Drugs frequently potent past expiration

By Laurie P. Cohen

Do drugs really stop working after the date stamped on the bottle? Fifteen years ago, the U.S. military decided to find out. Sitting on a $1 billion stockpile of drugs and facing the daunting process of destroying and replacing its supply every two to three years, the military began a testing program to see if it could extend the life of its inventory.

The testing, conducted by the U.S. Food and Drug Administration, ultimately covered more than 100 drugs, prescription and over-the-counter. The results, never before reported, show that about 90% of them were safe and effective far past their original expiration date, at least one for 15 years past it.

In light of these results, a former director of the testing program, Francis Flaherty, says he has concluded that expiration dates put on by manufacturers typically have no bearing on whether a drug is usable for longer. Mr. Flaherty notes that a drug maker is required to prove only that a drug is still good on whatever expiration date the company chooses to set. The expiration date doesn't mean, or even suggest, that the drug will stop being effective after that, nor that it will become harmful.

MARKETING ISSUE

"Manufacturers put expiration dates on for marketing, rather than scientific, reasons," says Mr. Flaherty, a pharmacist at the FDA until his retirement last year. "It's not profitable for them to have products on a shelf for 10 years. They want turnover."

The FDA cautions that there isn't enough evidence from the program, which is weighted toward drugs needed during combat and which tests only individual manufacturing batches, to conclude that most drugs in people's medicine cabinets are potent beyond the expiration date. Still, Joel Davis, a former FDA expiration-date compliance chief, says that with a handful of exceptions - notably nitroglycerin, insulin and some liquid antibiotics - most drugs are probably as durable as those the agency has tested for the military. "Most drugs degrade very slowly," he says. "In all likelihood, you can take a product you have at home and keep it for many years, especially if it's in the refrigerator."

MANUFACTURERS' VIEW

Drug-industry officials don't dispute the results of the FDA's testing, within what is called the Shelf Life Extension Program. And they acknowledge that expiration dates have a commercial dimension. But they say relatively short shelf lives make sense from a public-safety standpoint, as well.

New, more-beneficial drugs can be brought on the market more easily if the old ones are discarded within a couple of years, they say. Label redesigns work better when consumers don't have earlier versions on hand to create confusion. From the companies' perspective, any liability or safety risk is diminished by limiting the period during which a consumer might misuse or improperly store a drug.

"Two to three years is a very comfortable point of commercial convenience," says Mark van Arandonk, senior director for pharmaceutical development at Pharmacia & Upjohn Inc. "It gives us enough time to put the inventory in warehouses, ship it and ensure it will stay on shelves long enough to get used." But companies uniformly deny any effort to spur sales through planned obsolescence.

WHY NOT LONGER?

Now that the FDA has found that many drugs are still good long after they have supposedly expired, why doesn't it advocate later expiration dates for consumer drugs? One reason is that the consumer market lacks the military's logistical reasons to keep drugs around longer.

Frank Holcombe, associate director of the FDA's office of generic drugs, says that in many cases a manufacturer could extend expiration periods again and again, but to support those extensions, it would have to keep doing stability studies, and keep more in storage than it would like.

Mr. Davis adds: "It's not the job of the FDA to be concerned about a consumer's economic interest." It would be up to Congress to impose changes, he says. As things stand now, expiration dates get a lot of emphasis. For instance, there is a campaign, co-sponsored by some drug retailers, that urges people to discard pills when they reach the date on the label.

And that date often is even earlier than the one the maker set. That's because when pharmacists dispense a drug in any container other than what it came to them in, they routinely cut the expiration date to just one year after dispensing. Some states even require pharmacists to do this.

Meanwhile, poor countries - under urging from the World Health Organization - often reject drug-company donations of much-needed medicines if they are within a year of their expiration dates.

It isn't known how much of the $120 billion-plus spent annually in the U.S. on prescription and over-the-counter medicines goes to replace expired ones. But in a poll done for The Wall Street Journal by NPD Group Inc. of Port Washington, N.Y., 70% of 1,000 respondents said they probably wouldn't take a prescription drug after its expiration date; 72% said the same of an over-the-counter remedy.

"People think that, upon expiration, drugs suddenly turn toxic or lose all their potency," says Philip Alper, professor of medicine at University of California at San Francisco. In his own practice, Dr. Alper says, "I frequently hear - from patients who can't afford medicine - that they have thrown away

expired drugs." He says companies should be required to test drugs for longer periods and set later expiration dates when results warrant.

Some manufacturers first began putting expiration dates on drugs in the 1960s, although they didn't have to. When the FDA began requiring such dating in 1979, the main effect was to set uniform testing and reporting guidelines. As now required by the FDA, so-called stability testing analyzes the capacity of a drug to maintain its identity, strength, quality and purity for whatever period the manufacturer picks. If the company picks a two-year expiration date, it needn't test beyond that.

Testing for a two-year expiration doesn't initially entail holding a drug for two years. Rather, the drug is tested by subjecting it to extreme heat and humidity for several months, then chemically analyzing each ingredient's identity and strength. (After the date is set and the drug is marketed, testing continues for the full two years.) The FDA also uses chemical analysis in testing for possible shelf-life extension; it doesn't test on human subjects. Testing conditions are such that any medicine that meets, say, the standards for a two-year expiration date probably lasts longer, the FDA and drug companies agree.

STILL GOOD

Consider aspirin. Bayer AG puts two-year or three-year dates on aspirin and says that it should be discarded after that. Chris Allen, a vice president at the Bayer unit that makes aspirin, says the dating is "pretty conservative"; when Bayer has tested four-year-old aspirin, it remained 100% effective, he says.

So why doesn't Bayer set a four-year expiration date? Because the company often changes packaging, and it undertakes "continuous improvement programs," Mr. Allen says. Each change triggers a need for more expiration-date testing, he says, and testing each time for a four-year life would be impractical.

Bayer has never tested aspirin beyond four years, Mr. Allen says. But Jens Carstensen has. Dr. Carstensen, professor emeritus at the University of Wisconsin's pharmacy school, who wrote what is considered the main text on drug stability, says, "I did a study of different aspirins, and after five years, Bayer was still excellent. Aspirin, if made correctly, is very stable."

Only one report known to the medical community linked an old drug to human toxicity. A 1963 Journal of the American Medical Association article said degraded tetracycline caused kidney damage. Even this study, though, has been challenged by other scientists. Mr. Flaherty says the Shelf Life program encountered no toxicity with tetracycline and typically found batches effective for more than two years beyond their expiration dates.

PLEA FROM THE AIR FORCE

The program dates to a U.S. effort begun in 1981 to increase military readiness by buying large quantities of drugs and medical devices for the armed forces. Four years later, more than $1 billion of supplies had been stockpiled. The General Accounting Office audited Air Force troop hospitals in Europe and found many supplies at or near expiration. It warned that by the 1990s, more than $100 million would have to be spent yearly on replacements.

The Air Force Surgeon General's office asked the FDA if it could possibly extend the shelf life of these drugs. The FDA had the equipment for stability testing. And because it had approved the drugs' sale in the first place, it also had manufacturers' data on the testing protocols. Testing for the Air Force began in late 1985. In the first year, 58 medicines from 137 different manufacturing lots were shipped to the FDA from overseas storage, among them penicillin, lidocaine and Lactated Ringers, an intravenous solution for dehydration. After testing, the FDA extended more than 80% of the expired lots, by an average of 33 months.

In 1992, according to the FDA, more than half of the expired drugs that had been retested in 1985 were still fine. Even now, at least one still is. Such results came as a revelation for Army Col. George Crawford when he took over military oversight of the program in 1997. He is a pharmacist, but "nobody tells you in pharmacy school that shelf life is about marketing, turnover and profits," he says. (The drug makers don't agree that it is, however.)

HOW IT WORKS

The military's base for the program is a dingy barracks room in Fort Detrick, Md. There, a group headed by Air Force Lt. Col. Greg Russie, who recently took over from Col. Crawford, tracks drugs that are near expiration at defense facilities all over the world, selecting many for retesting. They are shipped to the FDA, which sends them to its laboratories.

The FDA's lab in Philadelphia recently tested five automatic injectors containing an antidote to chemical poisoning, which were purposely held for three months in conditions even hotter and more humid than the FDA requires in consumer testing of drugs. The FDA tested the drug contained in the injectors, pralidoxime chloride, by separating its ingredients and measuring the strength and quality of each, then applying a computer model to determine whether a shelf-life extension was warranted.

The injectors' original expiration date was November 1985. The FDA had retested them periodically ever since, each time approving their continued use. The batch, made by Ayerst Laboratories, now part of American Home Products Corp.'s Wyeth-Ayerst unit, is 18 years old. It is 15 years beyond the expiration date applied by Ayerst. The FDA found it is still good.

A spokesman for Wyeth-Ayerst says it "uses scientific data to establish expiration dates" and "tries to have the longest possible dating on products that scientific data supports." The company is aware of the FDA retesting program. It says it can't comment specifically on the injectors tested by the FDA.

A FEW FAIL

Shelf-life extensions are "intentionally conservative," the FDA's Mr. Flaherty told military brass in a 1992 speech. He says that if the agency extended an expiration date by 36 months, it had concluded the lot would retain all of its safety and efficacy for at least 72 months. A very few drugs aren't retested. The military has found that water-purification tablets and mefloquine hydrochloride, for malaria, routinely fail stability testing beyond their expiration dates, so it has removed them from the program.

Also excluded are large-volume intravenous solutions, such as saline. "We don't like to test those," says Col. Crawford. "Not because we can't, but because it would be politically sensitive if G.I. Joe was lying in bed and saw it had originally expired three years ago."

Mr. Flaherty has said that while he tested a handful of drug batches that didn't even make it to their expiration dates, most drugs were "surprisingly durable." In one instance, he says, drugs labeled for room-temperature storage had been kept for two years in a warehouse in Oman that averaged 135 degrees Fahrenheit in the daytime. Upon expiration, the drugs, which included the local anesthetic lidocaine and atropine, a nerve-gas antidote also used by eye doctors to dilate pupils, "were well within the standards for potency and other quality characteristics," he says.

STABLE MOLECULE

One medicine the FDA has endorsed for extensions is ciprofloxacin hydrochloride tablets, an antibiotic marketed by Bayer as Cipro. One batch had an expiration date of March 1989. More than 9 1/2 years later, the FDA found the tablets still good; it then extended some of them for 18 more months and others for 24 more months.

Albert Poirier, quality-assurance director for Bayer's pharmaceutical division, says he isn't surprised because Cipro "is a stable drug molecule" in tablet form. "We go for a shelf life that will be safest for patients," he says. "We want the drug to be used up within three years. We wouldn't want a patient to have it for 10 years because they'd have an old package insert" that might omit new information or contra-indications and because "we'd have no control over how they'd store the drug during this time."

Another extended drug is Thorazine, a tranquilizer chemically known as chlorpromazine tablets. Batches bearing December 1996 expiration dates - unused and unopened, as is the case with all

drugs evaluated in the Shelf Life program - were tested in July 1998 and extended for two years. A spokesman for the maker, SmithKline Beecham PLC, says it applies an expiration date 24 months after manufacture. "We think that is the appropriate expiration date," he says. "We don't benefit from short expiration dates."

Some other drugs the FDA has extended at least two years beyond their expiration dates are diazepam, sold as Valium; cimetidine, sold as Tagamet; phenytoin, sold as Dilantin; and the antibiotics tetracycline and penicillin.

BIG SAVINGS

On a cost-benefit basis, the program's returns have been huge. The first year, the Air Force paid the FDA $78,000 for testing and saved 59 times that sum by not needing to replace the drugs. After other services joined, the military from 1993 through 1998 spent about $3.9 million on testing and saved $263.4 million on drug expense, according to Lt. Col. Russie.

Says Mr. Flaherty: "We've cost the pharmaceutical companies hundreds of millions of dollars in sales of new stuff to the Department of Defense." More than 12 years ago, Messrs. Flaherty and Davis explained the program to drug-company chemists at a meeting of the American Association of Pharmaceutical Scientists in Woodbridge, N.J., going into detail about how the FDA decided whether to extend a given expiration date. Mr. Davis concluded by noting how much the U.S. had saved by extending shelf lives instead of "destroying large quantities of still-useful medical products... ."

Mr. Flaherty says the FDA was keenly aware that if its methodology was flawed, or its results incorrect even once, its credibility would be attacked. Yet FDA officials say that during the program's 15 years, drug makers have never objected to any of its procedures or findings. "They may not have liked what we were doing, but they weren't able to challenge it," he says.

THE MESSAGE TO CIVILIANS

While the military is finding it can keep most drugs longer, civilians hear quite a different message. For instance, a campaign called the National Expired and Unused Medication Drive has collected and destroyed 36 tons of drugs since 1991, says its founder, Kathilee Champlin. Ms. Champlin, of Colorado Springs, Colo., says her interest derives from experience working with the elderly and seeing how hard it was for them to keep track of all their medications. She says she wasn't aware of any FDA program to extend drugs' shelf lives.

Her group has gained sponsorship from the some big drug retailers, including Wal-Mart Stores Inc. It sponsors the campaign to be "a good corporate citizen," says Frank Seagrave, vice president of pharmacy merchandising. "We believe that people should dispose of unused prescription medicines a

year after they get them," he says, adding that Wal-Mart sometimes gives people a free bottle of vitamins if they bring in expired drugs.

Many pharmacists also play a role in shelf lives. The U.S. Pharmacopeia, a not-for-profit scientific group that develops standards for the drug industry, urged in 1985 that pharmacists set expiration dates at no more than one year if they were dispensing drugs in a bottle other than the manufacturer's original packaging. "New containers may let in more moisture and heat than the container the manufacturer used for the stability study," accelerating the drug's degradation, says the USP General Counsel Joseph Valentino.

The recommendation became a USP requirement in 1997. As a result, "the majority of pharmacists shorten the manufacturers' expiration dates" on prescription drugs to one year or less, says Susan Winckler, an official of the American Pharmaceutical Association. In fact, in 17 states, pharmacists now are legally required to do so. Ms. Winckler says shortening the dates makes sense because many people store drugs in moist bathrooms. She says the one-year rule is "motivated by product integrity and not by profit."

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