cation X. If these letter symbols are allowed to stand for concentration, and the subscripts r and w are used to indicate the resin and the outside solution, respectively, then one can write the classical law of mass action $N_r{}^a M_w{}^b / M_r{}^a N_w{}^b \simeq K$. If K is approximately constant for a given exchange, the numerical value is a measure of preference of the resin for the ion. Note, however, that K is dimensionless only if a and b are equal, so that comparison of ion affinities can be made only for exchanges of ions of the same type, that is, univalent-univalent, univalent-bivalent, *etc.* Despite the limitations of the theory, there is general knowledge that for similar ions affinity increases with increasing ionic charge.

On the basis of the foregoing discussion it is seen that the concentration of hydrochloric acid is critical. There must be enough to dissolve the sample in a reasonable time but not so much chloride ion present as to prevent complete exchange of phosphate. Additionally, a low hydrogen-ion concentration favors the multivalent anion in the equilibrium $H_2PO_4^- \rightleftarrows H^+ + HPO_4^{-2}$.

The importance to be attached to the difference in standard deviations between methods A and B is difficult to evaluate. The standard deviation for the assay of dibasic calcium phosphate is expected to be about 0.4 for either method. A collaborative study with sufficient replicates is needed to establish any real difference in the reproducibility of the two methods. The two methods yield the same result within the expected standard deviation.

No comparisons can be made in the assay of tribasic calcium phosphate as the official method is the determination of phosphate.

CONCLUSIONS

The proposed method is much more rapid than the official method of assay for dibasic calcium phosphate, has acceptable reproducibility, and yields the same result as the official method.

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Technical Articles

Pharmaceuticals Stored in Plastic Containers

By HAROLD M. BEAL, ROBERT J. DICENZO, PAUL J. JANNKE, HENRY A. PALMER, JULES PINSKY*, MORRIS SALAME*, and TULLY J. SPEAKER

IN THE DEVELOPMENT of light weight highly mobile combat support hospitals and medical treatment facilities, the U. S. Army Medical Research and Development Command recognizes the need for the standardization of pharmaceutical containers in addition to the reduction of their weight, cube, and breakage. The following excerpt from the USAMRDC bulletin, "Development Requirements," describes the general characteristics for nonglass containers which are sought for drugs, biologicals, and reagents:

"Purpose: The purpose of this requirement is to develop a family of immediate containers for drugs, biologicals and reagents that will materially reduce the packaged bulk of such items. These containers are to be compatible with contents and be suitable for use in any field environment and under all tactical conditions. They will be of standard size and shape, light weight, small cube and chemical-gas-temperature-breakage resistant."

Quite logically, the question arose as to the stability of drugs packaged in containers other than glass. Since certain plastics possess, at least in part, the characteristics sought, a project

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concerned with the stability of pharmaceuticals packaged in polyethylene containers was jointly conducted by the School of Pharmacy, University of Connecticut, and the Monsanto Co., under the auspices of the U. S. Army Medical Research and Development Command. Because a package is a two-phase system consisting of a container and its contents, and since both phases can react with their environment, either individually or jointly, it was deemed essential for the performance of the containers to be evaluated by specialists in the properties, manufacture, and testing of plastic bottles.

Extensive experience has shown that virtually all pharmaceuticals undergo deterioration of some order with the passage of time. Both the rate and the extent of deterioration vary widely among drugs, and the rate usually is influenced by environmental conditions. The basic question which then arises is, "Do these same drugs decompose more rapidly when packaged in plastic than they do when packaged in glass?" One of the primary features of the study, therefore, becomes the comparison of the stability of a given pharmaceutical which has been packaged in both types of containers. Attention was not directed to studying the basic stability *per se* of any one drug. Because of their inherent nature, however, data which have been accumulated can and will serve as a basis for recommending that certain drug preparations should not be stored at all, or at most for limited intervals at certain temperature-humidity conditions, irrespective of what the containers might be.

A second feature of the study is the evaluation of the performance of the plastic containers, both separately and in conjunction with their contents, leading ultimately to the drafting of chemical and physical specifications for the polymer resin (and additives) and for the plastic containers as well.

EXPERIMENTAL DESIGN

Pharmaceuticals Used

The pharmaceuticals upon which the study is based include 96 of those used in greatest quantity by the U.S. Army Medical Service in the treatment facilities of its 400 bed evacuation hospitals. Representing a typical variety of medicinal agents, the samples include 45 kinds of tablets, 6 of capsules, 17 of liquids, 19 of powders, and 9 of ointments. The drugs to be used were designated by the Army Medical Research and Development Command, and were purchased by the Defense Medical Supply Center from the usual suppliers of the respective drugs to the army. Taken from single manufacturing lots which were less than 6 months old, the drugs were shipped directly to the project laboratories at the University of Connecticut. The pharmaceuticals are identified by nonproprietary name in Table I.

Containers and Closures

The choice of polyethylene as test container was based on the recommendation of Mr. Jules Pinsky. It was pointed out that high density polyethylene (0.95–0.96) was being used extensively in the packaging of foods and household commodities, and that the polymer resin formulations could be selected from those which had been accepted by the Food and Drug Administration for the packaging of foods and related items. This was not intended to imply that FDA acceptance of polyethylene for the packaging of foods predetermined the acceptability of the plastic for packaging drugs. Such limited acceptance, however, did serve as a logical point of departure because foods and drugs have much in common with regard to their complexity, gross stability, *etc.*

The plastic containers used for packaging experimental samples initially were 125-ml. oblong, amber (meeting U.S.P. requirements for light resistance) bottles of 0.96 d. polyethylene supplied and recommended by the Monsanto Co. as being best suited for this purpose. Their weight was approximately 15 Gm., and the nominal wall thickness was 0.030 in. The high density polyethylene bottles were used preferentially because of their rigidity and lower permeability characteristics. They are, however, more subject to stress cracking than are the lower density, more pliable containers. Therefore, when cracking occurred or when excessive loss of volatiles was a problem, samples were repackaged in either 0.95 d. or epoxy-lined polyethylene containers, as conditions warranted. Identical drug samples intended to serve as controls were packaged in 4-oz., wide mouth, square amber jars manufactured by Armstrong Cork Co. of U.S.P. type III glass.

Both types of containers were fitted with white coated tinplate caps in which the liner was a 0.035-in. pulpboard faced with white pigmented Vinyliner. In addition, each bottle was fitted with another laminated cap liner which consisted of polyethylene-coated aluminum foil on a Kraft paper backing. This liner is identified as Flexkin 200F. Mil B-131, Acme Backing Co. In the case of the polyethylene bottles, this liner was heat sealed onto the bottles immediately after they were filled with drug samples, thereby producing a sealed and continuous enclosure for the contents. This was regarded as an effective means of limiting the loss of volatile components to the permeation process. Sealing with an adhesive was tested, but found to be less desirable. Heat seals applied with a thermostatically controlled sealing iron were found by positive pressure testing to be uniformly effective. The polyethylene laminate was not sealed onto the glass bottles. Screw caps were applied to all bottles with a torque of 15 in.-lb. Thus, the polyethylene bottles were heat-sealed, reinforced by a metal cap, while the glass bottles had a comparable pressure seal only. Thereupon, the loss of weight by the drug in polyethylene could be attributed to permeation, whereas loss by the drug in glass was a function of liner-cap leakage.

Storage Conditions

Reserves of all commodities are subjected to various storage conditions, the nature of which are dependent upon numerous factors. These conditions, supplemented by the conditions encountered

in transit, represent what might be designated as the "storage history" of the commodity. The storage history of commodities for the civilian market within the continental United States reflects only rarely conditions which are beyond control, if and when control is desired. Military materiel, on the other hand, can be subjected to indefinite transportation and storage conditions in domestic and foreign depots where regulated environmental conditions may be desired, but are wholly impossible. For many reasons, therefore, the environmental conditions to which drugs in both types of containers were exposed include and extend beyond those usually applied in conventional stability testing programs involving products for civilian use. It should be recognized, therefore, that these broad extremes tend to establish stability requirements which generally embrace and extend beyond the performance demanded for civilian market needs.

Automatically controlled walk-in type environmental chambers were specially constructed for the project by Harris Refrigeration Co., Cambridge, Mass. Each of the six units bore recording devices such that the constancy of the respective environments (temperature and humidity) could be noted and recorded. The environmental conditions employed throughout the storage intervals were as follows: 140°F., 14% relative humidity (ambient); 100°F., 27% relative humidity (ambient); 100°F., 80% relative humidity (controlled); 73°F., 50% relative humidity (controlled); 73°F., 80% relative humidity (controlled); 40°F., 80% relative humidity (ambient); −65°F., ambient relative humidity cycling between −65°F. and 140°F.

The condition described as 73°F., 50% relative humidity is that which prevailed throughout the air-conditioned laboratory in which the project was conducted. Samples of pharmaceuticals exposed to this environment were stored on open metal shelving, protected from direct sunlight, yet exposed to the prevailing complement of daylight and fluorescent light.

The environment called "cycling" was programmed so that each sample was subjected to a 6-day cycle consisting of 2 days at 140°F., then 2 days at −65°F., and finally another 2 days at 140° F., whereafter the samples were equilibrated to room temperature for evaluation. Samples were prepared for storage under all other environmental conditions described for intervals of 6, 12, 24, and 48 weeks. If gross container failure was noted at the end of any one interval, in any one environment, that drug was repackaged in 0.95 d. or in epoxy-lined polyethylene bottles, as conditions warranted; ideally, the lower density bottles to overcome stress cracking, and the epoxy-lined bottles to minimize loss of volatiles from the formulation.

If any sample showed physical or chemical decomposition slightly beyond the tolerable limits at the end of an exposure interval, other than 48 weeks, it was carried through the next exposure interval as a matter of assurance. Gross physical or chemical decomposition, on the other hand, was cause for immediate termination of further testing.

Preparation of Samples for Storage

At the initiation of this study, it was recognized that the rate of progress was substantially predetermined by the rate of assaying, which in turn was dependent on analytical methods, personnel, and equipment. Programming of the samples throughout the test period was therefore developed with these controlling factors in mind.

Six samples of each pharmaceutical product, 3 in polyethylene and 3 in glass to serve as controls, were packaged for storage in each of the environments for the intervals stated. (This amounted to 16,704 individual sample bottles, not counting repacks necessitated by container failure. For the latter reason, an additional 528 sample bottles were packaged.) Samples approximating 100 Gm. were weighed to the nearest milligram into tared test bottles, such that changes in net weight during exposure could be recorded. This information was of interest to the subcontractor, whose responsibility it was to evaluate the significance of the loss of volatiles by permeation. Simultaneous with the transfer of pharmaceuticals from their bulk containers to test bottles, moisture content and alcohol content of each sample were determined where applicable.

Stability Evaluation

Testing the stability of pharmaceuticals is designed to determine quantitatively and/or qualitatively the changes which the products undergo during storage. The changes can involve chemical composition and physical characteristics, both of which are usually well defined and are of a proper order in a newly made drug product of high quality. Changes in these features are signs of deterioration or instability of the drug, and measurement or evaluation of them from time to time provides an insight into the stability of the product.

Chemical Testing—Assay procedures were drawn from three sources. When a procedure given in the "United States Pharmacopeia" or in the "National Formulary" was both stability-indicating and applicable on a practical basis to large numbers of samples, the official procedure was used. Some official methods were modified slightly for the simple purpose of improvement or to facilitate multiple runs. Forty official methods were employed; 26 methods were furnished (on a confidential basis) by the manufacturers of the respective drug products; 32 additional stability-indicating procedures were developed in the project laboratories. The remainder were modified official procedures.

Physical Testing—Quite aside from their aesthetic features, the physical characteristics of drug products serve a very important function in therapeutic efficacy. Changes in these characteristics can alter the intended performance in many instances. Furthermore, any drug which has undergone change in physical characteristics is regarded with suspicion as to its wholesomeness, security, and efficacy by both the dispenser and the consumer.

Evaluation of the physical stability of the pharmaceuticals was carried out by the usual methods. Uncoated tablets were subjected to friability, hardness, and disintegration or dissolution tests. Friability was determined with a Roche Friabilator. Tablet hardness was measured with a modified Strong-Cobb hardness tester. Disintegration testing involved the use of the U.S.P. basket-rack assembly. Dissolution tests were carried out on those tablets intended for extemporaneous preparation of solutions. Moisture content was determined

by the Karl Fischer method, where applicable. In a small number of instances, moisture determination by desiccation was necessary. Coated tablets, plain or enteric, were examined for cracked, crazed, or dulled coatings, and were also tested for disintegration, using the appropriate U.S.P. method. Gelatin capsules were examined for cracks, leaks, embrittlement, and for changes in the moisture level of the contents. Liquid pharmaceuticals were examined for crystal growth, precipitation, particulate matter, color change, and solvent loss. Suspension stability was evaluated by degree and ease of resuspension. The consistency of ointments was determined by means of a Haake Roto-Visco viscosimeter and by observation of the extent of separation. Powders were examined for evidence of color change and caking. Finally, all samples were subjected to the usual organoleptic tests, where applicable.

Container Testing—The performance of polyethylene bottles used in the study was evaluated by two criteria—namely, visible and invisible. As samples were removed from the environmental chambers, it was unavoidable that physical changes in some of the polyethylene bottles should be noted. Indeed, in a small number of instances, rupturing of a bottle and loss of contents was evidenced by leakage residues in the chambers even before those samples were scheduled for removal.

The visible types of change included rupturing of the bottle due to one factor or another (see under *Container Failure*), and the swelling or collapse of a bottle. The former is a very positive change and cannot possibly be misjudged. The latter (swelling or collapse), however, occurred to different extents ranging from the obvious to the debatable. For this reason, swelling or collapse of polyethylene bottles is seldom mentioned in the summary report in Table I.

The search for invisible changes in the polyethylene bottles was conducted by the Packaging Division, Monsanto Co., Bloomfield, Conn. At scheduled intervals, plastic bottles from each of the test sets were emptied of their contents and forwarded to the subcontractor, who analyzed them for changes in impact strength, elongation, melt index, tensile strength, evidence of carbonyl oxidation, environmental stress cracking, and/or tensile rupture. In addition, the Monsanto Co. conducted infrared analyses for product absorption by the test bottles and they evaluated the permeability characteristics of the bottles, based on weight changes due to loss of volatiles or gain of moisture during the storage periods. The IBM runs on these data, performed at Monsanto's Data Center in St. Louis, are on file at the project laboratories.

Definitions of Failure

Product Failure—Product stability must be judged on the basis of chemical and physical characteristics and the changes which they undergo. Before a given product can be declared stable or unstable, it is necessary to establish working definitions of these terms, because they are relative rather than absolute. As originally conceived, the purpose of this study was to compare the stability of a drug packaged in plastic with the stability of that drug packaged in glass. A criterion for chemical failure was adopted wherein it was regarded as a loss of more than 10% of the active ingredients initially present; that is to say, a drug was regarded as stable if, after a given storage interval, it retained at least 90% of its zero-time assay value.

The criteria for judging physical test data cannot be defined so neatly as that used in determining chemical failure. This is due to the subjective nature of the physical tests. In these cases, sound judgment based on experience with good practice and an appreciation for consumer acceptance became the sole criteria. Of the more objective physical tests, the only one with official limits is that for disintegration time; if the limit was exceeded, the tablet in question was considered to have failed. Wherever applicable, military specifications for disintegration time limits were applied to tablets having no official status.

Container Failure—A polyethylene container was considered to have failed when it did not protect its contents to the same extent as did glass, except for the 10% tolerance limit adopted. In addition, failure took place when the container ruptured due to a combination of temperature and contents acting as stress cracking agents and/or generating high internal pressure that exceeded the long-term tensile strength of the bottle. Serious loss of volatiles by permeation was also regarded as a form of container failure, as were exudation of lipoidal substances through the bottle wall and excessive absorption of the product by the polyethylene.

SUMMARY OF EXPERIMENTAL RESULTS

The extensive data accumulated during the study are summarized in Table I. Even in abstract form, the tabulation is of necessity lengthy; consequently, repetition has been eliminated as much as possible, without risking misinterpretation, and abbreviation has been utilized extensively. The full meaning of abbreviations and symbols and the identification of specific parameters are given herewith, such that the tabulation conveys the full description of the circumstances which attended the stored drug samples and their containers.

Storage Conditions—Temperatures designated in the identification of all storage conditions are given in degrees Fahrenheit. Relative humidity (R.H.) is associated only with those environments in which the humidity level was under positive control. In all other instances, humidity was ambient. The duration of storage is indicated by an expression such as ". . . /24 wk. at 140°," which means that after being stored for 24 weeks at 140°F., 14% R.H., the product in question was found to have undergone some kind of failure or change. Likewise, the expression ". . . at 140°/6 wk." means that the product was stored at 140°F., 14% R.H., for 6 weeks.

Chemical Stability—Chemical stability is a variform expression of chemical failure. The latter has already been described under *Product Failure* as a loss of more than 10% of the initial concentration of active ingredient. Within the project, it was necessary to differentiate between comparative changes in percentage concentration and the types of container in which the changes occurred. The degrees of failure and the related containers are identified as follows.

Type (C-1): no loss in glass, loss in polyethylene

TABLE I—PRODUCT STABILITY AND CONTAINER PERFORMANCE

Product[f]	Chemical Stability	Physical Stability	Container Performance
1, Sulfadiazine tablets U.S.P., 0.5 Gm.	Passed under all storage conditions/48 wk.	(P-1)/24 wk. at 140° and (P-3)/48 wk. at 140°; both exceed U.S.P. disintegration time	0.96; passed under all storage conditions/48 wk.; permeability negligible; slight absorption of product at 140°/48 wk.; no effect on container function
2, Acetylsalicylic acid tablets U.S.P., 0.325 Gm.	Passed 12 wk. at 140°; see physical failure; passed all other storage conditions/48 wk.	(P-3)/12 wk. at 140°; (P-4)/6 wk. at 140° in glass; salicylic acid crystals on tablets; samples exceed U.S.P. disintegration time	0.96; bottle tensile rupture/12 wk. at 140°; passed all other storage conditions up to and including 100°/48 wk.; permeability negligible
3, Acetylsalicylic acid, phenacetin, and caffeine tablets N.F.	Failed (C-3) within 6 wk. at 140°; passed all other storage conditions/48 wk.	(P-3)/6 wk. at 140°; salicylic acid crystals on tablets	0.96; passed under all storage conditions/48 wk.; permeability negligible
4, Sodium chloride tablets U.S.P., 0.65 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
5, Deleted from study			
6, Deleted from study			
7, Meprobamate tablets U.S.P., 0.4 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
8, Sulfisoxazole tablets U.S.P., 0.5 Gm.	Passed/48 wk. at 140°; see physical failure; passed under all other storage conditions/48 wk.	(P-3)/12 wk. at 140°; samples exceed U.S.P. disintegration time	0.96; passed under all storage conditions/48 wk.; permeability negligible
9, Calcium lactate tablets N.F., 0.65 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; moisture permeability 4.6% gain/48 wk. at 100°; glass control showed 2.5% gain; product permeability negligible
10, Ferrous sulfate tablets U.S.P., 0.325 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
11, Penicillin G tablets U.S.P., 250,000 units	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
12, Deleted from study			
13, Dried aluminum hydroxide tablets U.S.P., 0.325 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; moisture permeability 6.6% loss/48 wk. at 100°; product permeability negligible
14, Sodium chloride for solution tablets, 2.25 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
15A, Erythromycin tablets U.S.P., 0.25 Gm.	Passed under all conditions between 40° and 100°/48 wk., and under cycling; failed (C-3) within 6 wk. at 140°; passed/6 wk. at −65°; see physical failure	(P-3)/6 wk. at 140°; (P-3)/6 wk. at −65°; (P-3)/cycling; in all instances, coating dull, with extensive surface cracking; this failure terminated assaying of −65° samples after 6 wk.	0.96; passed under all storage conditions up to and including 100°/48 wk.;[a] product permeability negligible; moisture permeability 1.1% gain/48 wk. at 100°; glass control also showed 1.1% gain
15B, Erythromycin tablets U.S.P., 0.25 Gm.	Passed under all conditions between −65° and 100°/24 wk.; 140° and cycling samples not assayed; see physical failure	(P-3)/6 wk. at 140°; (P-3)/cycling; pitted, peeling, and dulled coatings responsible for no assays on 140° and cycling samples	0.96; passed under all storage conditions/24 wk.;[b] permeability negligible
16, Chloroquine phosphate tablets U.S.P., 0.5 Gm.	Passed/24 wk. at 140°; passed under all other storage conditions/48 wk.	(P-3)/12 wk. at 140°; (P-3)/12 wk. at −65°; cracked coatings	0.96; passed under all storage conditions/48 wk.; permeability negligible
17, Sodium salicylate tablets U.S.P., 0.325 Gm.	Passed under all storage conditions up to and including 100°; physical failure precluded assay of 140° samples	(P-3)/6 wk. at 140°; extensive cracking; (P-3)/48 wk. at −65° and (P-3)/cycling due to crazing and cracking	0.96; passed under all storage conditions up to and including 100°/48 wk.;[a] permeability negligible
18, Chlorpheniramine maleate tablets U.S.P., 4 mg.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; slight absorption of product at 140°/48 wk.; none at 100°; no effect on container function
19, Chlorpheniramine, phenylephrine, aspirin, phenacetin, and caffeine tablets	Failed (C-3)/6 wk. at 140°; passed under all other storage conditions/48 wk.	(P-3)/6 wk. at 140° and (P-3)/cycling; discoloration and excessive disintegration time	0.96; passed under all storage conditions/48 wk.; slight absorption of product at 140°/48 wk.; none at 100°; no effect on container function
20, Tripelennamine hydrochloride tablets U.S.P., 50 mg.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
21, Methocarbamol tablets, 0.5 Gm.	Passed under all storage conditions/48 wk.	(P-3)/6 wk. at 140° and (P-3)/cycling; marked discoloration and strong amine odor	0.96; passed under all storage conditions/48 wk.; permeability negligible
22, Chlorothiazide tablets N.F., 0.5 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
23, Sodium bicarbonate, charcoal, and peppermint tablets	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; bottles lost heat seal at 140°/6 wk., due to internal pressure; otherwise passed all storage conditions/48 wk.; permeability negligible

(*Continued on next page.*)

TABLE I—(*Continued.*)

Product[f]	Chemical Stability	Physical Stability	Container Performance
24, Sodium *para* - aminobenzoate, sodium salicylate, and ascorbic acid tablets	Passed/12 wk. at 140° and at −65°; storage terminated —see physical failure; passed all other storage conditions/48 wk.	(P-3)/12 wk. at 140° and (P-3)/12 wk. at −65°; cracked tablet coatings	0.96; passed under all storage conditions up to and including 100°/48 wk.;[a] permeability negligible
25, Acetylsalicylic acid – ethoheptazine tablets	Failed (C-3)/6 wk. at 140°; passed under all other storage conditions/48 wk.	(P-3)/6 wk. at 140° due to crystal growth and discoloration; (P-3)/24 wk. at 100°, 27% R.H., at 100°, 80% R.H., −65° and at cycling; tablets split into two layers during friability test	0.96; bottle tensile rupture after 12 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; permeability negligible
26, Isoniazid tablets U.S.P., 100 mg.	Passed under all storage conditions/48 wk.	(P-3)/48 wk. at 140°; excessive darkening in color	0.96; passed under all storage conditions/48 wk.; product permeability negligible; moisture permeability 1.3% gain/48 wk. at 73°; glass same; slight product absorption/48 wk. at 140°; less at 100°; no effect on container function
27, Alkaline aromatic soln. tablets	Passed under all storage conditions/48 wk.	(P-1)/12 wk. at 140°; loss of aromatics	0.96; passed under all storage conditions/48 wk.; permeability negligible
28, Propantheline bromide tablets U.S.P., 15 mg.	Passed under all storage conditions/48 wk.	(P-3)/24 wk. at 140°; crystal growth on tablet surface	0.96; passed under all storage conditions/48 wk.; permeability negligible
29, Benzethonium chloride tablets, 0.25 Gm.	Failed (C-3)/24 wk. at 140°; passed under all other storage conditions/48 wk.	(P-3)/12 wk. at 140°; tablets discolored and produced discolored solutions	0.96; passed under all storage conditions/48 wk.; permeability negligible; slight container collapse/24 wk. at 140°; slight absorption of product/48 wk. at 140°; none at 100°; no effect on container function
30, Urine sugar test tablets	Failed (C-3)/12 wk. at 140°; passed under all other storage conditions/48 wk.	(P-3)/24 wk. at 140°; tablets discolored	0.96; passed under all storage conditions/48 wk.; permeability negligible; extensive damage to container *after* storage beyond 48 wk. test period; due to tablet reaction with moisture when bottles were opened for sampling; containers burst from heat and pressure
31, Mephenesin tablets N.F., 0.5 Gm.	Passed under all storage conditions/48 wk.	(P-3)/48 wk. at 140°; crystal growth on tablet surface	0.96; bottle rupture due to stress cracking at 140°/12 wk.; passed under all other storage conditions up to and including 100°/48 wk.; permeability negligible
32, Phenobarbital tablets U.S.P., 30 mg.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
33, Deleted from study			
34, Potassium chloride tablets U.S.P., 0.325 Gm.	Passed under all storage conditions up to and including 100°/48 wk.; 140° samples passed/6 wk.; see physical failure	(P-3)/6 wk. at 140°; (P-3)/6 wk. at −65° and/cycling; coatings cracked and/or crazed	0.96; passed under all storage conditions/48 wk.; permeability negligible
35, Aluminum acetate soln. tablets	Failed (C-3)/6 wk. at 140° and/cycling; failed (C-3)/12 wk. under all other storage conditions	(P-3)/6 wk. at 140° and/48 wk. at 100°, R.H. 27%, and 100°, R.H. 80%; tablets crumble to powder	0.96; passed under all storage conditions/48 wk.; permeability of moisture 8.6% gain/48 wk. at 100°; glass control gained 5.5%; permeability product 3.5% loss; glass control lost 6.0%; moderate product absorption/48 wk. at 100°; no effect on container function
36, Ascorbic acid tablets	Failed (C-3)/24 wk. at 140°; passed under all other storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.95; passed under all storage conditions/48 wk.; permeability negligible; slight product absorption at 140°, but less at 100°; no effect on container function
37, Sodium cyclamate and sodium saccharin tablets N.F.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
38, Chloroquine and primaquine phosphate tablets	Passed under all storage conditions/48 wk.	(P-3)/6 wk. at 140°; marked discoloration and foul odor	0.96; passed under all storage conditions up to and including 100°/48 wk.;[a] product permeability negligible; moisture permeability 1.1% gain/48 wk. at 100°; glass control same
39, Reserpine tablets U.S.P., 0.25 mg.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
40, Methenamine mandelate tablets U.S.P., 0.5 Gm.	Passed under all storage conditions/48 wk.	(P-3)/6 wk. at 140°; tablets dull and cracked	0.96; passed under all storage conditions/48 wk.; permeability negligible
41, Deleted from study			

(*Continued on next page.*)

TABLE I—(*Continued.*)

Product[f]	Chemical Stability	Physical Stability	Container Performance
42, Griseofulvin tablets U.S.P., 0.25 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
43, Belladonna alkaloids with phenobarbital tablets	Failed (C-5)/24 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.	(P-6)/24 wk. at 140°; samples darken in color	0.96; passed under all storage conditions/48 wk.; product permeability negligible; moisture permeability 2.1% loss/48 wk. at 100°; glass control 1.7% loss
44, Prednisone tablets U.S.P., 5 mg.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; product permeability negligible; moisture permeability 1.8% gain/48 wk. at 100°; glass control 1.1% gain
45, Ammonium chloride tablets U.S.P., 0.5 Gm.	Passed under all storage conditions up to and including 100°/48 wk.; 140° samples passed/24 wk.; see physical failure	(P-3)/6 wk. at 140°; (P-3)/6 wk. at −65° and/cycling; tablet coatings cracked and/or crazed	0.96; passed under all storage conditions up to and including 100°/48 wk.;[a] permeability negligible
46, Glutethimide tablets N.F., 0.5 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible; slight product absorption at 140°/48 wk.; less at 100°; no effect on container function
47, Probenecid tablets U.S.P., 0.5 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
48, Sodium aminosalicylate tablets U.S.P., 0.5 Gm.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; product permeability negligible; moisture permeability 2.3% gain/48 wk. at 100°; glass control 2.0% gain
49, Thiamine hydrochloride tablets U.S.P., 50 mg.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible; some product absorption/48 wk. at 140°; none at 100°; no effect on container function
50, Tetracycline hydrochloride tablets N.F., 0.25 Gm.	Passed under all storage conditions/48 wk.	(P-3)/48 wk. at 140°; excessive discoloration	0.96; passed under all storage conditions/48 wk.; permeability negligible; containers may show some collapse/48 wk. at 140°
51, Propoxyphene hydrochloride capsules U.S.P., 32 mg.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
52, Chloramphenicol capsules U.S.P., 0.25 Gm.	Passed under all storage conditions up to and including 100°/48 wk. and for 6 wk. at 140°	(P-3)/12 wk. at 140°; excessive discoloration	0.96; passed under all storage conditions/48 wk.; permeability negligible
53, Sodium diphenylhydantoin capsules U.S.P., 100 mg.	Passed under all storage conditions up to and including 100°/48 wk. and for 6 wk. at 140°; see physical failure	(P-3)/12 wk. at 140°; excessive discoloration	0.96; passed under all storage conditions/48 wk.; permeability negligible
54, Diphenhydramine hydrochloride capsules U.S.P., 50 mg.	Passed under all storage conditions up to and including 100°/48 wk. and for 12 wk. at 140°; see physical failure	(P-4)/24 wk. at 140°; product discolored; capsules embrittled in plastic bottles, but softened and stuck together in glass bottles	0.96; passed under all storage conditions/48 wk.; permeability negligible; increase in melt index/48 wk. at 140° about 10%; no change/48 wk. at 100° or 24 wk. at 140°; may be due to slight product absorption; no effect on container function
55, Oleovitamin A capsules, 50,000 units	Passed under all storage conditions/48 wk. except for 140° and cycling; see physical failure	(P-3)/6 wk. at 140° and/cycling; capsules fused into nearly solid mass	0.96; passed under all storage conditions up to and including 100°/48 wk.;[a] permeability negligible
56, Dextroamphetamine sulfate and amobarbital capsules, 15–97 mg.	Passed under all storage conditions up to and including 100°/48 wk.; see physical failure	(P-3)/6 wk. at 140°; discoloration and fusion of pellets within capsules	0.96; passed under all storage conditions up to and including 100°/48 wk.;[a] permeability negligible; elongation/48 wk. at 100° 170% higher than control; normal/24 wk. 100°; may be due to slight absorption of product; no effect on container function
57, Surgical soap with 5% hexachlorophene	Passed under all storage conditions between −65° and 100°/48 wk., and/6 wk. at 140°; see container failure	Passed under all storage conditions/48 wk.	0.96; bottle rupture due to stress cracking at 140°/24 wk. and under cycling; passed under all other storage conditions up to and including 100°/48 wk. may lose heat seals/6 wk. at 140°
58, Terpin hydrate elixir N.F.	Passed under all storage conditions up to and including 100°/12 wk.; see container failure	(P-3)/6 wk. at 140°; change in odor	0.96; bottle tensile rupture/6 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; product permeability 1.5% loss/48 wk. at 100°; moisture permeability negligible; 150% increase

(*Continued on next page.*)

TABLE I—(*Continued.*)

Product[f]	Chemical Stability	Physical Stability	Container Performance
			in resin elongation/48 wk. at 100°; normal values/24 wk. at 100° and/48 wk. at 73°; increase may be due to product absorption; no effect on container function
59, Phenylephrine hydrochloride soln. U.S.P., 1%	Passed under all storage conditions up to and including 100°/48 wk. and at 140°/12 wk.; see physical failure	(P-1)/6 wk. at 140°; (P-3)/12 wk. at 140°; (P-3)/24 wk. at 100°; discoloration	0.96; bottle tensile rupture/24 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; permeability negligible
60, Thimerosal tincture N.F.	Passed under all storage conditions from −65° up to and including 100°/48 wk.; see container failure	Passed under all storage conditions from −65° up to and including 100°/48 wk.	0.96; bottle tensile rupture/6 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; moisture permeability negligible; product permeability 2.7% loss/48 wk. at 100°; glass control 2.5% loss; 0.95 epoxy-lined bottles passed/6 wk. at 140°
61, Piperazine citrate syrup, U.S.P.	Passed under all storage conditions up to and including 100°/48 wk. and/6 wk. at 140°; physical failure/12 wk. at 140° precluded assaying of 12-wk. samples	(P-3)/12 wk. at 140°; (P-3)/48 wk. at 100°, R.H. 27% and at 100°, R.H. 80%; darkening in color	0.96; bottle rupture due to stress cracking at 140°/6 wk.; passed under all other storage conditions up to and including 100°/48 wk.; permeability negligible; some product absorption/48 wk. at 100°; none/24 wk. at 100° or/48 wk. at 73°; no effect on container function
62, Paregoric U.S.P.	Passed under all storage conditions up to and including 73°/48 wk.; see physical failure	(P-3)/6 wk. at 140°, at 100°, R.H. 27%, at 100°, R.H. 80% and at cycling; loss of aromatics	0.95; bottle tensile rupture/12 wk. at 140°; passed under all other storage conditions up to and including 73°/48 wk.;[e] permeability negligible; 0.95 epoxy-lined bottles passed/6 wk. at 140°
63, Alcohol U.S.P.	Passed under all storage conditions up to and including 100°/48 wk.; see container failure	Passed under all storage conditions up to and including 100°/48 wk.	0.95; bottle tensile rupture/12 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; moisture permeability negligible; product permeabibity 2.2% loss at 100°/48 wk.; bottles may lose heat seals/6 wk. at 140°
64, Phenolated and mentholated calamine lotion	Product not assayed	(P-1)/6 wk. at 140°, at 100°, R.H. 27%, at 100° R.H. 80%, and at cycling; loss of menthol and phenol; (P-3)/6 wk. at 40° and at −65°; excessive separation and lowered viscosity	0.96; bottle stress crack/24 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; moisture permeability negligible; product permeability 1.3% loss at 100°/48 wk.
65, Benzalkonium chloride soln. U.S.P., 10%	Passed under all storage conditions up to and including 100°/48 wk.; container failure precluded assay of 140° samples	Passed under all storage conditions/48 wk.	0.96; bottle stress crack/6 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; permeability negligible; 0.95 epoxy-lined bottles passed/6 wk. at 140°
66, Thimerosal soln. N.F.	Passed under all storage conditions/24 wk.; 48-wk. samples not available for assay	Passed under all storage conditions/24 wk.[d]	0.96; bottle stress crack/24 wk. at 140°; passed under all other storage conditions up to and including 100°/24 wk.; permeability negligible
67, Glacial acetic acid	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; bottle tensile rupture/12 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; moisture permeability negligible; product permeability 7.7% loss/48 wk. at 100°; glass control 2.3% loss; some product absorption at 140°, less at 100°; no effect on container function
68, Glycerin U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
69, Compd. benzoin tincture U.S.P.	Passed (loss of volatiles) under all storage conditions up to and including 100°/48 wk.; 140° samples lost by container failure	(P-2)/6 wk. at 140°; (P-3)/12 wk. at 140°; excessive loss of volatiles	0.96; bottle tensile rupture/12 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; moisture permeability negligible; product permeability 1.7% loss/48 wk. at 100°

(*Continued on next page.*)

TABLE I—(*Continued.*)

Product[f]	Chemical Stability	Physical Stability	Container Performance
70, Oxytetracycline oral suspension	Failed (C-3)/6 wk. at 140° and/48 wk. at 100°, passed under all other storage conditions up to and including 73°/48 wk.	(P-3)/6 wk. at 140° and/12 wk. at 100°; discoloration	0.96; passed under all storage conditions/48 wk.; permeability negligible
71, Glycyrrhiza fluid extract U.S.P.	Passed under all storage conditions up to and including 100°/48 wk.; see container failure	Passed under all storage conditions up to and including 100°/48 wk.	0.96; bottle tensile rupture/6 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; moisture permeability negligible; product permeability 2% loss/48 wk. at 100°; 0.95 epoxy-lined bottles passed/6 wk. at 140°
72, Belladonna tincture U.S.P.	Passed under all storage conditions up to and including 100°/48 wk.; see container failure	Passed under all storage conditions up to and including 100°/48 wk.; see container failure	0.95; bottle stress crack/6 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; moisture permeability negligible; product permeability 2.5% loss/48 wk. at 100°; 0.95 epoxy-lined bottles passed/6 wk. at 140°
73, Trisulfapyrimidines oral suspension U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; bottle stress crack/12 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; permeability negligible
74, Deleted from study			
75, Sodium bicarbonate U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
76, Ammonium chloride U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
77, Talc U.S.P.	Sample not assayed	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible; moderate product absorption at 140°; no effect on container function
78, Zinc oxide U.S.P.	Passed under all storage conditions/48 wk.; only 48-wk. samples assayed	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
79, Boric acid U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
80, Bismuth subcarbonate U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible; 83% increase in elongation/48 wk. at 140° which is 22% greater than normal variation; 48-wk. bottles at 100° closer to normal value; may be due to product absorption and plasticization of polyethylene; no effect on container function
81, Pumice U.S.P.	Samples not assayed	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
82, Potassium phenoxymethyl penicillin for oral soln., 3,200,000 units	Passed under all storage conditions/48 wk.	(P-3)/6 wk. at 140° and during cycling; darkening in color and development of foreign odor	0.96; passed under all storage conditions/48 wk.; permeability negligible
83, Acetylsalicylic acid U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.95; passed under all storage conditions/48 wk.; permeability negligible
84, Sodium citrate U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
85, Potassium iodide U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible; melt index increase 17% at 140°/48 wk., but normal at 140°/24 wk. and at 100°/48 wk.; slight absorption of product at 140°, but none at 100°; no effect on container function
86, Sodium borate U.S.P.	Failed (C-3)/24 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
87, Terpin hydrate N.F.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
88, Citric acid U.S.P.	Passed under all storage conditions/48 wk.	(P-1)/48 wk. at 140°; loss of water; (P-3)/48 wk. at 100°; samples caked	0.96; passed under all storage conditions/48 wk.; product permeability negligible; moisture permeability 1.0% loss/48 wk. at 100°
89, Monohydrated sodium carbonate U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible

(*Continued on next page.*)

TABLE I—(*Continued.*)

Product[f]	Chemical Stability	Physical Stability	Container Performance
90, Calamine U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible; increase in elongation 83% which is 22% higher than normal expected at 140°; may be due to product absorption; no effect on container function
91, Magnesium carbonate N.F.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; product permeability negligible; moisture permeability 3.3% loss/48 wk. at 100°; glass control 6.2% loss
92, Magnesium oxide U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
93, Precipitated sulfur U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible
94, Green soap N.F.	Passed under all storage conditions/48 wk. on basis of pH value	(P-2)/12 wk. at 140° and at 100°, R.H. 27% and at 100°, R.H. 80%; discoloration; (P-2)/24 wk. under all other storage conditions; discoloration progressively increasing with time, ultimately dark brown	0.96; bottle stress crack/48 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.; increase in melt index 10%/48 wk. at 140°; normal value for bottles at 100°/48 wk. and at 140°/24 wk.; may be due to product absorption; no effect on container function
95, Ointment base	Product not assayed	(P-3)/12 wk. at 140° and/12 wk. at −65°; excessive separation of phases	0.96; passed under all storage conditions up to and including 100°/48 wk.; also for at least 24 wk. at 140°; borderline acceptability/48 wk. at 140°; slight to moderate increase in tensile strength and melt index/48 wk. at 140°; permeability negligible; some product absorption
96, Hydrophilic ointment U.S.P.	Product not assayed	(P-3)/6 wk. at 140°, /cycling and/12 wk. at −65°; excessive separation of phases	0.96; passed under all storage conditions up to and including 100°/48 wk.;[e] permeability negligible; increase in melt index 35% at 100°, but normal value for 73°/48 wk.; container collapse may occur in the 73° to 140° range/48 wk.; slight product absorption; no effect on container function
97, Zinc oxide ointment U.S.P.	Passed under all storage conditions/48 wk.	(P-3)/6 wk. at 140° and/cycling; excessive separation	0.96; passed under all storage conditions up to and including 100°/48 wk.;[e] permeability negligible; increase in melt index 20% at 100°; normal value/48 wk. at 73°; may be due to product absorption; no effect on container function
98, Nitrofurazone ointment N.F.	Failed (C-3)/6 wk. at 140°; passed under all other storage conditions up to and including 100°/48 wk.	(P-3)/12 wk. at 140°; darkening of color	0.96; passed under all storage conditions up to and including 100°/48 wk.;[e] permeability negligible
99, Modified tar compd. ointment	Passed under all storage conditions up to and including 73°/48 wk.; passed/6 wk. at 100°, R.H. 27% and at 100°, R.H. 80%; see physical failure	(P-3)/6 wk. at 140°; (P-3)/12 wk. at 100°, R.H. 27% and 100°, R.H. 80%; (P-3)/24 wk. at −65°; separation of phases	0.96; passed under all storage conditions up to and including 73°/24 wk.; after 48 wk. at 73° product absorption is too high; tar odor outside of bottles/6 wk. at 140° and/12 wk. at 100°; 0.95 epoxy-lined bottles passed/6 wk. at 140°; no tar odor on outside of bottles
100, Anhydrous lanolin U.S.P.	Passed under all storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; bottle stress crack/12 wk. at 140° and/48 wk. at 100°; passed under all other storage conditions up to and including 73°/48 wk.; melt index increases 90%/48 wk. at 140°; normal value/6 wk. at 140° and/48 wk. at 73°; may be due to product absorption; permeability negligible; 0.96, 0.95, and 0.95 epoxy-lined bottles showed seepage or leakage of product/6 wk. at 140°
101, Ammoniated mercury ointment U.S.P.	Passed under all storage conditions/48 wk.	(P-3)/12 wk. at 140°; excessive separation	0.96; passed under all storage conditions up to and including 100°/48 wk.;[e] in-

(*Continued on next page.*)

TABLE I—(*Continued.*)

Product[f]	Chemical Stability	Physical Stability	Container Performance
			crease in melt index 18% at 100°; normal value at 73°; slight product absorption at 100°, none at 73°; no effect on container function
102, Zinc oxide paste U.S.P.	Failed (C-3)/48 wk. at 140°; passed under all other storage conditions/48 wk.	Passed under all storage conditions/48 wk.	0.96; passed under all storage conditions/48 wk.; permeability negligible; increase in tensile strength 16% at 140°; value normal at 100°/48 wk.; increase in melt index 300% at 140° but only 10%/48 wk. at 100°; may be due to product absorption; no effect on container function

[a] Only 6 wk./140° bottles available; all passed. [b] Assay procedure difficulties delayed initiation of storage such that 48-wk. data are not available. [c] Only 12-wk./100° bottles tested; all passed. [d] Time elapsed due to failure of assay procedure prevented storage of samples for 48 wk. [e] Only 12-wk./140° bottles available; all passed. [f] Names and compendia designations for drugs are as of U.S.P. XVI and N.F. XI since the study commenced while those editions were official.

greater than 10%; type (C-2): loss in glass less than 10%, loss in polyethylene at least 15% greater; type (C-3): parallel or nearly parallel loss in glass and in polyethylene, both being in excess of 10%; type (C-4): loss in polyethylene less than 10%, loss in glass at least 15% greater; type (C-5): no loss in polyethylene, loss in glass greater than 10%; type (C-6): uncertain interpretation of data because of magnitude of experimental error.

Parenthetically, it is interesting to note that only type (C-3) and type (C-5) were encountered; the other possibilities are listed merely to emphasize their absence in the study.

The expression employed throughout to describe chemical stability—namely, "passed under all storage conditions/48 wk.," means that the samples from all environments assayed at the end of 6, 12, 24, and 48 weeks had not lost more than 10% of their initial content of active constituent. Environments and intervals for which this did not hold true are characterized by the expression "failed (C-x)/6 wk. at 140°," and variations thereon. This means that the concentration of active constituent did drop by more than 10% during the 6-week interval when stored at 140°F.

In instances when a sample underwent gross physical failure, it was not practical to assay it; attention is therefore called to the physical failure. In other instances, samples were lost because of container rupture and were not available for assay. Attention is then directed to container failure described in the same tabulation.

Physical Stability—It is noteworthy that the word "failed" is deliberately omitted from all descriptions of physical behavior of drug samples during storage. In some instances, as when coated tablets literally exploded, there is no doubt about the physical failure. In many instances, however, there was a physical change whose significance, as regards the usability of a drug which tested out well chemically, is open to debate. None of those products was declared to have failed outright; their departure from the normal condition is noted, and the reader is urged to impose his own evaluation of the significance of the change.

Physical changes occurred in different degrees and in both kinds of containers. The relationships are identified as follows.

Type (P-1): little or no change in glass, major change in polyethylene; type (P-2): some change in glass, major change in polyethylene; type (P-3): major change in both glass and polyethylene; type (P-4): some change in polyethylene, major change in glass; type (P-5): little or no change in polyethylene, major change in glass; type (P-6): uncertain applicability of other relations as in types (P-1), (P-2), (P-3), (P-4), and (P-5).

Whenever a physical change occurred (failure?), it is so indicated; for example, "(P-3)/6 wk. at 140°," which means that the product in question underwent a parallel change in glass and in polyethylene during 6 weeks of storage at 140°F. Similar expressions are to be interpreted in like manner. If specific reference is made to a physical change at a given environment, it is to be understood that the product maintained its physical integrity at all other environments which have not been so mentioned. The expression "passed under all storage conditions/48 wk." means that the product, taken from all environments, was found to be physically acceptable or intact at the end of 6, 12, 24, and 48 weeks. Variations of this are indicated where they apply. Insofar as is possible, the nature of the physical change which occurred is identified.

Container Performance—Each comment on container performance opens with the identification, *e.g.*, 0.96, of the kind of polyethylene bottle to which the subsequent comments apply. Outright and visible failure of a bottle is positively stated in each instance where it occurred. A common expression used in describing container performance is "passed under all storage conditions/48 wk." This is intended to mean that the polyethylene bottles so described were tested at the end of 48 weeks of exposure and were found to pass all of the evaluating tests described here. Any exceptions to this generalization are specifically noted. In all instances, the container testing program involved comparisons between the test bottles and unused polyethylene controls, and the results are expressed as changes from the normal control values. The specific tests which were applied include the following.

Impact Resistance—The purpose of this test is to determine whether the drug or the environment exercised any deleterious effect on the impact or breakage resistance of the bottle. Test bottles rinsed free of adhering drug were filled (120 ml.) with 50% ethanol and conditioned for 24 hr. at

−10°F., whereupon they were capped and dropped (while cold) from a height of 17 ft. Normal virgin containers do not break on impact.

Average Tensile Strength (ASTM D412-64T)—This is the standard test for the physical strength of plastics. A strip of plastic cut from the wall of a sample bottle is stretched in an Instron tester at the relative rate of 20 in. per minute. The maximum tensile force applied during stretching to the point of rupture is the tensile strength of the specimen.

Average Ultimate Elongation (ASTM 412-64T)—Conducted in conjunction with the tensile strength measurement, this value describes the maximum elongation of the specimen before rupture occurs. It is the ratio of the length of the sample at rupture to its initial length, expressed as per cent.

Melt Index (ASTM 1238-65T)—This is the standard test for measuring flow rate (decigrams/minute) of a molten plastic. It is inversely proportional to the molecular weight, provided other variables are not involved. If the plastic has absorbed any chemical which can act as a plasticizer, the flow rate, or the melt index, will not correlate with the molecular weight.

Infrared Analysis—Comparison of the I.R. absorption spectra for a sample taken from a test bottle and for the unused plastic discloses whether the polyethylene has absorbed drug components or has degraded. A Perkin-Elmer model 21 infrared spectrophotometer was used to scan the samples between 2 and 15 μ. Product absorption in the range of 1% is readily detectable. These spectrograms are on file at the University of Connecticut.

Moisture Permeability—Standard procedure for the plastics industry measures moisture permeability at 100°F., and standard acceptance limits it to 3% per year.

RECOMMENDATIONS

Based on measurements and observations made during the study, it is possible to offer recommendations concerning the use of high density polyethylene bottles for the packaging of drugs, and concerning limitations on the over-all storage of drugs. While the initial intent of the project was to draw a comparison between drug stability in glass and drug stability in plastic containers, the authors would be remiss in their professional responsibilities if they neglected to mention those obvious limitations on the storage of drugs, irrespective of container and environment identity, which they encountered. It must be understood that any recommendations which are offered are limited in their scope to such parameters as are defined in the testing program conditions. Any projection of these recommendations and any extrapolation of the test results become individually assumed responsibilities. Indeed, because of product variation from one manufacturer to another, it may be well for each to use these results merely as guidelines in the testing of his own products.

The major recommendations which have resulted from this study are grouped in two broad categories, based on whether the polyethylene bottles were found to be acceptable or unacceptable containers for the pharmaceuticals in question, strictly within the limits imposed by the test conditions. These recommendations are listed together with the item numbers to which they pertain. (See Table I for number identification and pertinent details.) An asterisk (*) preceding an item number indicates that the regular 0.96 d. polyethylene bottle failed under certain test conditions because of cracking or excessive loss of volatiles from the drug product contained therein. In these cases, epoxy-lined 0.95 d. polyethylene bottles were substituted and were tested for 6 weeks under the same environmental conditions which had caused prior failure of the 0.96 d. bottles. In most instances, the epoxy-lined bottles withstood the test for the 6-week period, but their long-term behavior at environmental extremes is not known.

The instances of acceptability of polyethylene bottles as drug containers are outlined in Table II.

TABLE II—INSTANCES OF ACCEPTABILITY OF POLYETHYLENE BOTTLES AS DRUG CONTAINERS

1. Polyethylene bottles *are* acceptable containers for these items (passed under all conditions of testing):

Items No.		
4	*39*	*79*
7	*42*	*80*
9	*44*	*81*
11	*46*	*83*
13	*47*	*84*
14	*48*	*85*
18	*49*	*87*
20	*51*	*89*
22	*75*	*90*
23	*76*	*91*
32	*77*	*92*
37	*78*	*93*

2. Polyethylene bottles *are* acceptable containers for these items. However, storage in *any* container at temperatures greater than 100° F. should be avoided.

Items No.		
1	*28*	*54*
2	*29*	*55*
3	*31*	*56*
8	*36*	*68*
10	*38*	*82*
15A	*40*	*97*
19	*43*	*98*
21	*50*	*101*
26	*52*	*102*
27[a]	*53*	

3. Polyethylene bottles *are* acceptable containers for these items. However, storage in *any* container at temperatures greater than 100°F. or less than 40°F. should be avoided.

Items No.	
15B	*34*
16	*45*
17	*95*
24	*96*

4. Polyethylene bottles *are* acceptable containers for these items. However, storage in *any* container at temperatures greater than 73°F. should be avoided.

Items No.	
35	*61*

5. Polyethylene bottles *are* acceptable containers for this item. However, storage in *any* container at temperatures greater than 73°F. or less than 40°F. should be avoided.

Item No.
25

[a] This is a tentative assignment. The sample is being retested in epoxy-lined bottles.

The instances of nonacceptability and of limited acceptability of polyethylene bottles as drug containers are outlined in Table III.

TABLE III—INSTANCES OF NONACCEPTABILITY AND LIMITED ACCEPTABILITY OF POLYETHYLENE BOTTLES AS DRUG CONTAINERS

6. Polyethylene bottles *cannot* be recommended for this item unless storage temperatures greater than 73°F. can be avoided. Storage in *any* container at temperatures greater than 73°F. or less than 40°F. should be avoided.

Item No.

*99

7. Polyethylene bottles *cannot* be recommended for these items unless storage temperatures greater than 100°F. can be avoided. Storage in *any* container at temperatures greater than 73°F. should be avoided because of changes in physical characteristics.

Items No.

59	88

8. Polyethylene bottles *cannot* be recommended for these items unless storage temperatures greater than 100°F. can be avoided.

Items No.

57	*65	*71
58	66	*72
*60	67	73
63	69	86

9. Polyethylene bottles *cannot* be recommended for these items (based on gross failure under test conditions).

Items No.

30[a]	94	*100

10. Polyethylene bottles *cannot* be recommended for these items. Storage in *any* container at temperatures greater than 73°F. should be avoided.

Items No.

*62	70

11. Polyethylene bottles *cannot* be recommended for this item. Storage in *any* container at temperatures greater than 73°F. or less than 40°F. should be avoided.

Item No.

64

[a] Throughout the various storage intervals, this item remained intact in the tightly closed containers. However, after all of the tests had been completed, the tablets in glass showed marked physical deterioration, while those in polyethylene had reacted with such intensity that the bottles were partially melted and ruptured. This deterioration was due to the hygroscopic character of the tablets which caused them to take on moisture when their original containers were opened for sampling.

CONCLUSIONS

Certain general conclusions of outstanding nature can be drawn, and numerous others can be derived, from the observations recorded in Table I. Among the most significant are the following.

1. Polyethylene bottles can be used for packaging most of the pharmaceuticals tested under the various environmental conditions. Their performance with regard to the protection of their contents is parallel to that of glass, in most instances.

2. Outright incompatibility of the polyethylene bottle with its contents was rarely encountered under the test conditions.

3. In most instances, the polyethylene bottles themselves stood up well, both chemically and physically.

4. Polyethylene bottles of 0.95 d. offered no apparent advantage over the 0.96 d. bottles where the latter failed because of tensile rupture and/or stress cracking.

5. In most instances of drug failure, whether chemical or physical, failure of the same nature and magnitude occurred both in polyethylene and in glass containers. Thereupon, such failure must have been environmentally induced.

6. The vast majority of product and/or container failures which did occur are associated with the environmental extremes, namely, −65°F., and 140°F., and cycling; the 140°F. temperature was the most damaging.

7. Product and/or container failures were few in number between 40°F. and 100°F.

8. Differences in humidity, *e.g.*, 100°F., 27% R.H., and 100°F., 80% R.H., did not play a significant part in product stability or in container performance. This may be due to the fact that polyethylene is one of the best moisture barrier plastics known.

9. The majority of product failures which did occur were of the physical type rather than of the chemical type.

10. The most common failure among coated tablets was the cracking or crazing of the coating at the very low temperature (−65°F.) and during cycling.

11. Pharmaceuticals which contain highly volatile solvents, such as acetone and alcohol, invariably cause rupture of the polyethylene bottles due to high internal pressure, when stored at elevated temperature. Packaging in 0.95 d. polyethylene bottles provides little or no advantage.

12. Aspirin tablets and formulations containing aspirin failed both chemically and physically within 6 weeks, when stored at 140°F., 14% R.H. At all other temperatures, such tablets were stable throughout the 48-week storage intervals. It is noteworthy that the raw chemical, aspirin U.S.P., is stable even at 140°F., presumably because of the nearly anhydrous character of the chemical.