MAYO CLINIC

Extending Shelf Life Just Makes Sense

Dayna G. Diven, MD; Diana W. Bartenstein, AB; and Daniel R. Carroll, PharmD

From The University of Texas Dell Medical School, Austin (D.G.D.); Tufts University School of Medicine, Boston, MA (D.W.B.); and Pharmacy, Northwest Hills Surgical Hospital, Austin, TX (D.R.C.).

Since 1979, the US Food and Drug Administration (FDA) has required pharmaceutical companies to provide rigorous proof that their medication is stable over the course of months when submitting a New Drug Application or an Abbreviated Drug Application.[1,2] A medication's shelf life, or expiration date, is the time frame in which a medication has been proven safe and effective despite exposure to various environmental factors including temperature, humidity, and light.[2] Although expiration dates guarantee a certain length of stability, the FDA has no requirement for long-term testing. Many medications may have much longer shelf lives than labeled.

The best evidence indicating that medications can last longer than their labeled expiration date comes from the Shelf Life Extension Program (SLEP). Rather than disposing of billions of dollars of the military's stockpiled medications that were set to expire in the 1980s, the FDA tested various batches of the medications in their supplies to provide extensions in shelf life.[3] In their studies of 122 different medication products, nearly 90% met the requirements for an extension. Table 1 includes medications for which all lots tested by SLEP when approaching their expiration dates met the criteria for initial shelf life extension, and Table 2 lists medications for which less than 50% of lots tested were initially extended. Whereas the shelf life of most medications in the United States is 1 to 5 years, the average additional extension length by SLEP was 5.5 years, and some lots were extended by more than 20 years.[4]

Cantrell et al,[5] in another study, tested medications that had expired 28 to 40 years earlier that were discovered unopened and in their original containers at a retail pharmacy. Twelve of the 14 active ingredients were present in at least 90% of the labeled amount, meeting our standard of acceptable minimum potency. Given these data, it seems that many labeled expiration dates do not reflect true longevity.

Despite extensive federal data on the long-term quality of many medications, shelf life extensions that occur in our national stockpiles do not transfer to state or local supplies, let alone hospitals, pharmacies, and those of individual patients, although more accurate expiration dates could reduce costs.[6] As an example, Tufts Medical Center in Boston, Massachusetts, disposes of approximately $200,000 worth of expired medications per year (written personal communication, Department of Pharmacy at Tufts Medical Center, January 8, 2015).

The current standards for shelf life assignment are especially troublesome when populations that are unable to afford medications are considered. Infrastructural obstacles can delay health care distribution in developing countries,[7] but medications cannot be donated internationally if they do not meet the donor country's standards.[8] A donated drug that reaches a developing country past its stated expiration date must be discarded, although SLEP evidence suggests longer-term stability. Furthermore, it is illegal to dispense expired medication to any American regardless of whether they can obtain it otherwise.[9]

Longer shelf lives could also play a role in decreasing medication shortages. Many medication shortages occur for an unknown reason and without warning.[10] If we had evidence that medications were stable for longer periods, pharmacy operation managers might have more flexibility to avoid shortages and paying the higher prices that are often associated with medications in short supply.[11] Of the 15 medications that SLEP determined to be top performers in shelf life extension, 12 (80%) are currently in shortage or have been in shortage since 2013.[4,12] Extending the expiration dates for these medications could possibly help some providers, pharmacists, and patients during medication shortages.

TABLE 1. SLEP Medication Stability Testing Results: All Lots Initially Extended[4]

Medication	Form	Extension time (mo) mean
Triamterene and hydrochlorothiazide	Capsules	19
Amoxicillin sodium	Tablets	23
Acetaminophen pseudoephedrine	Capsules	24
Dextrose 10%	Injection solution	25
Doxycycline hyclate	Powder	27
Atropine sulfate pralidoxime chloride	Autoinjector	31
Morphine sulfate	Autoinjector	32
Ciprofloxacin	Suspension	32
Flurazepam HCl	Capsules	35
Metaraminol bitartrate	Syringe needles	40
Mepivacaine HCl	Cartridge needle	41
Cimetidine HCl	Injection solution	42
Hydrocortisone sodium succinate	Injection solution	43
Prochloroperazine edisylate	Injection solution	43
Hetastarch in sodium chloride	Injection solution	44
Benzonatate	Capsules	44
Cefoperzone sodium	Powder	46
Ephedrine sulfate	Injection solution	46
Dobutamine HCl	Injection solution	47
Enflurane	Liquid	48
Ampicillin	Capsules	49
Calcium glucepate	Injection solution	49
Bretylium tosylate	Injection solution	49
Sodium chloride	Injection solution	50
Tetracycline HCl	Capsules	50
Doxycycline hyclate	Capsules	50
Iothalamate meglumine	Injection solution	51
Promethazine HCl	Injection solution	51
Chlorpromazine HCl	Tablets	52
Ophthalmic irrigating	Solution	52
Naproxen	Tablets	52
Ringer's, lactated and dextrose	Injection solution	53
Thiopental sodium	Powder	54
Sodium polystyrene sulfonate	Powder	55
Ciprofloxacin	Tablets	55
Sodium bicarbonate	Injection solution	55
Oxacillin sodium	Powder	56
Sulfisoxazole	Tablets	56
Ampicillin sodium	Injection solution	57
Furosemide	Injection solution	57
Sulfadiazine silver	Cream	57
Cephalexin	Capsules	57
Mebendazole	Tablets	58
Amyl nitrite	Inhalant	59
Mafenide acetate	Cream	59
Tubocurarine chloride	Injection solution	59
Ceftriaxone sodium	Powder	60
Erythromycin lactobionate	Powder	60
Neostigmine methylsulfate	Injection solution	60
Phenylephrine HCl	Injection solution	60
Dexamethasone sodium phosphate	Syringe needle	61
Phenytoin sodium	Injection solution	63

Continued on next page

Finally, it is possible that extending shelf lives could have a positive environmental effect. Scientists recently found evidence of contamination by many medications in water and sediment samples from Lake Michigan at concentrations that pose "medium or high ecological risk."[13,p2120] If longer shelf lives could reduce medication disposal, perhaps such a measure could also abate harmful environmental consequences.

How do we implement a policy to establish more accurate expiration date labeling? One option is to require all pharmaceutical companies to complete long-term stability testing. Just as pharmaceutical companies must conduct ongoing monitoring for adverse effects after releasing a new medication, they could continue efficacy testing to see how long their medications truly last. Expiration dates could be preliminary and then updated. A second option is to create noncommercial, independent testing for the true lengths of medication stability. SLEP has provided the chemistry and protocol for ongoing testing, and a similar protocol could be applied for civilian medications. Perhaps the FDA or the US Pharmacopeial Convention could preside over this initiative. These proposals would require funding, but the potential benefits of such initiatives at least deserve consideration of their feasibility.

Or, we could take the current data from SLEP and extend expiration dates for top-performing medications, before they are dispensed, that have already been monitored for years. If the ciprofloxacin in the federal supplies was active for more than 20 years, the FDA might consider granting this medication a shelf-life extension for the general public as well, at least in pharmacies that have maintained optimal storage conditions. At a minimum, individual states that keep supplies of medications in proper storage conditions so as to respond to a pandemic or terrorist attack before federal supplies arrive[6] should be able to use SLEP data to extend the shelf lives of medications in their local stockpiles.

Even the age-old adage of particular expired medications being toxic may no longer be true. Although degraded tetracycline is thought to cause renal tubular insufficiency,

manufacturing was changed decades ago to substantially reduce the likelihood of tetracycline formulations breaking down.[14] Of course, subsequent monitoring for and reporting of adverse effects in medications of extended shelf life would be essential for ensuring patient safety; however, controversies from decades ago may need to be revisited for their validity.

For most medications, the concern is for loss of potency under imperfect conditions more than for degraded metabolites that are toxic. One could argue that people do not always keep their medications in ideal conditions, as occurred with our federal supplies. This is a valid concern given our currently limited understanding of long-term drug stability, but investment in rigorous testing and surveillance could resolve this uncertainty.

Whereas many decisions in health care must balance the competing interests of cost and quality, extending expiration dates to reflect the true amount of time that a medication is safe and effective might sacrifice neither. Implementing such a measure could decrease the amount of money spent on prescription medications in the United States due to reduced medication disposal and could also improve health care quality by improving access to pharmacologic treatment.

The logistics of implementing shelf life extensions for the general population would not be simple, but the remarkable evidence provided by SLEP indicates that careful consideration is deserved. It only makes sense.

Expiration dates guarantee a certain length of stability, but many drugs may have much longer shelf lives than is labeled because there is no requirement for long-term efficacy testing. SLEP, pioneered by the FDA to conserve drugs stockpiled by the military, provides convincing data about the safety and efficacy of many medications past their expiration dates. If we were to apply shelf life extensions more broadly, it might be possible to reduce national health care costs, reduce drug shortages, and provide medications to those who would otherwise be unable to afford them.

ACKNOWLEDGMENTS

We thank Tiffany Lieu, MD, for her help with the literature search.

TABLE 1. Continued

Medication	Form	Extension time (mo) mean
Ketamine HCl	Injection solution	64
Chloroquine HCl	Injection solution	64
Dextrose and sodium chloride	Injection solution	64
Protamine sulfate	Powder	64
Dextrose (5%)	Injection solution	65
Povidone iodine	Ointment	65
Edrophonium chloride	Injection solution	65
Mannitol	Injection solution	66
Halothane	Liquid	67
Cimetidine HCl	Tablets	67
Undecylenic acid and zinc salt	Powder	68
Potassium iodide	Tablets	69
Penicillin G benzathine	Suspension	70
Succinylcholine chloride	Powder	72
Sodium chloride	Irrigation	72
Cephapirin sodium	Powder	74
Chlorpromazine HCl	Injection solution	74
Diphenhydramine HCl	Syringe needle	76
Naloxone HCl	Injection solution	77
Cellulose, oxidized, regenerated	Dermal	79
Pancuronium bromide	Injection solution	79
Calcium chloride	Injection solution	81
Hexachlorophene cleansing	Emulsion	81
Fentanyl citrate	Injection solution	84
Guaifenesin	Extended-release tablets	85
Bupivacaine HCl	Injection solution	88
Morhpine sulfate	Syringe needle	89
Sodium nitrite	Injection solution	89
Meperidine HCl	Injection solution	89
Sodium thiosulfate	Injection solution	131
Potassium iodide	Granules	254

FDA = Food and Drug Administration; HCl = hydrochloride; SLEP = Shelf Life Extension Program.

TABLE 2. SLEP Medication Stability Testing Results: <50% of Lots Initially Extended[4]

Medication	Form	Extension time (mo), mean
Albuterol	Inhalant	NA
Diphenhydramine HCl	Spray	NA
Levarterenol bitartrate	Injection solution	22
Ergotamine tartrate and caffeine	Tablets	24
Lidocaine HCl and epineprhine	Injection solution	29
Physostigmine salicylate	Injection solution	31
Mefloquine HCl	Tablets	36
Isoproterenol HCl	Injection solution	45
Phenobarbital sodium	Cartridge needle	56
Penicillin G procaine	Powder	70

HCl = hydrochloride; NA = not available; SLEP = Shelf Life Extension Program.

Abbreviations and Acronyms: **FDA** = Food and Drug Administration; **HCl** = hydrochloride; **SLEP** = Shelf Life Extension Program

Correspondence: Address to Dayna G. Diven, MD, 601 E 15th St, CEC 2.443, Austin, TX 78701 (dgdiven@seton.org).

REFERENCES

1. Expiration dating and stability testing for human drug products. US Food and Drug Administration website. http://www.fda.gov/ICECI/Inspections/InspectionGuides/InspectionTechnicalGuides/ucm072919.htm. Accessed July 23, 2015.
2. International Conference on Harmonization. Guidance for industry Q1A(R2) stability testing of new drug substances and products. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf. Published November 2003. Accessed July 23, 2015.
3. SLEP: The DOD/FDA shelf life extension program. https://slep.dmsbfda.army.mil/portal/page/portal/SLEP_PAGE_GRP/SLEP_HOME_NEW. Accessed July 23, 2015.
4. Lyon RC, Taylor JS, Porter DA, Prasanna HR, Hussain AS. Stability profiles of medication products extended beyond labeled expiration dates. *J Pharm Sci*. 2006;95(7):1549-1560.
5. Cantrell L, Suchard JR, Wu A, Gerona RR. Stability of active ingredients in long expired prescription medications. *Arch Intern Med*. 2012;172(21):1685-1687.
6. Courtney B, Easton J, Inglesby TV, SooHoo C. Maximizing state and local medical countermeasure stockpile investments through the Shelf-Life Extension Program. *Biosecur Bioterror*. 2009;7(1):101-107.
7. Hoekenga MT. The role of pharmaceuticals in the total health care of developing countries. *Am J Trop Med Hyg*. 1983;32(3):437-446.
8. World Health Organization. Guidelines for drug donations. http://www.who.int/hac/techguidance/guidelines_for_drug_donations.pdf. Revised 1999. Accessed July 23, 2015.
9. Text of the Prescription Drug Marketing Act of 1987. US Food and Drug Administration website. http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/PrescriptionDrugMarketingActof1987/ucm201702.htm. Updated March 1, 2010. Accessed July 23, 2015.
10. American Society of Health-Systems. Drug shortages summit summary report. http://www.ashp.org/drugshortages/summitreport. Published November 5, 2010. Accessed July 23, 2015.
11. Ventola CL. The drug shortage crisis in the United States: Causes, impact, and management strategies. *P T*. 2011;36(11):740-757.
12. Drug shortages. American Society of Health-System Pharmacists website. http://www.ashp.org/menu/DrugShortages. Accessed July 23, 2015.
13. Blair BD, Crago JP, Hedman CJ, Klaper RD. Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern. *Chemosphere*. 2013;93(9):2116-2123.
14. Clendenning WE. Complications of tetracycline therapy. *Arch Dermatol*. 1965;91(6):628-632.