JUN 2 1970

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May 27, 1970

TO: All Members of the SPI Food, Drug and Cosmetics Packaging Materials Committee

Gentlemen:

In accordance with the plan agreed upon at the last meeting of the Food, Drug and Cosmetics Packaging Materials Committee, and with the instructions now given us by Wat Ackart, we are herewith enclosing a May 22 letter to all of you from Wat. As you will note, the letter covers a report of our PMA liaison subcommittee which is also enclosed.

The intent at the present time is to discuss the enclosed draft at the June 10 meeting with a view towards a full committee vote on proceeding with the project outlined in the report. In other words, you are requested to review the PMA liaison subcommittee draft so that you can come to the June 10 meeting prepared to vote on its approval and the follow-up action described therein on page three.

If you have any comments on this matter prior to the meeting, you will note that Mr. Ackart has requested that they be directed to him.

Cordially yours,

Jerome H. Heckman

Enclosure
cc: Members of the SPI Food and Drug Bottling Committee

UNION CARBIDE CORPORATION

CHEMICALS AND PLASTICS

RIVER ROAD, BOUND BROOK, N J. 08805 • TELEPHONE (201) 356-8000

May 22, 1970

To: Members, SPI Food, Drug, and Cosmetic Packaging Materials Committee

Re: Regulatory Aspects of Packaging Dry Drugs in Polyolefin Containers

Gentlemen:

At the February 26, 1970 meeting of the SPI F D & C Packaging Materials Committee, the PMA Liaison sub-committee reported completion of a final draft of a proposal for regulating the packaging of dry drugs in polyolefin containers. A copy of this draft is attached for your consideration.

Please note that this draft is subject to approval by the SPI F D & C Packaging Materials Committee as a whole before we approach the PMA and ultimately the Food and Drug Administration.

Please send any comments you may have to me, at Union Carbide Corporation, Chemicals and Plastics, 1 River Road, Bound Brook, N. J., 08805, or bring them to the June 10 meeting.

Very truly yours,

W. B. Ackart

W. B. Ackart,
Chairman,
PMA Liaison Sub-Committee

WBA/rch
att.

REGULATORY ASPECTS OF PACKAGING DRY DRUGS

(POWDERS AND TABLETS) IN POLYOLEFIN CONTAINERS

The regulatory problems associated with packaging drug products in plastic containers have been discussed in the SPI bulletin Plastics Packaging for Drug Products - The Regulatory Story published in September 1967. This bulletin points out that the Food and Drug Administration does not give "blanket approvals" for drug packaging materials even to the limited extent that this is done in the Food Additive Regulations. Rather the agency considers each specific case individually on the basis of data establishing the safety and effectiveness of the drug, per se, and as it will be distributed in a particular package. These data are included in the New Drug Application filed with the FDA by the drug manufacturer. Clearances so obtained are in most cases specific for a given container produced by a given manufacturer from a specific material. Once a drug and its packaging material are approved, any change in either may require the filing of a Supplemental New Drug Application containing data demonstrating that, for example, the proposed new package will not adversely affect the drug's efficacy or safety.

It is obvious that this clearance procedure has the inherent disadvantage of locking the drug manufacturer in on the original package specified in his N.D.A. or supplemental N.D.A. since he understandably will be reluctant to reopen the FDA status of his product, once it is approved. What is needed is a means to establish the interchangeability in dry drug packaging of a polyolefin with any other manufacturer's generic counterpart, where the basic specifications are the same, without the necessity of filing a Supplemental N.D.A. For example, polyethylene produced by Supplier A should be interchangeable with polyethylene produced by Suppliers B, C, D or E but cannot be replaced by polypropylene produced by Suppliers A, B, C, D or E.

In our opinion this can be done safely at least as to dry drugs at the present time by means of several relatively minor changes in the clearance procedure. These changes, of course, must be accepted first within the plastics industry, then by the pharmaceutical industry and finally officially by the Food and Drug Administration.

The key premise in this concept is that polyolefin materials for drug packaging be defined in terms of performance rather than chemical composition, physical properties, or company origin. Performance can be

measured against a series of standardized test procedures, with well-defined limits, that are designed to measure critical parameters. Suitable test procedures are currently available and have been evaluated in a series of round-robin tests carried out in laboratories of both the plastics and pharmaceutical manufacturers. These test procedures consist of physicochemical methods for extractable heavy metals, total non-volatile extractives, density, water vapor permeability, and possibly percent light transmission. They, as well as the results of the round-robin testing, have been widely disseminated within both the SPI and the PMA.

It is anticipated that the plastics manufacturer wishing to participate in this market will test his products sufficiently to enable him to certify that they meet the specified limits. It is not proposed that these procedures must be applied to each and every batch; however, each manufacturer must satisfy himself as to the probability that any given batch will comply with the specifications. The proposed specified limits reflect the values obtained in the original round-robin testing program.

Obviously in any such testing program there must be an official standard test procedure. It is proposed that every effort be made to make these procedures official by means of their publication, with limits, in the National Formulary and/or the U. S. Pharmacopoeia. A copy of the proposed publication is given in the Appendix attached.

Up to the present time there has been some reluctance within the Pharmaceutical Manufacturers Association toward publication of the physicochemical test procedures. The need for another set of official procedures with no specified limits is indeed questionable. However, consideration of these procedures as a set of performance specifications defining a polyolefin drug container, to be carried out and certified to by the container supplier or the resin manufacturer, we believe would remove any objections within the PMA to publication of the methods in the NF and/or the USP.

The non-toxicity of extractives from the polyolefin container can be demonstrated by an acute systemic toxicity test carried out on mice using as extracting media both cottonseed oil and a 1 to 20 solution of ethanol in physiological saline. This test procedure is also given in the Appendix attached. It is proposed that as a matter of convenience the toxicity tests should become the responsibility of the drug manufacturer since few plastics manufacturers are equipped with animal testing facilities. Presumably these data would also become part of the NDA.

The pharmaceutical manufacturer, of course, still must demonstrate the safety and suitability of the package for his particular drug product. Presumably this would continue to be done prior to the filing of his N.D.A.

and these data, as usual, would constitute part of his submission. Such data normally consist of appropriate toxicity tests on the drug product, initially and after 30, 60, and 90 days of storage in the proposed package at elevated temperatures and relative humidities. Additional testing is dependent upon the presence or absence of changes during storage. The proposed physicochemical test procedures are not intended to supplant these storage stability tests and cannot be considered as establishing the suitability of the container for any particular drug. However, the results of the physicochemical test procedures as certified by the supplier also would become part of the N.D.A. The resin or container supplier also might wish to place the results of these tests in his own FDA Master File for his product.

If and when the drug manufacturer decides that a change to a different polyolefin container is in order, he must first assure himself that the new container is functionally suitable and does not adversely affect his product. If, for example, it is believed that the change would decrease stability or lead to an incompatibility or reactivity between product and container obviously the change cannot be made. However, if it is clear that the proposed container is at least equivalent to the old, the drug manufacturer now should be free to make the package change. The new package must be fully described and the supporting data completely documented in the next periodic report filed with the FDA for that particular drug. The drug manufacturer may or may not wish to discuss the results of his tests with FDA prior to actually making the change.

We believe the following steps must be taken in support of the proposed regulatory scheme.

1. Consideration by the SPI Food, Drug, and Cosmetic Packaging Materials Committee. It is suggested that all concerned suppliers would be well advised to examine their products according to the given methodology to insure that they fall within the proposed limits. It is assumed that the basic philosophy and specific procedural details can be modified so as to obtain committee approval.

2. Consideration by the Plastics Committee of the Quality Control Section of the PMA, and subsequent approval by the parent Quality Control Section and the PMA itself. We would rely upon our established contacts with the PMA for assistance. Since the PMA is in effect our customer, no action should be taken without prior discussion with them.

3. Possible publication of the methodology in the NF and the USP through the PMA.

4. A proposal to the Food and Drug Administration, either by the PMA, jointly by the PMA and SPI, or by the SPI alone with the concurrence of the PMA. Preliminary discussions with FDA personnel would seem advisable.

5. Hopefully some type of acceptance by the FDA and publication as an amendment to the New-Drug Procedural Regulations.

METHODOLOGY FOR TESTING POLYOLEFIN CONTAINERS

FOR TABLETS, CAPSULES, ORAL POWDERS, AND GRANULES

The following Physicochemical and Biological Test Procedures are the result of the combined efforts of the Plastics Committee of the Quality Control Section of the Pharmaceutical Manufacturers Association and the Food, Drug, and Cosmetic Packaging Materials Committee of the Society of the Plastics Industry. The tests are general in scope but applicable for testing a wide variety of polyolefin containers in use today. The purpose of these procedures is to measure and define the performance characteristics of polyolefin materials which may come into contact with pharmaceutical compounds. They are not intended to supplant storage stability tests and cannot be used as the sole criteria for establishing the suitability of the container for any particular drug.

Definitions:

Polyolefins are polymers prepared by the polymerization of an olefin or olefins as essentially the sole monomer or monomers and identified by their characteristic infrared spectra.

Container - the device which holds the drug and which is or may be in direct contact with the drug.

Sample - polyolefin specimen under test or the extract prepared from such specimen.

Blank - consists of the same quantities of the same extracting medium used for the extraction of the specimen under test, treated in the same manner as the extracting medium containing the specimen under test.

POLYOLEFINS - PHYSICOCHEMICAL TEST PROCEDURES

Extracting Media

Water equivalent to Sterile Water for injection (U.S.P. XVII, page 754) is suitable.

Special Apparatus

Oven - Use a forced-circulation model, which will maintain an operating temperature of $70^{\circ} \pm 1^{\circ}C$.

Preparation of Apparatus

Clean all glassware thoroughly with chromic acid cleaning solution and, if necessary, with hot nitric acid followed by prolonged rinsing with distilled water.

Extraction Containers

Use only containers such as ampuls or screw-cap culture test tubes, of borosilicate glass. Culture test tubes, if used, are closed with screwcaps having suitable rubber liners. The exposed surface of the rubber liner must be protected with an inert solid disk 0.05 mm. to 0.075 mm. in thickness. A suitable disk can be fabricated from a polytetrafluorethylene resin.

Procedure

Preparation of Sample - Select from a homogeneous polyolefin sample the amount listed in Table V, N.F. XII, page 523*, for each 10 ml. of extracting medium and subdivide the sample as indicated. Remove particulate matter, such as lint and free particles, by treating each subdivided sample as follows: Place the cuts in a clean 250 ml., glass-stoppered graduated cylinder of borosilicate glass, and add about 160 ml. of water for injection. Agitate for about 30 seconds and drain off the water. Repeat this step and dry those pieces prepared for the extraction in an oven not exceeding 50°C. (Note - Do not clean the plastic with a dry or wet cloth or by rinsing or washing with an organic solvent, a surfactant, etc.)

*

Table V. Surface Area of Plastic to be Used

Form of Plastic	Thickness*	Amount of Plastic per 10 ml. Extracting Medium	Subdivided Into
Film or sheet	a	60 cm.² total surface area	Strips of about 10 cm. × 0.3 cm.
	b	30 cm.² total surface area	
Tubing	a†	Length = $\frac{60 \text{ cm.}^2}{\text{I.D. circumference} + \text{O.D. circumference}}$	Sections of about 10 cm. × 0.3 cm.
	b†	Length = $\frac{30 \text{ cm.}^2}{\text{I.D. circumference} + \text{O.D. circumference}}$	
Monofilament	a	Length = $\frac{60 \text{ cm.}^2}{\text{circumference}}$	Sections of about 10 cm.
	b	Length = $\frac{30 \text{ cm.}^2}{\text{circumference}}$	
Slabs, tubing, and molded items	c	2.0 Gm. (based on material of specific gravity 1.0)	Pieces of about 0.3 cm. in overall diameter.

* a = <0.5 mm. (0.020 in.); b = 0.5 mm. to 1 mm. (0.020 in. to 0.040 in.); c = >1 mm. (0.040 in.).
† Wall thickness of tubing.

Extracts - Place 2 properly prepared Samples of the plastic to be tested in separate extraction flasks and add to each flask 100 ml. of special distilled water. Also prepare one 100 ml. Blank of the medium. Extract by heating in an oven at 70°C for 24 hours. Allow adequate time for the liquid within the container to reach the extraction temperature. (Note - The extraction conditions should not in any instance cause physical changes such as fusion or melting of the plastic pieces in any way beyond a slight adherence of one portion to another. Always add the cleaned pieces individually to the extraction medium.) Cool all containers to about room temperature but not below 22°C, shake vigorously, and decant each extract into properly cleansed containers. Store the extracts at a temperature between 22°C and 30°C and test within the following 24 hours.

Heavy Metals (U.S.P. XVII, page 876) Limits: Less than 1.0 ppm in extract

Pipette 20 ml. aliquots of the Blank and Sample Extract solutions into separate Nessler tubes. Also pipette 1 ml. (0.5 ppm) and 2 ml. (1.0 ppm) of Standard Lead Solution (0.01 mg. Pb/ml) into separate Nessler tubes. Add 2 ml. of dilute acetic acid to all four tubes. Dilute each tube to 25 ml. with special distilled water. Add 10 ml. of freshly prepared hydrogen sulfide T.S. to each tube, mix (preferably with a stirring rod having a loop at the lower end), allow to stand for 5 minutes and view downward over a white surface. Determine the amount of heavy metals (as lead) in the Blank and Sample Extract solutions by comparing the amount of darkening in each solution against that in the standard solutions.

Nonvolatile Residue Limits: Less than 20 ppm in extract

Pipette 50 ml. aliquots of the Blank and Sample Extract solutions into separate, previously tared crucibles that have been dried to constant weight under the same conditions to be employed in the determination. Evaporate on a steam bath, using a current of air, to dryness. Dry the crucibles in a 105°C oven for 1 hour. Cool and weigh. (Note - If an oily residue is obtained, inspect the crucible repeatedly during the evaporation and drying period since such oils may creep along the walls of the crucible.) The difference obtained from the Sample Extract and the Blank is the nonvolatile residue.

Density Limits: 0.85 to 1.00 (Where one polyolefin is to be substituted for another of the same generic type, the density of the new material should be essentially the same, i.e. within 0.020 g. per cc)

The preferred method for the determination of density is the density-gradient technique, ASTM designation D-1505-67. In the event that density gradient equipment is not available a satisfactory alternate method is by displacement of water, ASTM Designation D792-66. Abstracts of both methods are as follows:

Density by The Density Gradient Technique

Scope - This method covers the determination of the density of solid plastics by observing the level to which a test specimen sinks in a liquid column exhibiting a density gradient, in comparison with standards of known density.

Apparatus - (1) Density-Gradient Tube consisting of a suitable graduate with ground-glass stopper, (2) Constant-Temperature Bath adjusted to 23 ± 0.01°C, (3) Calibrated glass floats covering the density range to be studied, (4) Pycnometer, (5) Liquids suitable for the preparation of a density gradient (Table I), (6) Hydrometers covering the range of densities to be measured and having 0.001 density graduations, (7) Analytical balance with a sensitivity of 0.001 g, (8) Siphon or pipet for filling gradient tube.

TABLE 1—LIQUID SYSTEMS FOR DENSITY-GRADIENT TUBES

System	Density Range, g/cm³
Methanol - benzyl alcohol	0.80 to 0.92
Isopropanol - water	0.79 to 1.00
Isopropanol - diethylene glycol	0.79 to 1.11
Ethanol - carbon tetrachloride	0.79 to 1.59
Toluene - carbon tetrachloride	0.87 to 1.59
Water - sodium bromide	1.00 to 1.41
Water - calcium nitrate	1.00 to 1.60
Carbon tetrachloride - trimethylene dibromide	1.60 to 1.99
Trimethylene dibromide - ethylene bromide	1.99 to 2.18
Ethylene bromide - bromoform	2.18 to 2.89

Test Specimen - The specimen shall consist of a piece of the material under test cut to any shape convenient for easy identification, but with dimensions that permit the most accurate position measurement of the center of volume of the floating specimen. It shall be free of foreign matter and voids.

Preparation of Density Gradient Columns

(1) Preparation of Standard Glass Floats - Prepare glass floats by any convenient method such that they are fully annealed, approximately spherical, and have a maximum diameter of 5 mm. Prepare a solution (400 to 600 ml) of the liquids to be used in the gradient tube such that the density of the solution is approximately equal to the desired lowest density. When the floats are at room temperature, drop them gently into the solution. Save the floats that sink very slowly, and discard those that sink very fast.

(2) Calibration of Standard Glass Floats - Place a tall cylinder in the constant-temperature bath maintained at 23 ± 0.1°C. Then fill the cylinder about two thirds full with a solution of two suitable liquids, the density of which can be varied over the desired range by the addition of either liquid to the mixture. After the cylinder and solution have attained temperature equilibrium, place the float in the solution, and adjust the density of the mixture by addition of either component with good stirring until the float remains stationary within the liquid for at least 30 min. During this period of time, the cylinder shall be covered. Then fill a freshly cleaned and dried pycnometer with the solution and place it in the 23 ± 0.1°C bath for sufficient time to allow temperature equilibrium of the glass. Determine the density of the solution by normal methods and make "in vacuo" corrections for all weighings. Record this as the density of the float. Repeat the procedure for each float.

(3) Gradient Tube Preparation - Using the two liquids that will give the desired density range, and sensitivity (S) in grams per cubic centimeter per millimeter, prepare four or more solutions such that each differs from the next heavier by 80 S g per cu cm. The number of solutions will depend upon the desired density range of the column and shall be determined as follows:

$$\text{Number of solutions to prepare density-gradient column} = \frac{1 + D_2 - D_1}{80\,S}$$

where: D_2 = upper limit of density range desired,
D_1 = lower limit of density range desired, and
S = sensitivity, in grams per cubic centimeter per millimeter.

To prepare these solutions, proceed as follows: Using the hydrometers, mix the two liquids in the proportions necessary to obtain the desired solutions. Remove the dissolved air from the solutions by gently heating or an applied vacuum. Then check the density of the solutions at 23 ± 0.1°C by means of the hydrometers and, if necessary, add the appropriate air-free liquid until the desired density is obtained.

By means of a siphon or pipet, fill the gradient tube with an equal volume of each liquid starting with the heaviest, taking appropriate measures to prevent air from being dissolved in the liquid. After the addition of the heaviest liquid, very carefully and slowly pour an equal volume of the second heaviest liquid down the side of the column by holding the siphon or pipet against the side of the tube at a slight angle. Avoid excess agitation and turbulence. In this manner, the "building" of the tube shall be completed.

Transfer the tube, with as little agitation as possible, to the constant-temperature bath maintained at 23 ± 0.1°C.

For every 254 mm of length of tube, dip a minimum of five clean calibrated floats, spanning the effective range of the column, into the less dense solvent used in the preparation of the gradient tube and add them to the tube. By means of a stirrer mix the different layers of the tube gently by stirring horizontally until the least dense and most dense floats span the required range of the gradient tube. Cap the tube and keep it in the constant-temperature bath for a minimum of 24 hr.

At the end of this time, plot the density of floats versus the height of floats. A fairly smooth and nearly linear curve should be obtained.

Procedure - Wet three representative test specimens with the less dense of the two liquids used in the tube and gently place them in the tube. Allow the tube and specimens to reach equilibrium, which will require 10 or more min. Rechecking after several hours is advisable. Read the height of the floats and specimens by using a line through their center of volume.

Calculations - The densities of the samples may be determined graphically or by calculation from the levels to which the samples settle by either of the following methods.

(a) Graphical Calculation - Plot float position versus float density on a chart large enough to be read accurately to ± 1 mm and the desired precision of density. Plot the positions of the unknown specimens on the chart and read their corresponding densities.

(b) Numerical Calculation - Calculate the density by interpolation as follows:

$$\text{Density at } x = a + \frac{(x - y)(b - a)}{(z - y)}$$

where: a and b = densities of the two standard floats,
y and z = distances of the two standards, a and b, respectively, bracketing the unknown measured from an arbitrary level, and
x = distance of unknown above the same arbitrary level.

Density by Displacement

Scope - This method involves weighing a one-piece specimen of 1 to 50 g. in water using a sinker.

Apparatus - (1) Analytical balance equipped with a stationary support for the immersion vessel above the balance pan, (2) corrosion resistant wire for suspending the specimen, (3) a corrosion-resistant sinker, having smooth surfaces and a regular shape and slightly heavier than necessary to sink the specimen, (4) immersion vessel, (5) thermometer.

Materials - The water shall be substantially air-free, distilled or demineralized and containing a few drops of wetting agent so as to wet the specimen.

Test Specimen - The specimen shall be a single piece of the material of any convenient size and shape provided its volume is not less than 1 cm. It shall be free from foreign matter.

Procedure - Weigh the specimen in air to the nearest 0.1 mg. Attach to the balance a piece of fine wire sufficiently long to reach from the hook above the pan to the support for the immersion vessel. Attach the specimen to the wire such that it is suspended about 2.5 cm above the vessel support. Mount the immersion vessel on the support and completely immerse the suspended specimen and sinker in water at a temperature of 23 $\pm$ 2°C. The vessel must not touch wire or specimen. Remove any bubbles adhering to the specimen, wire, or sinker. Weigh the suspended specimen to the nearest 0.1 mg. Record this weight as b (the weight of the specimen, sinker, and the partially immersed wire). Weigh the wire and sinker to the same depth as used in the previous step. Record this weight as w (weight of the wire and sinker in the liquid).

Calculate the specific gravity of the plastic as follows:

$$\text{Sp. gr. } 23/23^{\circ}\text{C} = \frac{a}{a + w - b}$$

where: a = apparent weight of specimen without wire or sinker in air,
b = apparent weight of specimen and sinker completely immersed and of the wire partially immersed in the liquid,
w = apparent weight of totally immersed sinker and of partially immersed wire.

Calculate the density of the plastic as follows:

$$D^{23^{\circ}C}, g/cm^3 = \text{Sp. gr. } 23/23^{\circ}C \times 0.9975$$

Water Vapor Permeability Limit: WVP shall not exceed WVP of previously used container and shall be less than

$$\frac{1.20 \text{ g., mils}}{100 \text{ sq. in./day}}$$

Definition - Water vapor permeability is a property of polyolefins describing their ability to transmit water vapor from one side of a sheet or film to the other side. Water vapor permeability may be defined as the quantity of water vapor passing through a specified thickness of plastic per unit of time, per unit of area, under controlled conditions of temperature and relative humidity. WVP may be conveniently expressed as weight (grams) times thickness (mils) per unit area (100 sq. in.) per day.

Apparatus - Constant temperature and relative humidity cabinet 38°C ± 1°C, 92% ± 2% relative humidity, calcium chloride (anhydrous) -4 or 8 mesh, polyethylene/aluminum laminate, heat sealing iron, calipers and rule capable of measuring to the nearest hundredth inch, and an analytical balance.

Procedure - Weigh the empty plastic container without the cap. Determine the density of the plastic container. Determine the total surface area of the test container by using the calipers to measure the diameters of the body (D) and neck (d) and the height (h) of the container from the shoulder to the bottom. The surface area can be calculated as follows:

$$A = 2\pi \frac{D}{2} \times h + 2\pi \frac{D^2}{4} - \pi \frac{(d)^2}{4}$$

(Note: This formula is only correct when the area between the shoulder and neck minus the top opening is equivalent to the area of the bottom. Containers shaped differently must be calculated accordingly. Moreover, no calculation is made for the area of the neck.)

Place the anhydrous calcium chloride into the plastic container to be tested and fill to the shoulder neck opening. Heat seal the container with polyethylene/aluminum laminate, cap with the conventional closure and weigh. Place the container into the controlled atmosphere cabinet. Weigh the container after 1 day, 3 days, 7 days, 14 days, and 28 days. (Note - After removal of the container from the cabinet, allow only enough time for the container to cool to ambient temperature before weighing. Replace bottle immediately after weighing. At each weighing interval, shake container in

in order to expose the fresh surface of calcium chloride to vapor inside container.) Plot the total weight gained against time interval (days) on linear graph paper. Determine the weight gain per day by calculating the slope of the line at equilibrium, i.e. where the curve becomes linear toward the end of the test. The last 3 points should be on a straight line. Further testing until equilibrium is reached may be necessary. The water vapor permeability is calculated from the following formula:

$$WVP = \left(\frac{\text{grams}}{\text{day}}\right)\left(\frac{\text{Wt. Container, g}}{\text{Density}}\right)\left(\frac{6100}{A^2}\right) = \frac{\text{g, mils}}{\text{100 sq. in./day}}$$

Light Transmission

The measurement of light transmitted through glass or plastics must include all the emerging radiation regardless of its angle of emergence. This is especially important when measurements of semi-transparent or translucent polyolefin plastics are desired.

Polyolefin plastics are opaque or translucent, depending upon thickness, and scatter light rather than transmitting it directly.

In conventional spectrophotometric instrumentation, the light detector is positioned to receive only the light emerging that is coincident with the source. Scattered light is largely undetected. Special instrumentation is necessary to collect the scattered light, to integrate it and to measure it. The heart of this instrumentation is an "integrating sphere". Light passing through the translucent sample regardless of its angle of emergence falls upon the white, totally reflecting inside surface of this sphere. All portions of this inside surface are equally illuminated because of its reflection quality. The photodetector tube may be positioned anywhere on the sphere (except in a position in front of the incident light).

A true measure of transmitted light through translucent materials is obtained only by utilizing the integrating sphere.

Transmission curves of polyolefins obtained with and without the use of an integrating sphere reveal the importance of measuring all transmitted light. Measurements made without the sphere indicate, erroneously, no transmission of light throughout the ultraviolet and most of the visible regions of the spectrum. Measurements with the sphere give a true picture of light transmission, showing appreciable transmission of ultraviolet and visible wavelengths.

The pharmaceutical industry, recognizing the sensitivity of many drug products to light, has published specifications for containers to be used for packaging light-sensitive products. The Seventeenth Revision of the U. S.

Pharmocopoeia sets a specification of less than 10% transmission at wavelengths between 290-mμ and 450-mu for general packaging of light-sensitive products.

Polyolefin containers meeting the requirements of this standard are easily formulated by the addition of white or amber pigmentation to the natural plastic. ASTM D-1003-61 provides a method of measuring luminous transmittance of plastics using a recording spectrophotometer equipped with an integrating sphere.

PLASTICS - BIOLOGICAL TESTS

Extracting Media

The following are used as extracting media:

1 in 20 SOLUTION OF ALCOHOL in Sodium Chloride Injection.
COTTONSEED OIL (see U.S.P. XVII, page 151).

Apparatus

Oven - Use an oven, preferably a forced-draft model, which will maintain operating temperatures of 50°C and 70°C within ± 1 C.

Extraction Containers - Use only containers, such as ampuls or screw-cap culture test tubes, of borosilicate glass. If used, culture test tubes are closed with screw caps having suitable rubber liners. The exposed surface of the rubber liner is completely protected with an inert solid disk 0.5 mm. to 0.075 mm. in thickness. A suitable disk can be fabricated from a polytetrafluorethylene resin.

Preparation of Apparatus

Clean all glassware thoroughly with chromic acid cleansing mixture, or if necessary with hot nitric acid, followed by prolonged rinsing with purified water. Clean cutting devices by an appropriate method (e.g., successive cleaning with acetone and methylene chloride) prior to use in subdividing a specimen. Clean all other equipment by thoroughly scrubbing with a suitable detergent and prolonged rinsing with purified water.

Render containers and devices used for extraction, and in transfer and administration of test materials, sterile and dry by a suitable process. (Note - If ethylene oxide is used as the sterilizing agent, allow adequate time for complete de-gassing.)

Test Animals

For the Acute Systemic Toxicity Test select healthy, not previously used albino mice each weighing between 17 and 23 gm. For each test group, use only mice of the same source. Offer food and water, commonly used for laboratory animals and known as to composition, ad libitum.

Procedure

Preparation of Sample - Obtain 6 g. of a representative sample from a homogeneous polyolefin sample. Cut into 3 mm. x 3 mm. pieces. Sieve and save all the pieces that pass through a No. 6 sieve (3.36 mm.) but are retained on a No. 7 sieve (2.83 mm.). Place 4.0 g. of the Sample pieces in a glass-stoppered 100 ml. graduated cylinder of borosilicate glass and clean by shaking for about 30 seconds with 70 ml. of water for injection. Repeat, discarding the wash water each time. Allow the portions to drain dry, and, in addition further dry those intended for extraction in Cottonseed Oil in an oven below 50°C for 1 hour. Prepare in duplicate. (Note - Do not clean with a dry or wet cloth or with an organic solvent, surfactant, etc.)

Add 20 ml. portions of the appropriate Extracting Media to separate extraction containers and place a properly prepared Sample of the polyolefin to be tested in each of the two extraction containers. Close each container with a suitable cap or pressure sensitive tape and disperse the pieces of polyolefin by swirling in the extraction medium. (Repeat these directions for each extracting medium required for testing.) Prepare one 20.0 ml. Blank for each extracting medium for parallel injections and comparisons. Extract by heating in an oven at 70°C for 24 hours. The extraction should not result in gross physical changes in the samples, such as fusion of the two portions in any way beyond a slight adherence of one portion to another. Cool to about room temperature, but not below 25°C, shake vigorously and decant each extract, using aseptic precautions, into a dry sterile vessel. Seal and store the extracts at a temperature of 25°C and do not use for tests after 24 hours.

Acute Systemic Toxicity Test

The acute systemic toxicity test is designed to determine the biological response of mice to polyolefins by the single dose injection of specific extracts prepared from a polyolefin. Of importance is the contact of the extracting medium with the available surface area of the plastic and the time and temperature during extraction, the proper cooling, agitation and decanting process, as well as the aseptic handling and storage of the extracts following extraction. (Note - Each extract must be agitated vigorously prior to withdrawal of each injection dose to insure even distribution of the extracted matter.)

Procedure - For this test, the mice are individually identified in a suitable manner (color, coding, ear-nicking, etc.). Each mouse in the Sample and Blank groups is weighed and the initial weights recorded. Inject into groups of 10 mice each the extract of the Sample and Blank as outlined in the table below:

Injection Procedure

EXTRACT OR BLANK	DOSE per Kg.	ROUTE	INJECTION RATE (ml./sec.)
1 in 20 Solution of Alcohol in Sodium Chloride Injection	50 ml.	I.V.	0.1
Cottonseed Oil	50 ml.	I.P.	...

Observe the animals immediately after injection, and at 4, 24, 48, and 72 hour intervals.