United States Food and Drug Administration and Department of Defense Shelf-Life Extension Program of Pharmaceutical Products: Progress and Promise

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ABSTRACT: The Department of Defense (DoD)–United States Food and Drug Administration (FDA) shelf-life extension program (SLEP) was established in 1986 through an intra-agency agreement between the DoD and the FDA to extend the shelf life of product nearing expiry. During the early stages of development, special attention was paid to program operation, labeling requirements, and the cost benefits associated with this program. In addition to the substantial cost benefits, the program also provides the FDA's Center for Drug Evaluation and Research with significant scientific understanding and pharmaceutical resource. As a result of this unique resource, numerous regulatory research opportunities to improve public health present themselves from this distinctive scientific database, which includes examples of products shelf life, their long-term stability issues, and various physical and chemical tests to identify such failures. The database also serves as a scientific resource for mechanistic understanding and identification of test failures leading to the development of new formulations or more robust packaging. It has been recognized that SLEP is very important in maintaining both national security and public welfare by confirming that the stockpiled pharmaceutical products meet quality standards after the "expiration date" assigned by the sponsor. SLEP research is an example of regulatory science that is needed to best ensure product performance past the original shelf life. The objective of this article is to provide a brief history and background and most importantly the public health benefits of the SLEP. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1331–1336, 2014

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INTRODUCTION

The pharmaceutical product shelf life, also referred as the expiration date, is the time period during which the product is expected to retain its identity, purity, quality, and strength when properly stored as specified in the container label.[1] Performance of the drug product beyond the manufacturer set shelf life has been a subject of study over past several decades. Studies have shown that many drug products retain their shelf-life quality characteristics such as potency and efficacy, several years beyond the expiration date if stored properly.[1–3] To estimate the drug product shelf life, stability tests are carried out under variety of stress conditions, such as temperature, humidity, and light, as described under the 21 CFR 211.137 and 211.166 documents.[4] Based on the stability data, the pharmaceutical companies assign the expiration date for the drug products which is required documentation for new drug application (NDA) or the abbreviated new drug application (ANDA).[3] Based on the accelerated and real-time stability data, the initial expiration date can be extended. Drug manufacturers are allowed to conduct long-term stability tests to prove that their products are stable for long-term storage. But this is optional and there is little incentive for manufactures to extend the expiration date. However, the expiration date can be extended if the manufacturer demonstrates long-term stability of the product beyond the initial expiration date granted at the time of the drug approval.

In 1981, the military services began purchasing large quantities of drugs and medical devices for stockpiling.[5] Significant quantities of these products sit in the stockpiles around the world and are not rotatable for the peacetime use of the products. As the drug product approaches expiration date, these stockpiles are disposed of and replaced with new stocks. In 1987, Joel et al.[5] reported that, of 1 billion dollar worth of medical supplies being procured, an estimated $300 million worth of material are shelf-life sensitive. The United States Food and Drug Administration (FDA) administers the shelf-life extension program (SLEP) for the United States Military as a comprehensive testing and evaluation program designed to justify an extension of the shelf life of stockpiled drug products. The program was initiated in 1985 as a result of an audit of Department of Defense (DoD) stockpiled drugs that documented the high cost associated with replacing the expired drug products. This article provides a brief overview of the SLEP background and its operations; with special focus on sample procurement procedures, evaluation, analysis, and the labeling requirements of the tested drug products. In addition, this article also discusses the associated cost benefits, and some of the challenges

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encountered in the effective implementation and expansion of the program.

SLEP BACKGROUND

The Government Accountability Office (GAO) in 1985 reported that the $9 million worth of stockpiled drug product was about to reach its labeled expiration date and needed replacement.[6] As there were no alternate measures available, it was standard practice to dispose the expired drug products and seek additional funds for the purchase of replacement drug products. This resulted in significant replacement cost each year.

In an effort to defer the overall costs and reduce the taxpayer burden for replacing the expired drug stockpiles, organizations such as: the FDA, the defense medical standardization board US. Military branches, Defense Supply Center-Philadelphia, Strategic National Stockpile (SNS), and the veteran affairs (VA) emergency pharmacy services, joined together to develop the SLEP.[5] A pilot project was initially initiated in 1985 to assess the feasibility of this program by the representatives of the Air Force Surgeon General's office and the FDA. Fifty-six items were initially tested by the FDA. After 8 months of testing, 84% of the lots tested were extended for up to a period of 3 years or more past their labeled expiration date.[5] After the success of the pilot program, in 1986, an agreement was reached to initiate the SLEP on a permanent basis. An interagency agreement was signed in 1986 between the FDA and the DOD to "*conduct a comprehensive, scientifically sound testing and evaluation program that will determine whether there is justification for extending the shelf life of stored medical items owned by components of DOD or their authorized program partners*."[6,7] Testing of the items began in Fiscal Year (FY) 87, and by FY 91, the program gained enough success that DOD and the FDA had to increase the monetary and laboratory resources to support the growing needs.

PROGRAM OPERATION

The Office of Regulatory Affairs (ORA) within the FDA serves as an interphase between the program participants and the testing laboratories. Once a drug product has been identified as possible test candidate, the FDA gets the list of all possible pharmaceutical products in which category that are nominated as candidates for SLEP by the various program participants. The Defense Medical Material Program Office (DMMPO) maintains a database of the candidate items. The database is then used to select the products submitted for inclusion in a test project. Upon completion of testing, FDA field laboratory forwards the results to the ORA project manager who in turn sends it to the Center for Drug Evaluation and Research (CDER) SLEP chemist for a comprehensive evaluation of the submitted physical, chemical, and spectroscopic data and a final mathematical evaluation is made. Based on the final testing results and the evaluation, the FDA SLEP chemist decides whether to extend the shelf life of the product or not. Once the initial testing is carried out the product will be retested annually or biannually until it reaches its maximum extension when the product fails testing or when the stocks are depleted.

The DoD database requires all users to enter their on-hand inventory of Chemical, Biological, Radiological, and Nuclear (CBRN) medical material, pandemic influenza, and antimalaria pharmaceuticals as soon as they receive those items. They are then required to update their inventory once a quarter. Customer service point of contact (POC) now uses this data for budgeting, reporting, and management of CBRN and antimalaria material.

Once a quarter, the SLEP program manager at the DMMPO pulls the on-hand inventories of all products expiring within the next 180 days. This list is cross-referenced against the total on-hand quantities and the original expiration date of the item. In order for the program to be cost effective, there should be at least $10,000 worth of stockpiled drugs on hand during the time of testing. However, there are exceptions, for example, if an item is in short supply and required for possible/actual event/operation, such stockpile are considered under this program. Also, it was originally established that no item will be extended beyond 10 years. However, some items such as silver sulfadiazine cream have shorter maximum extension date. Hence, great importance is placed on SLEP users to ensure that all stock is identified in the SLEP website to ensure testing decisions are based on the most accurate information.

Once a lot has been identified as a possible test candidate, the FDA gets the list of all possible test lots that are approaching their labeled expiration date within the next 180 days and then the FDA requests samples. Samples are then requested through the automated system to the POC. Service POCs then provide the material to the FDA based on the lot and SNS number. The FDA requires the sample to be received within 45 days of the request. The items are then shipped to one of three FDA laboratory testing sites. Noncontrolled drugs are shipped to the FDA headquarters in Rockville, Maryland and controlled drugs are shipped to Detroit or Philadelphia or other FDA field laboratories. Figure 1 shows the SLEP operation flow that highlights the programs major activities. The CDER staff involved in the SLEP program assists with the evaluation of products for SLEP suitability by evaluating previous reviews of NDAs and ANDAs and related supplements for current release test procedures; evaluating tests for applicability as stability indicating assays; initiating and developing new procedures as needed; and forwarding the appropriate testing procedures to field laboratories. Upon receiving the test results from field laboratory, the CDER scientific staff reviews the data and is responsible for recommending or denying shelf-life extension for the specific product based on the quality attributes such potency (assay), impurities, water content, color, particulates, dissolution, pH, preservative content, and physical appearance. These attributes vary depending on the nature of the dosage form. For examples, oral solid dosage forms are tested for potency, physical attributes, water content, dissolution, and impurities, whereas injectable are tested for potency, impurities, pH, physical appearance, and preservatives. The test and their specifications are based on the United States Pharmacopeia (USP) Compendial methods or test specifications described in the NDA submission.

When the FDA has received all the samples for the new testing period, or it has been 45 days since the request for samples was sent, the FDA assigns a project number, sends the list of products by lot numbers that will be tested and, a list of lot numbers that will not be tested to DMMPO. The DMMPO enters this information into the database system and then sends an email message out to all users of the SLEP system with affected inventory and service POCs. Any SLEP participating activity having those declared items in the database by lot