirin and amphetamine) were present in amounts of less than 90% of labeled content. One compound (phenacetin) was present at greater than 90% of labeled amounts from 1 medication tested, but less than 90% in another medication that contained that drug (Table).

**Comment.** The US Food and Drug Administration (FDA) permits “reasonable variation,” such that most medications marketed in the United States contain 90% to 110% of the amount of the active ingredient claimed on the label. Drug expiration dates typically range from 12 to 60 months after their production. However, FDA regulations do not require determination of how long medications remain potent after that, allowing manufacturers to arbitrarily establish expiration dates without determining actual long-term drug stability.

The Shelf-Life Extension Program (SLEP) checks long-term stability of federal drug stockpiles. Eighty-eight percent of 122 different drugs stored under ideal environmental conditions had their expiration dates extended more than 1 year, with an average extension of 66 months and a maximum extension of 278...
months. In our data set, 12 of 14 medications retained full potency for at least 336 months, and 8 of these for at least 480 months. Given our inability to confirm ideal storage conditions for our samples, our results support the effectiveness of broadly extending expiration dates for many drugs, the efficacy of which has been demonstrated by SLEP in a more controlled fashion.

The 3 drugs found with less than 90% of their labeled potency were amphetamine and aspirin in both samples tested and phenacetin in 1 of 2 samples tested. Aspirin is known to degrade in vitro, but there are no such published data regarding amphetamine. For phenacetin, the difference in recovery between the 2 samples could be due to differences in packaging or storage of the containers. Aside from aspirin, all drugs in Fiorinal (butalbital, aspirin, caffeine, and codeine phosphate) had almost 100% of labeled concentrations, while those of Codemiral No. 3 (phenacetin with codeine phosphate) were all less than 95%. Since the codeine measured in Codemiral No. 3 was also lower than that of Fiorinal (90% vs 99%), this suggests that Codemiral’s packaging was less intact, allowing moisture to penetrate, which can promote hydrolysis. Because phenacetin has an amide functional group, it is more prone to this type of degradation than codeine.

Three drugs were unexpectedly found in our samples at potencies greater than 110% of the labeled amounts. Some samples may have been produced prior to 1963, when FDA-mandated quality control measures were instituted (Paula R. Katz, Regulatory Counsel, FDA, Center for Drug Evaluation and Research, Division of Manufacturing and Product Quality, Guidance and Policy; e-mail communication, May 23, 2011); however, exact dating of all our samples was not possible. Alternately, these drugs could have come from lots untested by the manufacturer, or the accuracy between analytical methods used in this study compared with those used decades ago could be questioned.

The most important implication of our study involves the potential cost savings resulting from lengthier product expiration dating. Each dollar spent on SLEP to demonstrate longer than labeled drug stability results in $13 to $94 saved on reacquisition costs. Given that Americans currently spend more than $300 billion annually on prescription medications, extending drug expiration dates could yield enormous health care expenditure savings.

In conclusion, this study provides additional evidence that many prescription pharmaceuticals retain their full potency for decades beyond their manufacturer-ascribed expiration dates. Given the potential cost-savings, we suggest the current practices of drug expiration dating be reconsidered.

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1. Title 21 CFR 211.166(a) and (b). Current good manufacturing practice in manufacturing for finished pharmaceuticals and expiration dating (2012).