REPORT 1 OF THE COUNCIL ON SCIENTIFIC AFFAIRS (A-01)
Pharmaceutical Expiration Dates
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. To evaluate the issue of drug expiration dates and the clinical and fiscal consequences of setting such dates.

Methods. Letters sent to the Food and Drug Administration (FDA), the United States Pharmacopeia (USP), and the Pharmaceutical Research and Manufacturers of America (PhRMA) elicited information on how expiration dates are determined for pharmaceutical products, whether the actual shelf life of many drug products exceeds the posted expiration date, and whether data exist on the clinical or fiscal impact of expiration dates. In addition, literature searches were conducted in the MEDLINE and HealthSTAR databases, and the Web sites of the FDA, USP, PhRMA and Defenselink were searched for information.

Data Synthesis. Pharmaceutical manufacturers are required to place an expiration date on the container/label of a drug product as a prerequisite to marketing the product in the United States. Expiration dates are determined by stability assessments that follow scientifically based procedures that have been harmonized by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance. Expiration dates only apply when the drug product is stored under defined conditions. For most U.S. drug products, expiration dating ranges from 12 to 60 months from the time of original manufacture.

Based on the Shelf-Life Extension Program (SLEP), a stability testing program the FDA has administered for the United States military, the actual shelf lives of some drug products may be longer than their labeled expiration dates. The Department of Defense has reportedly saved substantial money as the result of extending pharmaceutical expiration dates.

Currently, there are no reliable data on the clinical or fiscal impact of pharmaceutical expiration dates in the civilian environment. PhRMA has informed our American Medical Association (AMA) that lengthening expiration dating for drug products in the civilian environment would not provide the same economic benefits that SLEP has provided to the military; that additional stability testing would add substantial costs to drug development and manufacturing; that most innovator drug products that are close to expiration can be returned to the manufacturer for credit; and that, whereas the military stores its drug products under optimal conditions, this would be far less likely in the civilian environment.

Once the manufacturer's container is opened and drug product is transferred to another container for dispensing or repackaging, the expiration date no longer applies. The USP has developed recommendations for pharmacists to place a "beyond-use" date on the label of the new container. There is little scientific basis for "beyond-use" dates. However, the American Pharmaceutical Association (APhA) encourages, and 17 states require, that pharmacists place a "beyond-use" date on the label of the prescription container that is dispensed to the patient.

Conclusions. The Council on Scientific Affairs recommends that AMA Policy H-115.983 (AMA Policy Database) be modified.

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2Action of the AMA House of Delegates 2001 Annual Meeting: Council on Scientific
3Affairs Report 1 Recommendation Adopted as Amended and the Remainder of the Report
4filed.

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

CSA Report 1-A-01

Subject: Pharmaceutical Expiration Dates

Presented by: Michael A. Williams, MD, Chair

Referred to: Reference Committee E
(Richard R. Johnston, MD, Chair)

At the 2000 Annual Meeting, the House of Delegates adopted amended Resolution 527, Pharmaceutical Expiration Dates. This resolution asks our American Medical Association (AMA) to urge that the Food and Drug Administration (FDA), the United States Pharmacopeia (USP), and the pharmaceutical industry evaluate the issue of drug expiration dates, the clinical consequences of setting such dates, and the fiscal impact. Furthermore, the Council on Scientific Affairs (CSA) was asked to monitor this activity and report back to the House of Delegates at the 2001 Annual Meeting.

Methods

Subsequent to the adoption of amended Resolution 527, our AMA sent letters to the FDA, the USP, and the Pharmaceutical Research and Manufacturers of America (PhRMA), the trade association that represents the research-based pharmaceutical industry. These letters raised the question of whether the actual "shelf life" of many pharmaceutical products might be considerably longer than the expiration date that appears on the manufacturer's container, which could result in unnecessary waste, higher pharmaceutical costs, and possibly reduced access to necessary drugs for some patients. Specifically, the letters asked each organization to provide relevant information on how expiration dates are determined for pharmaceutical products, whether the actual shelf life of many products is greater than the posted expiration date, and if there were any data on either the clinical or fiscal impact of expiration dates at this time.

Literature searches were conducted in the MEDLINE and HealthSTAR databases for English-language articles published between 1966 (or 1993 for HealthSTAR) and January 2001 using the terms "expiration date" and "drug." The MEDLINE database also was searched using the terms "dosage forms," "drug stability," "chemistry, pharmaceutical," "drug storage," and "pharmaceutical preparations." Additionally, the Web sites of the FDA, USP, PhRMA and Defenselink were searched for information.

Scope of Report

Based on the responses from the FDA, the USP, and PhRMA, as well as the limited published research on this subject, this report is intended to inform the House of Delegates about the following:

- How expiration dates are determined for prescription drug products;

Action of the AMA House of Delegates 2001 Annual Meeting: Council on Scientific Affairs Report 1 Recommendation Adopted as Amended and the Remainder of the Report filed.

- Whether the actual shelf lives of many drug products are greater than their labeled expiration dates;
- Whether there are any data on the clinical or fiscal impact of expiration dates; and
- How expiration dates differ from “beyond-use” dates that appear on prescription drug containers dispensed to patients by pharmacies.

How are expiration dates determined for prescription drug products?

Under Section 501(a)(2)(B) of the federal Food, Drug and Cosmetic Act (FDCA), manufacturers of prescription drug products must establish controls for the manufacture, processing, packing, and holding of drug products to ensure their safety, identity, strength, quality, and purity. Requirements for these controls, also known as current good manufacturing practices (CGMPs), are established and monitored by the FDA.

As part of the CGMP regulations, the FDA requires that drug products bear an expiration date determined by appropriate stability testing (21 CFR 211.137 and 211.166). The FDA defines an expiration date as “the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications if stored under defined conditions, and after which it may not be used.”[1]

Part of the technical documentation that must be submitted by a manufacturer to the FDA in a New Drug Application (NDA) is a stability assessment of both the new drug substance and the new drug product (the dosage form, including the new [active] drug substance and [inactive] excipients, in the final immediate packaging intended for marketing). The stability assessment follows scientifically based technical procedures that have been agreed to by the United States, the European Union, and Japan under the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The most recent guidance on this subject is entitled, “Draft Revised Guidance on Q1A(R) Stability Testing of New Drug Substances and Products,” which was published in the Federal Register on April 21, 2000.[1]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and enables recommended storage conditions, retest periods, and shelf lives (expiration dates) to be established. Stability information should cover, as appropriate, the physical, chemical, biological, and microbiological attributes of the drug substance and the drug product.[1]

The stability assessment starts with stress testing of the new drug substance. This establishes the inherent stability characteristics of the molecule, such as degradation pathways, and leads to identification of degradation products and, therefore, supports the suitability of proposed analytical procedures. The nature of these studies depends on the individual drug substance, but usually the effects of elevated temperature and humidity, oxidation and photolysis, and hydrolysis over a wide range of pH values (when the drug substance is in solution or suspension) are evaluated.[1]

The new drug substance and, subsequently the new drug product, are then subjected to formal stability testing over time under rigorously defined storage conditions of temperature and humidity. Initially, at least three batches of the drug substance must be subjected to stability testing. All three batches should be manufactured to a minimum of pilot scale and the synthetic

route and method of manufacture should simulate the final process to be used on a full manufacturing scale. Similarly, at least three batches of the new drug product, preferably from different batches of drug substance, also must be subjected to stability testing. At least two of the three batches should be manufactured to a minimum of pilot scale and the manufacturing process should simulate that to be applied to full production batches and, furthermore, should provide product of the same quality and meet the same specifications as that intended for marketing. Stability testing should be conducted on the dosage form stored in the packaging proposed for marketing.[1]

Typically, both the new drug substance and the new drug product are subjected to long-term stability testing (storage conditions, 25 ºC +/- 2 ºC/60% RH +/- 5% RH) for a minimum of 12 months and also to accelerated stability testing (storage conditions, 40 ºC +/- 2 ºC/75% RH +/- 5% RH) for six months. In some cases, intermediate stability testing also may be necessary. The storage condition at which the long-term testing is conducted will be reflected in the labeling and expiration date. Data from the accelerated storage condition may be used to evaluate the impact of short-term excursions outside the label storage conditions (such as might occur during shipping).[1]

According to the FDA, expiration dates for prescription drugs (and over-the-counter drugs) that are subject to premarket approval requirements generally are based on the amount of real-time data available at the time of FDA approval of the NDA. However, the expiration date may be extended a maximum of six months, provided the accelerated stability data submitted with the NDA are acceptable, and such an extension must be verified with actual real-time data at a later date.[2] According to PhRMA, the initial expiration dating for prescription drug products usually falls between 18 and 24 months.[3]

Since stability data submitted with an NDA commonly are based on pilot scale batches of drug product, the expiration date granted at the time of FDA approval is generally considered to be a tentative one. The FDA expects that stability study data from the first three production batches will be submitted in annual reports from the drug's manufacturer. The expiration date may be extended by the manufacturer with notification to the FDA in an annual report based on data from these batches; the FDA emphasizes that this period applies to drug product stored under controlled conditions as discussed above. The expiration date may be extended as many times as requested by the manufacturer as long as adequate data are provided.[2] Because manufacturers can extend expiration dating periods based on satisfactory long-term stability data on full production batches accumulated years after the original approval, mature products tend to have longer expiration dating periods than those products that have been on the market for a short period of time. It should be emphasized, however, that extension of drug product expiration dating periods is strictly voluntary for pharmaceutical manufacturers.[4]

The amount of stability testing required for generic drug products subject to Abbreviated New Drug Applications (ANDAs) depends on the availability of significant information and experience with the stability profile of the innovator product and on the complexity of the drug product/dosage form. For "simple dosage forms," the FDA typically will accept three months of accelerated stability testing for one batch (pilot scale) to support a tentative expiration dating period of 24 months.[3,5]

According to PhRMA, marketed prescription drug products in the United States have expiration dating ranging from 12 months to up to 60 months from the time of original manufacture. PhRMA is unaware of expiration dating for drug products beyond 60 months.[3]

Are the actual shelf lives of many prescription drug products greater than their labeled expiration dates?

The FDA defines shelf life as "the time interval that a drug product is expected to remain within the approved shelf life specification provided that it is stored under conditions defined on the label in the proposed containers and closures."[1] Using this definition, it appears that the actual shelf lives of some drug products are greater than their labeled expiration dates on containers/packages. The best evidence to support this comes from the Shelf-Life Extension Program (SLEP).[6]

In 1985, the United States Air Force was faced with a large (war reserve) stockpile of drugs that were approaching their expiration dates. The Air Force asked the FDA if it could determine if the drugs were safe and potent beyond the expiration dates set by the manufacturers. Since 1986, the FDA has administered SLEP for the United States military. According to the FDA, this is an internal program for conducting real-time and accelerated stability tests for drug products based on the same procedures that are outlined in the NDAs and the United States Pharmacopeia and National Formulary (USP 24/NF 19) (official January 1, 2000).[2] The SLEP program only applies to "stockpiled" drugs and not to other prescription (and over-the-counter) drugs that the military purchases each year. Also, every batch of a to-be-stockpiled drug product purchased by the military is tested and tracked in order to extend the expiration date for that batch.[4]

To date, the SLEP program has evaluated and tested 312 drug products to determine if specific drugs maintained their stability profiles past their labeled expiration dates. Many of the drug products tested did maintain their stability profiles well past their expiration date, up to as much as an additional 107 months. However, not all of the tested products maintained their stability profiles past the labeled expiration dates. Furthermore, certain lots of some drug products did not maintain their stability profiles past the expiration date, while other lots of the same drug product did. The reason for this disparity between lots of single drug products is not always evident. No other aspects of drug product safety and effectiveness are evaluated and tested under SLEP.[2]

It is imperative to note that the military stores these drugs under optimal conditions, either in carefully monitored controlled room temperature warehouses or, when appropriate, in refrigeration devices.[6] However, it is unclear whether SLEP would have applicability to the civilian environment. The actual shelf life of a drug product depends on the conditions under which it is stored, among other factors. A drug product stored in an unopened container under recommended conditions of temperature, relative humidity, and light likely will have a longer shelf life than the same drug product stored in an opened container under less than ideal conditions. Thus, while pharmaceutical manufacturers could probably get longer expiration dating for some drug products by extending stability testing for longer periods of time, once the drug product leaves the domain of the manufacturer, variable storage conditions (e.g., in pharmacies and especially in patients' homes) could negatively impact product stability. In its response to the AMA, PhRMA emphasized these important differences between the military and civilian environments and its potential impact on public safety.[3]

Are there data on the clinical and fiscal impact of pharmaceutical expiration dates?

The FDA and PhRMA were unaware of any comprehensive studies that addressed the clinical impact of pharmaceutical expiration dates and no such studies were found in the peer reviewed scientific literature.[2,3]

It is important to emphasize that the FDA, USP, PhRMA, and various pharmacy organizations recommend that drug products not be used after their expiration dates.[1,7,8] This also is the current policy of our AMA (Policy H-115.983, AMA Policy Database). Because the potency and other quality attributes of a drug product cannot be reliably predicted after its expiration date, there is the potential for a suboptimal therapeutic response or some other safety problem.

Reliable data, available in the public domain, on the fiscal impact of expiration dates also appear to be very limited. The CSA did not identify any comprehensive studies in its literature searches. Also, the FDA and PhRMA were unaware of any comprehensive studies that addressed this issue. The FDA noted that it lacks the resources to pursue such studies.[2,3]

News media articles on SLEP report that, on a cost-benefit basis, the Department of Defense has saved substantial amounts of money on drug expenses for a relatively small investment.[6,8] According to an article in The Wall Street Journal, the military claims it spent $3.9 million on stability testing and saved $263.4 million on drug expenses from 1993 through 1998.[8] In its article, The Wall Street Journal suggests that similar savings could be achieved for consumers in the civilian environment, but that pharmaceutical manufacturers deliberately put shorter expiration dates on their drug products for marketing, rather than scientific, reasons.[8] However, the author of this article did concede that it is not known how much of the $120 billion-plus spent annually in the United States on prescription and over-the-counter medicines goes to replace those that have expired.[8]

In its response to the AMA, PhRMA vigorously disputed the assertions made in The Wall Street Journal article. PhRMA emphasized a number of points in its letter. First, PhRMA argued that the development of stability data to support the original or an extended expiration dating period for a given lot of drug product is costly and time consuming. This cost is added to an already expensive drug development and manufacturing process and ultimately has to be passed on to patients. PhRMA also emphasized that most innovator drug products in the distribution stream are subject to take-back-for-credit arrangements (within about six months of remaining shelf life) for “nearly expired” drug products. Pharmacies can take advantage of these return arrangements either directly with the manufacturer or through a distributor/wholesaler. Finally, PhRMA argues that the consumer market lacks the military’s logistical capability to properly store drug products for prolonged periods of time. PhRMA believes this poses potential problems of reduced efficacy and safety for patients. As noted in the above discussion of SLEP, the military stores these drug products under optimal conditions. However, in the civilian environment, this often is not necessarily the case. For example, hospitals may repackage bulk drug product into unit dose containers, retail pharmacies usually transfer drug product from a large stock bottle to a small prescription container that is given to the patient, and patients are known to store their prescription drugs in bathrooms where storage conditions are far from optimal.[3]

PhRMA and the FDA also noted the important differences between the needs and operations of the military when compared to the private sector. While the military stockpiles drugs for disasters, the private sector generally prefers a high turnover rate of stock to minimize inventories and the capital tied up with it.[3,4]

Based on the limited information available, it remains unclear whether lengthier expiration dates on pharmaceuticals would ultimately lower the cost of drug products for patients.

How do expiration dates differ from "beyond-use" dates?

As discussed above, pharmaceutical expiration dates are placed on containers/labels of manufacturers' drug products. Expiration dates are determined by stability assessments that follow scientifically based technical procedures that have been harmonized under ICH guidance. Expiration dates only apply when the drug product is stored in the manufacturer's original, unopened container under defined conditions. The FDA approves the expiration date for a drug product and, the USP 24/NF 19 requires that the label of an official drug product bear an expiration date.

A "beyond-use" date is different from an expiration date. By removing a drug product from the manufacturer's marketed container or bulk dosage container and placing the drug product in a different container for dispensing to a patient or for repackaging (e.g., into unit dose packages for further dispensing in a hospital), pharmacists may be altering the expiration date. In such instances, the USP has developed recommendations to place a "beyond-use" date on the label of the new container, as follows:

> The beyond-use date placed on the label shall be no later than the expiration date on the manufacturer's container. The beyond-use date is a date after which an article [drug product] must not be used. Based on the information supplied by the manufacturer, the dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article.
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> For articles requiring constitution prior to use, a suitable beyond-use date for the constituted product shall be identified in the labeling.
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> For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such a beyond-use date shall be no later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be one year or less, unless stability data or the

manufacturer's labeling indicate otherwise.* For all other types of nonsterile dosage forms, the beyond-use date is one year or the time remaining of the expiration date.

The repackager must maintain the repackaging facility at a temperature, such that the mean kinetic temperature is not greater than 25°. The repackaged dosage forms are similarly stored. The plastic material used in repackaging must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation.[7]

Unlike the substantial, scientifically derived stability data that determine an expiration date, there is little scientific basis for "beyond-use" dating. However, the recommendations of the USP on "beyond-use" dates generally are well accepted within the pharmacy community. The American Pharmaceutical Association (APhA) encourages, and 17 states require by either law or regulation, that pharmacists place a "beyond-use" date on the label of the prescription container that is dispensed to the patient.[8,9] Current AMA policy (H-115.983) also recommends that pharmacists place a "beyond-use" date on the labeling of all prescription medications dispensed to patients and, that the "beyond-use" date be based on USP recommendations.

Summary

Pharmaceutical manufacturers are required by federal law and regulation to place an expiration date on the container/label of a drug product as a prerequisite to marketing the product in the United States. Expiration dates are determined by stability assessments that follow scientifically based technical procedures that have been harmonized under ICH guidance. Expiration dates only apply when the drug product is stored in the manufacturer's original, unopened container under defined conditions. For most drug products in the United States, expiration dating ranges from 12 months to up to 60 months from the time of original manufacture.

Based on SLEP, a stability testing program that the FDA has administered for the United States military, it appears that the actual shelf lives of some drug products are longer than their labeled expiration dates. Furthermore, it has been reported that the Department of Defense has saved substantial amounts of money on drug expenses as the result of extending pharmaceutical expiration dates.

Currently, there essentially are no reliable data on the clinical or fiscal impact of pharmaceutical expiration dates in the civilian environment. PhRMA, the trade association representing the research-based pharmaceutical industry, has informed our AMA that lengthening expiration dating for drug products in the civilian environment would not provide the same economic benefits that SLEP has provided to the military. PhRMA contends that additional stability testing would add substantial costs to drug development and manufacturing. Furthermore, PhRMA notes that most innovator drug products that are close to expiration can be returned to the manufacturer for credit. Finally, PhRMA argues that, whereas the military stores its drug products under optimal conditions, this would be far less likely in the civilian environment. PhRMA believes this poses potential problems of reduced efficacy and safety for patients.

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* The FDA commented that the USP's "beyond-use" dating recommendations do not apply to drug products repackaged into unit dose containers by manufacturers and commercial repackagers. For solid and liquid oral dosage forms, FDA's Compliance Policy Guide 7132.b11 applies, and it allows repackagers to assign up to 25% of the remaining expiry on the manufacturer's bulk container, not to exceed six months, to the repackaged unit.[4]

Once the manufacturer's container is opened and drug product is transferred to another container for dispensing or repackaging, the expiration date no longer applies. The USP has developed recommendations for pharmacists to place a "beyond-use" date on the label of the new container. The "beyond-use" date can be no longer than the manufacturer's expiration date and often may be shorter, i.e., one year. Unlike expiration dates, there is little scientific basis for "beyond-use" dates. However, the APhA encourages, and 17 states require, that pharmacists place a "beyond-use" date on the label of the prescription container that is dispensed to the patient. Current AMA policy (H-115.983) also recommends that pharmacists place a "beyond-use" date on labels of prescription containers dispensed to patients and, that the "beyond-use" date be based on the USP's recommendations.

RECOMMENDATION

The Council on Scientific Affairs recommends that AMA Policy H-115.983 be modified as follows and that the remainder of this report be filed.

H-115.983 Expiration Dates and Beyond-Use Dates of Prescription Drugs ~~Products~~

> Our AMA: (1) supports the inclusion of expiration dates on the containers/labels of prescription drug products and recommends that expiration dates be determined by pharmaceutical manufacturers using scientifically based stability testing with subsequent approval by the Food and Drug Administration (FDA); (2) urges the pharmaceutical industry, in collaboration with purchasers, the FDA, and the United States Pharmacopeia (USP), to determine whether lengthening of expiration dates will provide clinical and/or economic benefits or risks for patients and, if this is the case, to conduct longer stability testing on their drug products; (3) ~~(1)~~ recommends that pharmacists place a beyond-use date on the labeling of all prescription medications dispensed to patients, and that the beyond-use date be based on the recommendations in the most recent edition of the *United States Pharmacopeia and National Formulary* (currently *USP 24-NF 19*) (official January 1, 2000) ~~(USP 23-NF 18) (official January 1, 1995)~~; and (4) ~~(2)~~ encourages the U~~nited~~ S~~tates~~ P~~harmacopeial Convention, Inc.~~, in collaboration with pharmaceutical manufacturers, pharmacy organizations, and the FDA ~~Food and Drug Administration~~, to continue to explore the development of appropriate stability tests for the determination of ~~more~~ scientifically sound beyond-use dates for repackaged products. ~~(3) urges that the FDA, United States Pharmacopeia, and the pharmaceutical industry evaluate the issue of drug expiration dates, the clinical consequences of setting such dates, and the fiscal impact.~~ **(Modify Current HOD Policy)**

References

1. International Conference on Harmonization; Draft Revised Guidance on Q1A(R) Stability Testing of New Drug Substances and Products. Federal Register. April 21, 2000; 65(78):21446-21453.

2. Letter from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, Food and Drug Administration. December 15, 2000.

3. Letter from Alan F. Holmer, President, Pharmaceutical Research and Manufacturers of America. November 17, 2000.

4. Letter from Jeffrey E. Shuren, MD, JD, Food and Drug Administration. March 28, 2001.

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