These two methods, the so-called "paddle-water" and "paddle-acid" methods, are described below and are identical with the exception of the nature of the dissolution medium used in the procedures (i.e., distilled or deionized water vs. dilute hydrochloric acid (0.6 percent volume/volume)). The dissolution apparatus used in these two methods differs significantly from the apparatus described in the method in the compendium. The Food and Drug Administration is aware that the three methods (i.e., USP, "paddle-water," and "paddle-acid") show significant differences in dissolution in comparative tests on some formulations. Definitive bioavailability data to compare the relative value of each of these methods to predict bioavailability of the few formulations where the methods show significant differences in dissolution rate are not now available. Manufacturers who conduct research utilizing the "paddle-water" and "paddle-acid" methods, particularly in comparison with the method in The United States Pharmacopeia, shall submit any data obtained using these methods to the Food and Drug Administration pursuant to section 505(j) of the act.

(1) Dissolution apparatus. (NOTE: Throughout this procedure use scrupulously clean glassware, which previously has been rinsed with dilute hydrochloric acid, distilled or deionized water, then with alcohol, and carefully dried. Take precautions to prevent contamination from airborne, fluorescent particles and from metal and rubber surfaces.) The apparatus consists of a suitable water bath, a 1000 milliliter

glass vessel (Kimble Glass No. 26220 or equivalent), a motor, and a polytetrafluoroethylene stirring blade (Sargent S-76637, Size B, 3 inch length; or equivalent) on a glass stirring shaft (Sargent 5-76636, 14.5 inch length; or equivalent). The water bath may be of any convenient size that permits keeping the water temperature uniformly at 37° C. ± 0.5° C. throughout the test. The vessel is spherical, and is provided with three ports at the top, one of which is centered. The lower half of the vessel is 65 millimeters in inside radius and the vessel's nominal capacity is 1000 millliliters. The glass stirring shaft from the motor is placed in the center port, and one of the outer ports may be used for insertion of a thermometer. Samples may be removed for analysis through the other port. The motor is fitted with a speed-regulating device that allows the motor speed to be held at 50 rpm ± 2 rpm. The motor is suspended above the vessel in such a way that it may be raised or lowered to position the stirring blade. The glass stirring shaft is 10 millimeters in diameter and about 37 centimeters in length. It must run true on the motor axis without perceptible wobble. The polytetrafluoroethylene stirring blade is 4 millimeters thick and forms a section of a circle, whose diameter is 83 millimeters and which is subtended by parallel chords of 42 and 77 millimeters. The blade is positioned horizontally, with the 42-millimeter edge down, 2.5 centimeters ± 0.2 centimeter above the lowest inner surface of the vessel.

(2) Reagents--(i) Dissolution medium. For "paddle-water," use distilled or deionized water. For "paddle-acid," use dilute hydrochloric acid (0.6 percent volume/volume). Use the same batch of dissolution medium throughout the test.

(ii) Standard solutions. Accurately weigh approximately 25 milligrams of The United States Pharmacopeia Digoxin Reference Standard, dissolve in a minimum amount of 95 percent ethanol in a 500 milliliter volumetric flask and add 95 percent ethanol to volume and mix. Dilute 10.0 milliliters of this first solution to 100.0 milliliters with 95 percent ethanol and mix for the second solution. Just prior to use, individually dilute 1.0, 2.0, 3.0, 4.0, and 5.0 milliliter aliquots of the second solution with dissolution medium to 50.0 milliliters. These solutions are equivalent to 20, 40, 60, 80, and 100 percent of dissolution, respectively, for a 0.25 milligram digoxin tablet.

(iii) Extraction solvent. Prepare a solvent containing 6 volumes of chloroform, analytical reagent grade, with 1 volume of n-propyl alcohol, analytical reagent grade.

(iv) Ascorbic acid-methanol solution. Prepare a solution containing 2 milligrams of ascorbic acid, analytical reagent grade, per 1 milliliter of methanol, absolute, analytical reagent grade.

(v) Hydrochloric acid, concentrated reagent grade.

(vi) Hydrogen peroxide-methanol solution. On the day of use, dilute 2.0 milliliters of recently assayed 30 percent hydrogen peroxide, reagent grade, with methanol, absolute, analytical reagent grade to 100.0 milliliters. Store in a refrigerator. Just prior to use, dilute 2.0 milliliters of this solution with methanol to 100.0 milliliters.

(3) Procedure--(i) Dissolution. Place 500 milliliters of dissolution medium in the vessel, immerse it in the constant-temperature bath set at 37° C. ± 0.5° C., and allow the dissolution medium to assume the temperature of the bath. Position the shaft so that there is a distance of 2.5 centimeters ± 0.2 centimeter between the midpoint of the bottom of the blade and the bottom of the vessel. With the stirrer operating at a speed of 50 rpm ± 2 rpm, place 1 tablet into the flask. After 60 minutes, accurately timed, withdraw 25 milliliters, using a glass syringe connected to a glass sampling tube, of solution from a point midway between the stirring shaft and the wall of the vessel, and approximately midway in depth. Filter the solution promptly after withdrawal, using a suitable membrane filter of not greater than 0.8 micron porosity (Millipore AAWP 025 00, or equivalent), mounted in a suitable holder (Millipore Swinnex SX00 025 00, or equivalent), discarding the first 10 milliliters of filtrate. This is the test solution. Repeat the dissolution procedure on 5 additional tablets.

(ii) Extraction. Transfer 10.0 milliliters of each of the six filtrates, 10.0 milliliters of each of the five standard solutions, and 10.0 milliliters of dissolution medium, to provide a blank, in separate 60-milliliter separators. Extract each solution with two 10-milliliter portions of extraction solvent. Combine the extracts of each solution in separate, glass-stoppered, 50-milliliter conical flasks, and evaporate on a steam bath with the aid of a stream of nitrogen to dryness, rinsing the sides of the flasks with extraction solvent. Take care to ensure that all traces of solvent are removed, but avoid prolonged heating. For convenience the residues may be stored in a vacuum desiccator overnight.

(iii) Measurement of fluorescence. Begin with the standard solutions, and keep all flasks in the same sequence throughout, so that the elapsed time from addition of reagents to reading of fluorescence is the same for each. Carry the test solutions, standard solutions, and the blank through the determination in one group. Add the following three reagents in as rapid a sequence as possible, swirling after each addition, treating 1 flask at a time, in the order named: 1.0 milliliter of ascorbic acid-methanol solution, 3.0 milliliters of concentrated hydrochloric acid, and 1.0 milliliter of hydrogen peroxide-methanol solution. Insert the stoppers in the flasks, and after 2 hours, measure the fluorescence at about 485 millimicrons, using excitation at about 372 millimicrons. In order to provide a check on the stability of the fluorometer, reread one or more standard solutions. Correct each reading for the blank and plot a standard curve of fluorescence versus percentage dissolution. Determine the percentage dissolution of digoxin in the test solutions by reading from the standard graph.

(i) Digoxin tablets formulated so that the quantity of digoxin dissolved at one hour, when tested by the method in The United States Pharmacopeia (USP XVIII), is greater than 95 percent of the assayed amount of digoxin or so that the quantity of digoxin dissolved at 15 minutes is greater than 90 percent of the assayed amount of digoxin are new drugs which may be marketed only with an approved full new drug application as provided for in § 130.4. The application shall include, but not be limited to, clinical studies establishing significantly greater bioavailability than digoxin tablets meeting compendial requirements and dosage recommendations based on clinical studies establishing the safe and effective use of the more bioavailable digoxin product. Marketing of these digoxin products will be allowed only under a proprietary or trade name, established name, and labeling which differs from that used for digoxin tablets that meet all of the requirements in The United States Pharmacopeia (USP XVIII) and that are formulated so that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or so that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin. New drug applications for these digoxin products shall be submitted to the Food and Drug Administration, Bureau of Drugs, Office of Scientific Evaluation (HFD-100), 5600 Fishers Lane, Rockville, MD 20852.

Effective date. This order shall be effective (insert date of publication in the FEDERAL REGISTER). The Commissioner finds that immediate compliance with the requirements of this regulation is necessary to protect the public health and, therefore, notice, time for public comment, and delayed effective date are impracticable, unnecessary, and contrary to the public interest. Comments on this regulation may be submitted to the Hearing Clerk, Food and Drug Administration, Room 6-86, 5600 Fishers Lane, Rockville, MD 20852, on or before (insert date 30 days after date of publication in the FEDERAL REGISTER). Comments received and supportive materials may be seen in the above office during working hours, Monday through Friday. Comments received may result in modification of this section.

(Secs. 201(p), 501(b), 502, 505, 701(a), 52 Stat. 1041-1042, 1049-1053, 1055; 21 U.S.C. 321(p), 351(b), 352, 355, 371(a).)

Dated: Jan 10, 1974.

JAN 10 1974

A. M. Schmidt
Commissioner of Food and Drugs

EXHIBITS PROVIDED BY THE AMERICAN PHARMACEUTICAL ASSOCIATION

STATEMENT
OF THE
AMERICAN PHARMACEUTICAL ASSOCIATION
TO THE
SUBCOMMITTEE ON MONOPOLY
OF THE
SELECT COMMITTEE ON SMALL BUSINESS
OF THE
UNITED STATES SENATE
93RD CONGRESS, 2ND SESSION
WASHINGTON, D.C.
FEBRUARY 21, 1974

MR. CHAIRMAN, MEMBERS OF THE SUBCOMMITTEE, I AM DR. EDWARD G. FELDMANN, ASSOCIATE EXECUTIVE DIRECTOR FOR SCIENTIFIC AFFAIRS OF THE AMERICAN PHARMACEUTICAL ASSOCIATION (APHA), THE NATIONAL PROFESSIONAL SOCIETY OF PHARMACISTS IN THE UNITED STATES.

YOU HAVE REQUESTED THAT WE DISCUSS THE VIEWS OF THE AMERICAN PHARMACEUTICAL ASSOCIATION ON THE POTENTIAL VALUE AND USEFULNESS TO PHARMACY PRACTITIONERS OF DATA AND INFORMATION

SECURED BY THE DEFENSE PERSONNEL SUPPORT CENTER (DPSC) OF THE DEPARTMENT OF DEFENSE. IN ORDER TO PROVIDE A FRAME OF REFERENCE FOR OUR RESPONSE, AS WELL AS OUR INTEREST IN OBTAINING SUCH DATA AND INFORMATION FROM DPSC RELATIVE TO DRUG PRODUCTS AND PHARMACEUTICAL MANUFACTURERS, PERMIT ME TO DESCRIBE BRIEFLY OUR ONGOING INVOLVEMENT AND ACTIVITIES IN THE AREA OF DRUG PRODUCT QUALITY.

THE VERY FIRST OBJECT LISTED IN BOTH THE APHA CERTIFICATE OF INCORPORATION AND THE APHA CONSTITUTION IS DIRECTLY ADDRESSED TO THIS MATTER. SPECIFICALLY, OBJECT A OF THE ASSOCIATION'S CONSTITUTION READS AS FOLLOWS:

> **Article II. Objects.**
>
> This ASSOCIATION shall exist for the following purposes:
>
> A. To aid in improving, promoting, and safeguarding the public health and welfare in every practical manner and by all practical means–
>
> 1. By maintaining a compendium of standards and specifications calculated to promote the safety, efficacy, and purity of drugs, to be known as the *National Formulary*. Criteria for establishing such standards and specifications, and procedures to be followed in qualifying an article for admission to the *National Formulary*, shall be established by a Board, elected by the Board of Trustees, to be known as the National Formulary Board; and
>
> 2. By promoting the safe use of drugs and aiding in the detection and prevention of adulteration and misbranding of drugs and medicines, and by taking such steps, as an ASSOCIATION and in cooperation with other organizations, as will assure the production and distribution of drugs and medicines of the highest quality, in a manner consistent with practices deemed reasonably necessary to ensure their purity and safety.

SINCE ITS FOUNDING 122 YEARS AGO, APHA HAS PURSUED A CONSISTENT AND RELENTLESS EFFORT NOT ONLY TO FERRET OUT AND IDENTIFY ADULTERATED AND MISBRANDED DRUGS BUT ALSO TO

DISSEMINATE AND PUBLICIZE SUCH INFORMATION TO THE PHARMACY PROFESSION. IT HAS BEEN OUR FIRM BELIEF THAT SUCH INFORMATION IS NECESSARY IF PHARMACISTS ARE TO PRACTICE THEIR PROFESSION MOST CAPABLY AND IF THE PUBLIC IS TO BE BEST SERVED WITH PHARMACEUTICAL PRODUCTS WHICH ARE BOTH EFFECTIVE AND SAFE (SEE EXHIBIT A APPENDED AS ILLUSTRATION OF ARTICLE FROM AUGUST 1960 APHA JOURNAL EXPOSING UNQUALIFIED DRUG MANUFACTURERS).

MOREOVER, THE ASSOCIATION EACH MONTH PUBLISHES LISTS OF FDA DRUG RECALLS, COMPLETE WITH PERTINENT ANCILLARY INFORMATION PERTAINING TO EACH RECALL, IN ORDER TO ENSURE PROMPT AND WIDESPREAD DISSEMINATION OF SUCH INFORMATION TO PRACTICING PHARMACISTS (SEE EXHIBIT B APPENDED AS EXAMPLE FROM FEBRUARY 1974 APHA JOURNAL). AT TIMES, RECALL INFORMATION EITHER MAY NOT BE SUFFICIENT OR APPROPRIATE TO COMMUNICATE THE PECULIAR PROBLEMS WHICH MAY RELATE TO A CERTAIN DRUG, IN WHICH CASE APHA HAS PREPARED AND PUBLISHED SPECIALLY WRITTEN ARTICLES, SUCH AS THE RECENT SERIES IN CONNECTION WITH DIGOXIN (SEE EXHIBITS C, D, AND E; ARTICLES FROM APHA NEWSLETTERS DATED JUNE 23, 1973, JANUARY 19, 1974, AND FEBRUARY 2, 1974).

FURTHERMORE, WE HAVE VIEWED OUR RESPONSIBILITY AS BEING MORE THAN SERVING SIMPLY AS AN INFORMATION PIPELINE TO THE PROFESSION. AS THAT COMPONENT OF THE HEALTH CARE

COMMUNITY HAVING THE GREATEST IMMEDIATE TRAINING, EXPERIENCE, KNOWLEDGE, AND INTEREST IN DRUG QUALITY, AND IN THE FACTORS WHICH CUMULATIVELY GO INTO A QUALITY PHARMACEUTICAL PRODUCT, PHARMACY -- THROUGH THE ASSOCIATION -- HAS CONDUCTED A COMPREHENSIVE SPECTRUM OF ONGOING ACTIVITIES DESIGNED TO FOSTER AND REQUIRE QUALITY ATTRIBUTES RELATING TO DRUG EFFICACY AND SAFETY.

THESE ACTIVITIES INCLUDE: (A) SPONSORING MEETINGS AND SYMPOSIA, PRIMARILY THROUGH THE APHA ACADEMY OF PHARMACEUTICAL SCIENCES, AT WHICH SCIENTIFIC PAPERS AND REPORTS ARE PRESENTED DESCRIBING NEW TEST PROCEDURES AND METHODOLOGY; (B) THE PUBLICATION OF THE APHA'S JOURNAL OF PHARMACEUTICAL SCIENCES, WHICH SERVES AS THE PRIMARY VEHICLE FOR COMMUNICATING THE LATEST SUCH RESEARCH ON A WORLDWIDE BASIS AMONG SCIENTISTS; (C) THE COSPONSORSHIP -- WITH THE AMA AND THE USPC -- OF THE DRUG STANDARDS LABORATORY, WHICH IS HOUSED IN THE APHA BUILDING AND WHICH CONDUCTS LABORATORY STUDIES DESIGNED TO DEVELOP AND EVALUATE NEW DRUG TESTING PROCEDURES; (D) THE REVISION AND PUBLICATION PROGRAM OF THE NATIONAL FORMULARY, AN OFFICIAL COMPENDIUM RECOGNIZED UNDER FEDERAL AND STATE LAWS AS PROVIDING STANDARDS AND SPECIFICATIONS FOR DRUGS AND FOR THEIR DOSAGE FORMS; AND (E) THE ESTABLISHMENT OF A BIOAVAILABILITY PROJECT WHEREBY, IN AN EFFICIENT AND COORDINATED MANNER,

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SUCH INFORMATION MIGHT BE COMPILED, EVALUATED, AND MADE AVAILABLE RELATIVE TO COMPETING DRUG PRODUCT FORMULATIONS.

MOREOVER, THE ASSOCIATION HAS LENT ITS ENDORSEMENT, COOPERATION, AND STRENUOUS SUPPORT TO EFFORTS AND ACTIVITIES OF OTHER GROUPS ENGAGED IN COMPARABLE EFFORTS TO FOSTER THE RELIABILITY OF MARKETED DRUG PRODUCTS. TO MENTION BUT TWO EXAMPLES: (A) THE ASSOCIATION COLLABORATED WITH EFFORTS OF THE CALIFORNIA PHARMACEUTICAL ASSOCIATION IN SUPPORTING THE SO-CALLED "CROWN BILL" (A.B. 1404) AND REGULATIONS FOR ITS IMPLEMENTATION -- THIS LEGISLATION REQUIRES THE NAME OF THE ACTUAL MANUFACTURER OR FABRICATOR OF THE DRUG PRODUCT TO BE IDENTIFIED ON THE PRODUCT LABEL AS AN IMPORTANT PIECE OF INFORMATION TO ASSIST PRACTITIONERS IN MAKING QUALITY JUDGMENTS RELATIVE TO THAT ARTICLE; AND (B) THE ASSOCIATION ENDORSED AND COOPERATED WITH THE FOOD AND DRUG ADMINISTRATION AND THE U. S. PHARMACOPEIA IN A TYPE OF "GRASS-ROOTS" NATIONAL DRUG SURVEILLANCE PROGRAM DESIGNED TO PROVIDE A BROAD NETWORK FOR THE PURPOSE OF IDENTIFYING AND REPORTING TO RESPONSIBLE AGENCIES DRUG PRODUCT DEFECTS DETECTED AT THE PHARMACY PRACTITIONER LEVEL.

MR. CHAIRMAN, THE BROAD SPECTRUM OF ACTIVITIES BRIEFLY DESCRIBED ABOVE HAS AFFORDED US A UNIQUE PERSPECTIVE FROM WHICH TO ASSESS THE GENERAL QUALITY OF THE NATION'S DRUG

SUPPLY. EARLIER THIS MONTH, WE TESTIFIED BEFORE THE SENATE SUBCOMMITTEE ON HEALTH, AND IN OUR TESTIMONY WE CONCURRED IN THE ASSESSMENT THAT THE NATION'S DRUG SUPPLY IS OF THE HIGHEST QUALITY. AS WE NOTED THEN, NO MATTER HOW PERFECT ANY HUMAN SYSTEM MAY BE, NO MATTER HOW ADVANCED ANY TESTING AND STANDARDS MAY BECOME, THE DRUG INDUSTRY CAN NEVER ACHIEVE, NOR FDA ENFORCE, A "ZERO-DEFECT LEVEL." THE VARIOUS PROGRAMS AND ACTIVITIES CONDUCTED BY THE FDA INDICATE TO US THAT ALL REASONABLE STEPS ARE BEING TAKEN IN AN EFFORT TO ASSURE THE HIGHEST LEVEL OF QUALITY IN OUR DRUG SUPPLY AS THE PRESENT STATE OF KNOWLEDGE, SCIENCE, AND TECHNOLOGY PERMITS.

IN RECENT YEARS, WE HAVE HEARD A NUMBER OF DISQUIETING SPEECHES, AND WE HAVE READ A NUMBER OF DISTURBING ARTICLES -- ALL EMANATING FROM DPSC SPOKESMEN -- WHICH IN TOTO HAVE SERVED TO CAST DOUBTS AND SUSPICION ON VARIOUS UNIDENTIFIED DRUG PRODUCTS, AS WELL AS VARIOUS UNNAMED DRUG MANUFACTURERS. THESE SPEECHES AND ARTICLES HAVE SUGGESTED THAT PROBLEMS PERTAINING TO UNRELIABLE DRUGS, PRODUCED UNDER SHODDY CONDITION OF MANUFACTURE, ARE WIDELY PREVALENT ON THE AMERICAN DRUG MARKET.

SUCH IMPLICATIONS AND ALLEGATIONS APPEAR TO RUN CONTRARY TO INFORMATION AVAILABLE TO US FROM OTHER SOURCES. MOREOVER, BECAUSE OF THEIR VERY SERIOUS NATURE, THESE ASSERTIONS HAVE DEMANDED OUR ATTENTION AND INVESTIGATION.

IT IS OUR POSITION THAT SUCH CHARGES SHOULD NOT BE MADE, SUCH INFERENCES SHOULD NOT BE DRAWN, UNLESS FACTUAL EXPERIENCE WILL, IN FACT, SUPPORT THEM; AND, IF INDEED THERE IS FACTUAL EVIDENCE TO SUPPORT SUCH STATEMENTS, THEN IT IS ALSO OUR BELIEF THAT PROTECTION OF THE PUBLIC HEALTH DEMANDS THAT SUCH INFORMATION BE MADE PUBLICLY AVAILABLE TO THE HEALTH PROFESSIONS, IN ORDER THAT APPROPRIATE STEPS CAN BE TAKEN TO AVOID THE DISTRIBUTION, THE PRESCRIBING, AND THE DISPENSING OF HAZARDOUS OR INEFFECTIVE DRUG PRODUCTS.

IN OUR EFFORT TO ANALYZE THIS SUBJECT, WE HAVE CONSIDERED TWO POSSIBILITIES: EITHER (A) EXISTING STANDARDS AND SPECIFICATIONS MAY NOT BE GENERALLY ADEQUATE; OR (B) EXISTING STANDARDS AND SPECIFICATIONS ARE NOT BEING ADEQUATELY ENFORCED.

WITH RESPECT TO THE FORMER POSSIBILITY, WE NOTE THAT BRIG. GEN. GEORGE J. HAYES, MEDICAL CORPS, U. S. ARMY, PRINCIPAL DEPUTY ASSISTANT SECRETARY OF DEFENSE, TESTIFIED BEFORE YOUR SUBCOMMITTEE, MR. CHAIRMAN, ON FEBRUARY 3, 1971, AND IN HIS PREPARED STATEMENT HE SAID:

> "I SHALL NOW TURN FROM A DISCUSSION OF WHAT WE HAVE TO WHY WE HAVE IT, AND HOW WE GET IT. IT IS DOD POLICY THAT OUR STOCK LIST SHALL CONSIST OF QUALITY DRUG PRODUCTS PROCURED COMPETITIVELY ON GENERIC SPECIFICATIONS, AND AT THE MOST ECONOMICAL PRICES WE CAN OBTAIN.

> "WE CANNOT PROCURE COMPETITIVELY WITHOUT A GENERIC SPECIFICATION. OUR STANDARDS ARE BASICALLY THOSE OF THE U.S.P. AND N.F., SUPPLEMENTED WITH SUCH ADDITIONAL STANDARDS AS ARE NECESSARY TO ENSURE SUITABILITY NOT ONLY AT THE TIME OF PROCUREMENT, BUT ALSO FOLLOWING POSSIBLE LONG-TERM STORAGE THROUGHOUT THE WORLD IN ARCTIC, TEMPERATE, OR TORRID ZONES. MANY OF OUR SPECIFICATIONS INCLUDE STANDARDS WHICH HAVE BEEN OBTAINED FROM INDUSTRY DURING THE STANDARDIZATION PROCEDURE. IF WE ARE TO OBTAIN SUITABLE MATERIAL COMPETITIVELY, WE MUST INCLUDE THESE DETAILS IN ORDER TO PROVIDE OTHER THAN PRODUCT ORIGINATORS WITH THE NECESSARY PRODUCT INFORMATION."

AS BRIG. GEN. HAYES STATES, THE DPSC STANDARDS ARE BASICALLY THOSE OF THE OFFICIAL COMPENDIA SIMPLY SUPPLEMENTED WITH ADDITIONAL STANDARDS PECULIAR TO THE SPECIAL NEEDS OF THE MILITARY. CONSEQUENTLY, ALTHOUGH ADDITIONAL SPECIFICATIONS MAY BE ADOPTED BY THE DPSC, THIS DOES NOT MEAN THAT THE OFFICIAL COMPENDIA STANDARDS ARE INADEQUATE AS APPLIED TO DRUG PRODUCTS AS INTENDED FOR USE BY THE GENERAL PUBLIC. FOR EXAMPLE, THE CRITICAL CONSIDERATION OF MINIMIZING UNNECESSARY WEIGHT MIGHT NECESSITATE SPECIFYING THE USE OF A LIGHT-WEIGHT PLASTIC CONTAINER FOR DRUG PRODUCTS TO BE CARRIED ON BOARD SPACECRAFT. ON THE OTHER HAND, THE USE OF SOMEWHAT HEAVIER CONTAINERS, SUCH AS THOSE MADE OF GLASS, WOULD BE PERFECTLY APPROPRIATE FOR USE IN PACKAGING DRUG PRODUCTS INTENDED FOR NORMAL CHANNELS OF DISTRIBUTION.

HOWEVER, THE SPEECHES AND ARTICLES BY DPSC OFFICIALS PREVIOUSLY MENTIONED, HAVE SUGGESTED THAT DEFICIENCIES IN PRODUCTS AND MANUFACTURERS ARE NOT SIMPLY RELATED TO THE SPECIAL NEEDS OF THE MILITARY, BUT THAT THEY ARE FAR MORE SERIOUS AND REPRESENT A PUBLIC HEALTH HAZARD.

IF SUCH IS THE CASE, PHARMACISTS AND PHYSICIANS SHOULD BE MADE AWARE OF THE FACTS, IN ORDER THAT THEY MIGHT TAKE APPROPRIATE PROFESSIONAL ACTION EVEN BEFORE FDA TAKES LEGAL ACTION TO REMOVE SUCH PRODUCTS FROM THE MARKETPLACE. IN APHA'S ROLE, OF MONITORING AND DISSEMINATING SUCH INFORMATION, WE HAVE ATTEMPTED TO OBTAIN SPECIFIC DETAILS FROM DPSC AS TO WHICH DRUG PRODUCTS HAVE BEEN REJECTED AND THE BASIS FOR REJECTION, AS WELL AS WHICH DRUG MANUFACTURERS HAVE BEEN JUDGED TO BE UNSUITED TO MANUFACTURE PRODUCTS OF ACCEPTABLE QUALITY. REGRETTABLY, OUR EFFORTS IN THIS REGARD HAVE TO DATE MET WITH ABSOLUTELY NO SUCCESS. IN LIGHT OF THE FACT THAT OUR INFORMAL REQUESTS FOR SUCH INFORMATION HAVE BEEN REPEATEDLY REJECTED, THIS PAST SEPTEMBER A FORMAL REQUEST FOR SUCH INFORMATION WAS FILED WITH THE DEFENSE SUPPLY AGENCY OF DOD UNDER PROVISIONS OF THE REGULATION ENTITLED, "AVAILABILITY TO THE PUBLIC OF OFFICIAL INFORMATION," AS PROMULGATED IN THE FEDERAL REGISTER DATED SEPTEMBER 6, 1973; AGAIN, THIS EFFORT FAILED TO ELICIT THE KIND OF INFORMATION WE SEEK (SEE CORRESPONDENCE APPENDED AS EXHIBITS F AND G).

MR. CHAIRMAN, IT IS OUR POSITION THAT PHARMACISTS REQUIRE FACTUAL INFORMATION IN ORDER TO BE ABLE TO SELECT AND DISPENSE QUALITY DRUG PRODUCTS WHICH WILL BE SAFE AND EFFECTIVE FOR THE NEEDS OF THE PATIENT. MOREOVER, IT IS ALSO OUR POSITION THAT THE PHARMACIST REQUIRES SUCH INFORMATION IN ORDER THAT HE MIGHT BE ABLE TO SELECT FROM DUPLICATIVE DRUG PRODUCTS OF COMPARABLE QUALITY THAT

PRODUCT WHICH WILL REPRESENT THE MOST REASONABLE COST TO THE PATIENT. IF THE DEPARTMENT OF DEFENSE HAS INFORMATION WHICH WOULD BE USEFUL AND PERTINENT IN DISTINGUISHING BETWEEN GOOD AND BAD DRUG PRODUCTS OR IN DISTINGUISHING BETWEEN GOOD AND BAD DRUG MANUFACTURERS, IT IS OUR PLEA THAT YOUR COMMITTEE SEE THAT SUCH INFORMATION -- WHICH WAS DEVELOPED AT TAXPAYERS' EXPENSE -- IS MADE PUBLICLY AVAILABLE, SO THAT IT MIGHT BE USED TO THE PUBLIC'S BENEFIT. WE INTEND ALSO TO CONTINUE OUR EFFORTS TO OBTAIN SUCH INFORMATION FROM DOD DIRECTLY. BY THE SAME TOKEN, IF THE SUGGESTIONS OF WIDESPREAD AVAILABILITY OF DEFECTIVE DRUGS -- AND OF WIDESPREAD EXISTENCE OF INCOMPETENT MANUFACTURERS -- REPRESENT EXAGGERATIONS, HYPERBOLE, OR UNSUPPORTED PROPAGANDA, THEN YOUR COMMITTEE WOULD RENDER AN EQUALLY BENEFICIAL SERVICE BY EXPOSING THE TRUTH OF THE MATTER.

EXHIBIT B

Drug Recalls

The following data have been compiled from the Federal Food and Drug Administration Weekly Recall Reports covering the period October 18, 1973, to December 12, 1973. Pharmacists and others possessing drug inventories are reminded to check their stock again to be certain that they do not have any of the products on the list. Anyone who has additional facts on any of the listed recalls which he feels will assist in completing the recall is urged to send such data to the editor of this JOURNAL.

Product	Manufacturer or Distributor	Lot Number	Quantity	Recall Class	Recall Reason	Product Distribution
Afrodex Capsules (methyltestosterone 5 mg, yohimbine 5 mg, nux vomica extract 5 mg), 100's, 500's and 1,000's	ICN Pharmaceuticals (Covina, Calif.) Private Formulae (St. Louis, Mo.)	All lots	1,300,000 capsules	II	No approved NDA	National
APC Tablets (aspirin 3.5 gr, phenacetin 2.5 gr, caffeine 0.5 gr), 100's and 1,000's	Linden Labs (Los Angeles, Calif.) Vitamin Specialties (Brisbane, Calif.)	231208	Unknown	III	Content uniformity	California
Atropine sulfate injectable 0.01 gr, 1 ml ampules	Harvey Laboratories (Philadelphia, Pa.)	0522	1,500 ampules	III	Subpotency	National
AUS-tect for CEP Test (hepatitis associated antibody—anti-Australia antigen) 1 ml and 5 ml vials	Abbott Labs (Los Angeles, Calif.)	1 ml vials 28-013-BW antibody lot Z730330 5 ml vials 28-051-BW antibody lot Z730428	800 vials	II	Loss of potency	National
Celebenin (sodium methicillin for injection), 1 g, 4 g, and 6 g vials	Beecham—Massengill Pharmaceuticals (Piscataway, N.J.)	1 g vials A0119RH A0209RN A0259RP A0309SA A0319SA A0349SA A)359SA 4 g vials A0099RH A0199RN A0219RN 6 g vials A0299SA AB030	600 vials predominantly lot AB030	II	Pyrogens	National
Digitoxin tablets 0.2 mg, 1,000's and 5,000's	Zemmer Co. (Oakmont, Pa.)	389190	35,000 tablets	II	Content uniformity	National
H P Acthar Gel (repository corticotropin injection 40 USP units per ml) 1 ml and 5 ml vials	Armour Pharmaceutical Co. (Kankakee, Ill.) National Drug Co. (Cincinnati, Ohio)	J407	Unknown	II	Subpotency	National
Insulin syringe with needle (disposable), 1 cc, 100 unit	Sherwood Medical Industries (St. Louis, Mo.)	502195	Unknown	II	Cartons of 100/100 unit labeled as 100/40/80 units	National
Kidneaz (phenazopyridine 100 mg), 30's	Edward J. Moore Sons (Long Island City, N.Y.)	All lots	120,000 tablets	II	Label does not bear prescription legend	National
Mercuhydrin injection (meralluride sodium 30 mg, theophylline 48 mg per ml), 1 ml and 2 ml ampules, 10 cc multiple dose vials	Lakeside Laboratories (Milwaukee, Wisc.)	All lots	8,000 units	II	Precipitate	National
Otos Mosan otic solution (0.6 mg sulfathiazole, 60 mg sodium propionate, 125 mg urea per ml), 15 ml dropper bottles	Ayerst Labs (New York, N.Y.)	All lots	6,000 bottles	II	Drug efficacy study implementation	National
Secobarbital sodium capsules 1.5 gr, 100's and 1,000's	Interstate Drug Exchange (Plainview, N.Y.) Columbia Pharmaceuticals (Garden City, N.Y.)	2970	Unknown	III	Subpotency	National
Sodium Salicylate and Iodide with Colchicine, No. 1 (sodium salicylate 1 g, sodium iodide 1 g, colchicine 0.65 mg), 20 ml ampules	Upjohn Co. (Kalamazoo, Mich.)	All lots	1,000 ampules	II	Lack of evidence that the drug combination is safe and effective	National

FDA definitions for recall classes:

Class I Recalls—*This is an emergency situation involving the removal from the market of products in which the consequences are immediate or long-range, life-threatening and involve a direct cause-effect relationship.*

Class II Recalls—*This is a priority situation in which the consequences may be immediate or long-range and possibly or potentially life-threatening or hazardous to health.*

Class III Recalls—*This is a routine situation in which the consequences to life (if any) are remote or non-existent.*

EXHIBIT C

APhA Newsletter

Latiolais criticizes Proprietary Association's views on antacid monograph

APhA President Clifton J. Latiolais has branded as "entirely self-serving" a recent statement by the Proprietary Association challenging a Food and Drug Administration labeling proposal. The FDA recommendation would require labels of charcoal-containing antacid products to indicate that the products are not to be used "concurrently with a prescription drug except on the advice of your physician or pharmacist."

The PA statement, filed with FDA on June 4 in response to a *Federal Register* proposal to establish a monograph on o-t-c antacid products, attempted to minimize the importance of potential drug interactions "that are more theoretical in nature than of demonstrable significance."

"APhA does indeed recognize that not all reported drug interactions are clinically significant," President Latiolais stated. "This is the reason the Association undertook the project which resulted in the publication, *Evaluations of Drug Interactions—1973*. However, the fact that some interactions are theoretical and suspect at present due to inadequate documentation in no way decreases the need to guard the patient against those interactions that have been proven to be clinically significant. To categorize these potentially significant drug therapy problems with less important ones, and then to suggest that the medicating public not be apprised of a knowledgeable source of information is clearly not in the best interest of the self-medicating public."

The PA statement also questioned "whether the pharmacist has the time, expertise or inclination to provide this information to the consumer."

"To question the expertise of a health professional with five or six years of extensive training in drugs and drug therapy is completely ludicrous," President Latiolais declared. "Further, it is ironical that many of those pharmacists who do not have time to coun-

(Continued on page 2)

Contact IRS for information on the price freeze

The Cost of Living Council reports that "economic stabilization information" is available by phone from 58 district Internal Revenue Service offices across the country. Those pharmacists who wish to contact the Council should write Cost of Living Council, 2000 M St., N.W., Washington, D.C. 20508. The IRS, which has been a part of the economic stabilization plan, will answer questions and receive complaints. During the price freeze, ordered by President Nixon June 13 for a maximum of 60 days, services or products may not be available or sold at fees or prices above the highest charges or prices at which they were available during the previous June 1-8.

Commentary on digoxin bioavailability by Colaizzi

An April 9 editorial and an April 9 article in the Journal of the American Medical Association have caused pharmacists to be concerned about the bioavailability of digoxin tablets they dispense. The following commentary on the subject was prepared for the APhA Newsletter by John L. Colaizzi, Ph.D., Director of the APhA Bioavailability Pilot Project.

Digoxin is a widely utilized drug which possesses life-saving characteristics. Precise dosage regulation is particularly essential with digoxin and other digitalis derivatives due to the narrow margin between ineffective doses and therapeutic doses, and again between therapeutic and toxic doses. For these reasons, the U.S.P. has specified a content uniformity test for digoxin tablets; this requirement is designed to ensure uniform tablet-to-tablet potency within individual lots of the drug product.

Moreover, the Food and Drug Administration developed a voluntary certification program for digoxin tablets through which manufacturers voluntarily submit samples from each batch to FDA for content uniformity and other U.S.P. tests prior to releasing the batch on the market. In October, 1971, FDA's National Center for Drug Analysis reported that 47 percent of the batches investigated did not comply with the U.S.P. monograph requirements, chiefly because of failure in the content uniformity test.[1] FDA's monitoring efforts since 1971 have virtually ensured that digoxin tablets reaching pharmacists' shelves meet all U.S.P. specifications.

Moreover, the study by Lindenbaum *et al*[2], which reported significant differences in the biological availability of three different brands of digoxin tablets based on serum level determinations in human subjects, understandably caused concern among the medical and pharmaceutical professions when it appeared in December of 1971. Not only did this study reveal wide variations in serum levels obtained with the different brands of tablets, but also with different lots of tablets of the same brand. Following publication of this work, a number of deficiencies in the study were pointed out.[3, 4] For example, at least one of the lots of tablets studied by Lindenbaum *et al* was found to

(Continued on page 4)

APhA Newsletter June 23, 1973, page 4

Commentary on digoxin bioavailability by Colaizzi

(Continued from page 1)

be subject to recall due to failure to meet the U.S.P. content uniformity test. It was pointed out, therefore, that the low serum digoxin levels produced by these tablets could have been due to low tablet potency rather than poor bioavailability. Although another lot of tablets that showed differences in serum levels when compared with the innovator brand was found to meet all U.S.P. specifications, still other possible criticisms of the Lindenbaum study were noted, such as the use of too few subjects and failure to obtain serum levels over a more prolonged period of time than five hours.

In a more recent publication by Wagner *et al* [5], two brands of digoxin tablets were studied according to an experimental design which suffered from none of the shortcomings of the Lindenbaum *et al* study. The results of this study by Wagner *et al* confirm the implications of the Lindenbaum article that there may indeed be significant differences in bioavailability among different brands of digoxin tablets, even though such tablets may meet all current U.S.P. requirements.

While it now seems likely that significant bioavailability differences among chemically equivalent brands of digoxin tablets pose a distinct concern for the pharmacist, it should also be noted that the two studies cited [2, 5], as well as other recent findings, indicate that there are three other types of bioavailability problems with digoxin: (a) Significant differences in bioavailability may be expected depending upon whether digoxin is administered by the oral or parenteral routes.[3] (b) Significant differences in bioavailability may be expected between oral tablets and oral solutions.[5, 6] (c) Significant variations in bioavailability may be found even among different lots of the same brand of digoxin tablets. The latter variations arise out of formulation changes made by the manufacturer, such as those which caused a doubling of the bioavailability of the innovator's brand of digoxin tablets in England last year.[7, 8]

While the topic of digoxin bioavailability will be treated in somewhat greater detail in the forthcoming Bioavailability Pilot Project report to be published by APhA, the findings summarized above make it apparent that the following points should be given serious consideration by pharmacists at this time:

(1) Therapeutic inequivalence may result from differences in bioavailability between different brands of U.S.P. digoxin tablets.

(2) Different dosage forms (e.g., elixirs vs tablets), even from the same manufacturer, are likely to differ in their respective bioavailability for the same labeled strength, and dosage adjustments may be advisable when transferring a patient from one form to another.

(3) Different lots of the same brands regardless of the manufacturer or source, may not be equally bioavailable and, therefore, they may not be therapeutically equivalent. Consequently, pharmacists might wish to consider recording the lot number of digoxin tablets dispensed as well as the brand.

(4) The evidence, as presented in the study by Wagner *et al*, as well at other studies, documents strongly the need for knowledgeable pharmacist input regarding the choice of manufacturer and in dispensing digoxin products. A pharmacist should not blindly rely on using any brand of digoxin (no matter what the size or reputation of the manufacturer); rather, he should continually seek to request and evaluate data on digoxin tablets from his sources.

It would definitely be in the public interest for the pharmacist to demand—as a condition of purchase—bioavailability data from the suppliers of digoxin tablets, and to be certain that such information is properly and carefully evaluated.

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EXHIBIT D

APhA Newsletter Jan. 19, 1974, page 4

Keep lot number, manufacturer's name of digoxin tablets

Standards and specifications relating to digoxin tablets have been revised and augmented several times during the past few years with the intent of providing greater assurance of uniform and predictable effectiveness and safety of this critically important drug. In each instance, the Food and Drug Administration has subsequently expanded its program of drug monitoring to incorporate the additional requirements.

In November 1973, by way of an interim revision, the *U. S. Pharmacopeia* adopted a dissolution test and specification for digoxin tablets, and it is expected that batches of tablets not meeting this new standard soon will be recalled by the FDA.

Meanwhile, it is recommended that pharmacists keep a record of the lot number and manufacturer's name of digoxin tablets dispensed to each patient, as a source of such information in the event it becomes needed for recall purposes, dosage adjustment, or other reasons.

Nominees sought for Smith Award consideration

Do you know a community pharmacist who has distinguished himself and the profession by outstanding professional performance? The APhA Academy of General Practice invites you to nominate candidates for the 1974 Daniel B. Smith Award.

Named after the community practitioner who served as the first President of APhA, Daniel B. Smith, the Award is the highest honor the Academy can bestow. It will be presented at the Academy Annual Luncheon during the APhA Annual Meeting in Chicago.

Obtain nomination guidelines and official forms by contacting the Academy, 2215 Constitution Ave., N.W., Washington, DC 20037. Deadline for receipt of nominations (on official forms only, please) is March 1.

What is continuing competence? How do you maintain it?

What is continuing competence? How do you measure it? How do you maintain professional competence once away from academe? The APhA-AACP Task Force on Continuing Competence in Pharmacy would like your ideas.

The Task Force is in the process of drawing up a statement of basic principles and policies regarding the continuing competence of pharmacists which should help the profession in developing and implementing programs to ensure continuing professionalism of pharmacy practitioners.

The Task Force already has solicited national pharmacy organizations for comments and now needs input from the "grass roots" level of pharmacy. The Task Force is meeting in the Spring; therefore, all response from individual pharmacists should be submitted by mid-March. Send your thoughts to the Hon. Elmer Andersen, Chairman, Task Force on Continuing Competence, 2215 Constitution Ave., N.W., Washington, DC 20037.

What do you think would constitute a pharmacy specialty?

You asked for it. Now it's your turn.

APhA formed a Task Force on Specialties in Pharmacy in response to a House of Delegates mandate last summer. The Task Force has met and has already developed some preliminary guidelines for identifying pharmacy specialties.

What are your ideas as to what constitutes a specialty in the profession? Are there any, and if so, how do you recognize them and administer them?

Watch for an article in the February issue of the APhA *Journal* highlighting the Task Force's progress thus far. And after perusing the *JAPhA* article, send your comments no later than April 1 to Task Force Chairman Lloyd M. Parks, 2215 Constitution Ave., N.W., Washington, DC 20037.

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EXHIBIT E

APhA Newsletter

Feb. 2, 1974, page 4

Digoxin recalls requested by FDA based on new dissolution requirements

The Food and Drug Administration has announced new, more stringent requirements for the manufacture of oral digoxin products. As a result, pharmacists should expect a recall of many digoxin tablets in the near future. Under the program, FDA will test individual batches for conformance with compendial standards, including dissolution. The FDA bases the new requirements on clinical data which show a significant correlation between *in vivo* bioavailability and *in vitro* dissolution rates. According to the FDA, the digoxin tablets that dissolved more rapidly demonstrated a higher bioavailability.

Because of the narrow margin between the therapeutic and toxic levels of digoxin and the potential for serious risk to cardiac patients using digoxin products which vary in bioavailability, the FDA has determined that immediate steps must be taken to assure improved uniformity of all digoxin products. This includes a recall of all digoxin products now on the market which do not meet the new requirements for *in vitro* dissolution rates.

The new dissolution requirements are based largely on a test procedure and specifications adopted in the Sixth USP Interim Revision Announcement of Nov. 15, 1973. Under the FDA requirements, the dissolution rate must always fall within a certain range; it is as unacceptable for a digoxin tablet to dissolve too rapidly as it is for the tablet to dissolve too slowly.

The FDA has stated that, as more definitive bioavailability data becomes available, still more stringent dissolution rate requirements may be set for digoxin.

Although complete information is not yet available on those manufacturers which will be requested by FDA to recall their digoxin, FDA initially has requested the following firms to recall certain lots of their digoxin products: Barr Laboratories, Inc. (lot 2221032); Blueline Chemical Company (lot 81335); Cord Laboratories, Inc. (lot 27781); Heather Drug Co. Inc. (lot 210073); E. W. Heun Company (lot MD578A); Kasco Efco Laboratories—E. Fougera and Company (lots 2087, 2635, 2768, 2819); Marshall Pharmaceutical Corporation (lots 7595, 7623); Parke Davis and Company (lot LG312A); Premo Pharmaceutical Laboratories, Inc. (lot B32817); Rexall Drug Company (lot D32014); and Stanley Drug Products, Inc. (lot 077306).

As noted in the Jan. 19 *Newsletter*, pharmacists should keep a record of the lot number and manufacturer's name of digoxin tablets dispensed to each patient in the event that the information is necessary for dosage adjustments of digoxin patients. FDA plans to advise practitioners of the changes in digoxin bioavailability resulting from product reformulations.

FDA is very apprehensive that patients now taking a digoxin product not conforming to the new requirements might now receive digoxin tablets of greater bioavailability and, hence, experience overdigitalization.

Needs of practitioners to highlight AGP sessions at 1974 APhA annual meeting

Effective communication with patients and prescribers and efficient management practices are both essential for a successful pharmacy practice, and the Academy of General Practice of Pharmacy has retained specialists in these fields for Academy sessions at the 1974 APhA Annual Meeting in Chicago.

Schmidt, Pryor and Company, a Kansas City management consultant firm, through a grant from the Upjohn Company, will present two sessions for practitioners, AGP President Donald O. Fedder announced after the Jan. 14-15 meeting of Academy Officers in Washington, D.C. The firm has had broad experience with pharmacists and other health care professionals.

Radioactive pharmaceuticals require special knowledge by pharmacists who handle them, and the Academy will attempt to serve the needs of these practitioners at the 1974 Annual Meeting by sponsoring a day-long symposium on the subject. The program will feature presentations on education, legal aspects, organization and operation of a nuclear pharmacy.

AGP Officers also approved preliminary plans for an all-day seminar on techniques of dosage form administration, to be co-sponsored by the Illinois Academy of Preceptors. The program, which will utilize pharmacists and nurses as instructors, will deal with such topics as rectal and vaginal dosage forms, oral liquids and solids, ophthalmics, otics, nasal preparations, pediatric dosage forms and injections.

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EXHIBIT F

AMERICAN PHARMACEUTICAL ASSOCIATION

The National Professional Society of Pharmacists

September 27, 1973

Director
Defense Supply Agency
Attention: DSAH-XA
Cameron Station
Alexandria, VA 22314

Dear Sir:

It is my understanding that the Defense Personnel Support Center headquartered in Philadelphia, Pennsylvania has specific responsibility within the Defense Supply Agency for the procurement of medical supplies -- and specifically drugs and drug products -- to fill the needs of the U. S. Department of Defense.

From time to time officials affiliated with the DPSC have described the procedures employed within that agency which are intended and desired to ensure that satisfactory quality drugs and drug products are purchased by them. In describing these procedures, the DPSC has indicated that a key feature in this process is the determination of the capabilities and qualifications of individual manufacturers -- such determination by DPSC is being made on the basis of certain criteria including inspection of the manufacturing plant facilities, testing of the pertinent firm's drug products within the DPSC's laboratory, and other appropriate considerations to enable such judgments to be made.

At various times, DPSC staff have referred to the fact that as a result of operation of the above described procedure, lists of drug company names (either alone or in association with specific drugs) have been developed which may be described as "lists of acceptable or qualified bidders" and/or "lists of unacceptable or unqualified bidders."

Under provisions of the regulation entitled, "Availability to the Public of Official Information," which was recently published in the Federal Register (38 FR 24206-24210) I am hereby requesting copies of any and all the above described lists of acceptable and unacceptable bidders for drug contracts over the past approximately five-year period.

Your assistance and cooperation in this regard will be greatly appreciated.

Sincerely,

Edward G. Feldmann, Ph.D.
Associate Executive Director
for Scientific Affairs

ehb

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CABLE ADDRESS: AMPHARMA

EXHIBIT G

DEFENSE SUPPLY AGENCY
HEADQUARTERS
CAMERON STATION
ALEXANDRIA, VIRGINIA 22314

IN REPLY REFER TO DSAH-PRS

18 OCT 1973

Mr. Edward G. Feldmann, Ph. D.
Associate Executive Director
for Scientific Affairs
American Pharmaceutical Association
2215 Constitution Avenue, N. W.
Washington, D. C. 20037

RECEIVED OCT 23 1973

Dear Mr. Feldmann:

We are in receipt of your 27 September 1973 letter requesting lists of acceptable or unacceptable bidders for drug contracts. Please be advised that such lists are not developed nor maintained by the Defense Personnel Support Center or the Defense Supply Agency. Thus, we cannot respond to your request for such information.

The Armed Services Procurement Regulation requires that we seek the widest possible competition on each procurement by providing all interested firms with a copy of the solicitation. However, before making each award, the contracting officer must affirmatively determine that the low bidder is responsible. The regulation specifies the standards of responsibility, sources of information and investigative procedures in order to insure that the contracting officer's determination is based on current and sufficient evidence. Since the contracting officer must affirmatively determine on each procurement that the low bidder is responsible, a bidder's failure to qualify as responsible on previous procurements does not preclude his qualifying as responsible on a subsequent procurement for which he submits the low bid. To maintain a list of unacceptable bidders would be inconsistent with this policy.

Sincerely,

PERRY E. KIMERER
Colonel, USAF
Chief, Quality & Production Division
Directorate, Procurement & Production

Buy U. S. Savings Bonds -- Payroll Savings Plan!

AMERICAN PHARMACEUTICAL ASSOCIATION
The National Professional Society of Pharmacists

March 29, 1974

Honorable Gaylord Nelson
Chairman, Subcommittee on Monopoly
Select Committee on Small Business
Room 424
Old Senate Office Building
Washington, DC 20510

Dear Senator Nelson:

I welcome the opportunity to respond to Mr. Stetler's March 5 letter which you transmitted to me with your cover letter dated March 25.

The primary thrust or thesis of my testimony was to show that: (a) the specification establishment program of the DPSC Branch of the Department of Defense resulted in specifications which were, or are, simply duplicative of official compendia standards; or (b) that in virtually all other cases, where such specifications are not duplicative, that they have no medical or therapeutic significance. This was my point in reviewing item-by-item the specifications material which DOD submitted to your Subcommittee and of which Propylhexedrine Inhalant, NF (mentioned at the bottom of page one of Mr. Stetler's letter) was referred to in my testimony. This fact is quite clear from the same transcript page mentioned in Mr. Stetler's letter (namely, transcript page 10257; lines 21-23) which reads:

> "Going on with the four examples from the National Formulary that were cited in their response to you, Mr. Chairman, under propylhexedrine inhalant NF, they specify..."

As an extension of the above mentioned thesis, I cited several DPSC purchase descriptions which contained requirements that in my opinion had no medical or therapeutic justification and which I stated (transcript page 10254; lines 18-19):

> "It would appear that such specifications may be largely geared or skewed around one particular formulation."

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The purpose of my testimony, therefore, was to bring to the Committee's attention that the purchase specifications were developed in such a way -- by including trivial and even nonsensical requirements having no medical purpose or quality function -- as to be designed around the specific product of a single source (i.e., manufacturer).

I believe that the text I presented completely supports that contention. Moreover, nothing in Mr. Stetler's letter appears to refute, nor attempts to refute, that contention.

In his letter, Mr. Stetler states that it was my "thesis that DPSC specifications are designed to exclude lower cost suppliers." Since I do not profess any expertise as an economist, I specifically avoided making any statements which would bear on the matter of cost factors or price competition. Specifically, (transcript page 10255; line 8) when you mentioned elimination of competition, I responded that while such an effect "would appear" to be the case, "I am not in a position to be able to draw a conclusion from these things..." Moreover, when the Minority Counsel spoke of relative costs, I responded (transcript page 10269; lines 13-17) by clarifying that the economic conclusions were drawn by the Committee Chairman, and that I was simply taking note of his conclusion to the effect that this might have economic consequences.

In other words, the thrust of my testimony was to demonstrate the fact that DPSC bid specifications by and large (a) did not result in a higher quality drug product, and (b) did result in excluding every manufacturer except for the one product around which the specification was clearly drawn. I used several specific examples to suggest that this was being done -- namely, the pentagonal shape of one tablet specification, the yellow color specified in another tablet specification, the light tan color specified for a sugar coated tablet, and the pink body and blue cap required in a capsule specification -- and then went on to emphasize even more emphatically the point I was making that such DPSC purchase descriptions are simply a transparent effort to select the product of a single manufacturer, without explicitly so stating.

It was at this point in my testimony that I made the statement quoted in Mr. Stetler's letter to the effect "Now the message begins to come through here a little bit..." The examples I cited with respect to clindamycin hydrochloride hydrate capsules

and clomiphene citrate tablets were so carelessly prepared by DPSC that in the case of clindamycin hydrochloride hydrate capsules DPSC had obviously used draft language apparently obtained from the Upjohn Company, since DPSC inadvertently neglected to change the reference to another Upjohn drug -- namely lincomycin -- within that original clindamycin purchase description. Furthermore, as quoted in my testimony, the William S. Merrell trade name (Clomid) was indeed included in the clomiphene citrate purchase description.

Mr. Stetler, in his letter, mentions that the particular four drugs (out of the many mentioned during the testimony) are sole source products currently available only from single suppliers. Mr. Stetler is probably correct, but he neglects to point out that as soon as drugs go off patent there are generally a number of other firms which will immediately market competing products, and indeed some firms will even grant cross-licenses for products while they are still under patent. Consequently, if the DPSC specification today "locks-in" to one company's peculiar product characteristics, it would virtually guarantee a perpetual monopoly after the drug goes off patent -- that is, by this process, they have effectively and ingeniously circumvented those requirements, such as bidding by generic name, which are intended to instill genuine competitive bidding. [Ironically, if a future competitor were to produce a dosage form which so resembles the original producer's product as to be "pentagonal" in shape or to have "a pink body and a blue cap" the Pharmaceutical Manufacturers Association would loudly cry out -- as they have in the past -- that the second firm's product was a "counterfeit" purposely designed to resemble the original producer's article!]

In the final paragraph of Mr. Stetler's letter, he mentions that "contrary to the impression given in Dr. Feldmann's reported testimony, lincomycin is not a 'trade name' for clindamycin." Mr. Stetler is quite correct in this regard. Whether it was an error in the stenographer's transcript, or whether it was an inadvertent slip of the tongue on my part -- prior to the date of Mr. Stetler's letter -- I had already reported that (transcript page 10257; line 7) the words "trade name" (rather than "drug name" as I had intended to say) appear in the uncorrected transcript. An appropriate correction to this statement was entered on the draft transcript which was returned to the Subcommittee in early March. The point I was making, however, would have been equally valid in either case; namely, that a specific company's specification sheet was being used to draw unnecessarily restrictive specifications for another product produced by that same company. [Furthermore, another example which included a drug trade name (Clomid) was given immediately thereafter in my testimony.]

With this single clarification for the word "lincomycin," I believe that all aspects of the testimony I presented were accurate in every respect. Moreover, as you are aware, as enclosures to my letter dated February 25, addressed to you as Subcommittee Chairman, for examination and verification purposes, I supplied the Subcommittee with copies of all the documents referred to in my testimony, including the DPSC purchase specifications pertaining to the articles referred to in Mr. Stetler's letter.

Consequently, while I agree with Mr. Stetler's conclusion "that damaging inferences" could be drawn from my testimony, it is my opinion that these damaging inferences are justified and substantiated. Moreover, it is also my opinion that he has attempted to perpetuate a typical drug industry "snow job" on your Subcommittee in asserting that what I presented constituted "misinformation."

Sincerely,

Edward G. Feldmann, Ph.D.
Associate Executive Director
for Scientific Affairs

EGF:ehb

cc: Mr. John O. Adams, Minority Counsel
Mr. C. Joseph Stetler, PMA

United States Senate
SELECT COMMITTEE ON SMALL BUSINESS
(CREATED PURSUANT TO S. RES. 58, 81ST CONGRESS)
WASHINGTON, D.C. 20510

March 25, 1974

Dr. Edward Feldmann
American Pharmaceutial Association
2215 Constitution Avenue, N. W.
Washington, D. C. 20037

Dear Dr. Feldmann:

Enclosed is a copy of a letter which the Subcommittee received from Joseph Stetler, President of the Pharmaceutical Manufacturers Association.

It would be greatly appreciated if you would send me your comments on Mr. Stetler's claims.

Sincerely,

GAYLORD NELSON
Chairman
Subcommittee on Monopoly

Encl.

PHARMACEUTICAL MANUFACTURERS Association

C. JOSEPH STETLER
PRESIDENT

1155 FIFTEENTH STREET, N.W.
WASHINGTON, D.C. 20005
AREA CODE 202-296-2440

March 5, 1974

The Honorable Gaylord Nelson
Chairman, Subcommittee on Monopoly
Senate Small Business Committee
United States Senate
221 Russell Senate Office Building
Washington, D. C. 20510

Dear Senator Nelson:

As you are aware, the PMA did not request an opportunity to testify at your current hearings on the procurement policies of the Defense Supply Agency. We felt, and still feel, that it was the province of the government agencies involved to respond to any criticisms which might be expressed at the hearings.

On reading the transcript of the hearing for February 21, however, it struck me that it was important that there should be some correction, in the record, of certain statements by Dr. Edward Feldmann of the American Pharmaceutical Association.

As an example to illustrate his thesis that DPSC specifications are designed to exclude lower cost suppliers, Dr. Feldmann stated, according to page 10257 of the transcript:

> "Now the message begins to come through here a little bit. When one reads their purchase description for clindamycin hydrochloride hydrate capsules, on which they issued a correction that under the assay the word lincomycin is deleted, and substitute clindamycin. This suggests to me that the specifications may, or must have been written from a draft that had that trade name originally, and they forgot to delete it in one case."

On the same page, Dr. Feldmann gives two other examples of allegedly discriminatory specifications, for clomiphene citrate in which the brand name of Merrell's Clomid is specifically mentioned, and that of propylhexedrine inhalant NF (SKF's Benzedrex).

Dr. Feldmann's story of the deletion of the word "lincomycin" and the mention of the trade name "Clomid" apparently made quite an impression on the Subcommittee and its staff, for on page 10267 it states that Mr. Adams questioned Dr. Feldmann on these cases and was assured that they were being correctly reported.

I feel that the Subcommittee should be aware of the fact that all four of these drugs are sole source products. Since they are available only from single suppliers, I fail to see how the form of DPSC's specifications could be considered to have excluded potential competitors.

Furthermore, and contrary to the impression given in Dr. Feldmann's reported testimony, lincomycin is not a "trade name" for clindamycin. It is the official or generic name for the active ingredient in Upjohn's patented Lincocin. Clindamycin, although a related compound, is distinct and separate, with different indications. It is the generic or official name for the active ingredient in Upjohn's patented Cleocyn antibiotic. In view of the damaging inferences drawn from the misinformation presented by Dr. Feldmann, it is important that the record be corrected.

Sincerely,

C. Joseph Stetler

cc: Mr. John O. Adams
Minority Counsel

EXHIBITS PROVIDED BY THE UNITED STATES PHARMACOPEIA

Statement by: Dr. Daniel Banes
Director, Drug Standards Division
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, Maryland 20852

Before: Subcommittee on Monopoly
Senate Small Business Committee

Date: February 21, 1974

I am Daniel Banes, Director of the Drug Standards Division of the United States Pharmacopeia, a quasi-public, non-profit scientific institution whose published standards, tests and methods are recognized by law as officially authoritative. I have been active in that position since April, 1973. Previously, I had been an officer of the Food and Drug Administration for thirty-four years, having served as a research chemist specializing in the analysis and standardization of drugs, as Director of the Division of Antibiotics, as Director of the Office of Pharmaceutical Research and Testing, and as Associate Commissioner for Science. During the past decade, I also have been, and I continue to be, a consultant to the World Health Organization on drug standards, on measures for improving the quality of drug products throughout the world, and on the enforcement of drug control laws. For the past two decades, I have held a faculty appointment as Adjunct Professor of Chemistry at the American University in Washington, D. C., where I teach courses on the chemistry of drugs and the control of drugs. Thus, my entire professional career has been devoted to service in the public sector, and has been directed primarily toward improving the quality of drugs by the application of scientific principles and scientific findings.

I am grateful for your invitation to discuss with you the question proposed by your Subcommittee, namely, how well is the quality of the nation's drug supply being monitored and protected by our system of compendial specifications and standards coupled with FDA's enforcement of them? My answer, in brief, is that the system is working quite well, comparatively speaking, but that it could and should be working much better. I should like to enlarge upon that response in several dimensions.

In the first instance, if we consider progression on a time-scale, there can be no doubt that the standards and specifications of the United States Pharmacopeia are far more perceptive and more demanding than they were thirty-five years ago. Similarly, the potentialities of the Food and Drug Administration in monitoring the quality of our drug supply have been considerably extended during that time. The regulatory powers of the Food and Drug Administration have been significantly strengthened by several amendments to the Federal Food, Drug and Cosmetic Act of 1938 -- most notably the Kefauver-Harris Amendments of 1962, and the Good Manufacturing Practice provisions of that Amendment. Furthermore, the remarkable advances in all of the pharmaceutical sciences during the past three decades and particularly in drug analysis and biopharmaceutics, have stimulated the adoption of more exacting requirements in governmental and pharmacopeial standards and in manufacturers' drug quality control programs.

Second, if we compare the quality of the drug supply and the effectiveness of drug regulation in the United States with those encountered elsewhere, we can again affirm that we have much to which we can point with pride. The drug industry of the United States, the U. S. Food and Drug

Administration and the United States Pharmacopeia are generally cited as the hallmarks of preeminence in pharmaceutical circles throughout the world. Only Canada, Scandinavia, and Western Europe approach or equal the levels of excellence that we have established; none surpass them to a significant degree.

A third dimension to be considered in evaluating the effectiveness of the present system is the climate of attitudes toward the regulation of drug production and distribution. It seems to me that there is a growing recognition among drug manufacturers that strict compendial standards and active governmental enforcement of these standards -- measures intended primarily to protect the consumer -- also benefit the drug industry itself. I base this statement on the observation that many quality control scientists employed by industry now collaborate actively on a voluntary basis in helping to improve the standards and specifications of the USP for use as regulatory measures by the enforcement agency. Such an attitude not only reflects an awareness among enlightened members of the industry that these endeavors are necessary to assure the quality of drug products in the market and to protect the good health of both the consumers and the producers. It also results in adherence to good manufacturing practices within the factory, and the establishment of strict internal quality controls.

Please note that I have referred to enlightened members of the industry, for it must be admitted that the laudable attitude I have described does not command a unanimous consensus. In my ministrations as Director of the USP Drug Standards Division, I have sensed a reluctance on the part of some few companies to release scientific information necessary to the progressive

development of sound public standards for drugs. Previously, as an official of the Food and Drug Administration, I had reason to believe that more than a few companies were oblivious to the principles of good manufacturing practices and quality control.

At USP, we rely exclusively upon voluntary cooperation and the assessment of empirical scientific evidence by peer group review. Withholding of significant new data would result in the persistence of mediocre, archaic standards and analytical tests, unless the missing information can be developed by more cooperative scientists elsewhere in industry, or by research laboratories in the academic or governmental sectors. Fortunately, we have been able to enlist the aid of several interested research laboratories in this enterprise, particularly those of the Food and Drug Administration.

Another avenue for eliciting information leading to the revision of tests and standards is a new USP publication entitled "Comment Proof." This periodical, circulated on subscription, shows the tentative monographs for drug articles and the chapters on general tests proposed for adoption in forthcoming USP issuances, after deliberations by panels of USP advisors. The USP Committee of Revision receives comments and recommendations for changes in these proposals from representatives of trade associations and of individual manufacturers; from government officials, including those from the Defense Personnel Supply Center, the National Institutes of Health, the Veterans Administration and the Food and Drug Administration; from scientists in schools of pharmacy and medicine; from scientists associated with foreign pharmacopeias, foreign companies and foreign governments; and from unaffiliated scientists writing as private individuals. It is my responsibility to review these comments, in concert with the responsible

subcommittees of the USP Committee of Revision. We then incorporate those changes that are deemed scientifically valid and explain to proponents why certain changes they suggested have not been adopted. In this manner, the USP evolves publicly scrutinized, objective, scientifically verified standards, and practicable tests and assays, through the collaborative efforts of disinterested scientists. Except for their voluntary contributions of time expended in the laboratory and elsewhere, USP receives no financial grants from government, industry or any academic institution. It is entirely self-supporting through the sale of the compendium and related publications, and through the sale of reference materials used in analytical methods.

USP does receive funds for services rendered under not-for-profit contracts with government agencies where these projects bear upon the improvement of standards or test procedures, regardless of whether the drug products involved are USP articles. Although USP is increasing its standards-setting activities and USP XIX now in preparation will contain 38% more monographs for drugs than USP XVIII, the fact is that there will be no public compendial standards for more than half the drug products on the market. We believe that USP could quickly move to fill this void with appropriate support through not-for-profit contracts.

We must recognize, however, that regardless of the virtues written into compendial standards, they will remain meaningless dead letters unless they are effectively enforced. Under delegation of authority from the Secretary of HEW, the Food and Drug Administration is charged with responsibility for enforcing the provisions of the Federal Food, Drug and Cosmetic Act. The agency cannot discharge its responsibilities adequately unless it

has the requisite information and resources.

We are aware of charges that FDA does not inspect drug factories frequently enough to determine whether good manufacturing practices are in fact observed, or has failed to take notice of defective manufacturing practices known to officials from other agencies. In regard to the latter charge, it would be well to ascertain whether the alleged violations were indeed called to the attention of the responsible agency in a timely manner, and if not, why not? Unless the Food and Drug Administration has authenticated information, it cannot be expected to initiate punitive or corrective action. It is our impression that FDA does react rapidly to rectify problem situations. Under a recently instituted project, USP has been in a position to bring certain drug product problems to the attention of both FDA and the drug industry. To our knowledge, FDA has moved promptly to investigate these problems and to deal with them.

The other charge, relating to a low frequency of factory inspections, is far more serious in its implications. If it is true that FDA cannot investigate and correct poor manufacturing conditions among unenlightened producers because it does not have an adequate force of trained drug inspectors, then there is indeed a deficiency in the present enforcement of drug control standards. If this deficiency exists, it must be eliminated as rapidly as possible. It seems to me that if there is a group of trained drug inspectors elsewhere in government agencies, they should be transferred to the Food and Drug Administration forthwith, in accordance with the principle that the agency responsible for enforcing the law should be given the needed resources that will enable it to do so effectively. Furthermore, a cadre of

inspectors within FDA should be trained intensively for drug work and centralized under the direction of the agency unit responsible for monitoring drug quality. Specialization and centralization has markedly improved the efficiency of the FDA analytical drug laboratories during recent years. A similar regrouping of its drug inspection capabilities should likewise result in more efficient operations.

I believe that the measures proposed for strengthening the drug control apparatus of FDA, together with our own progress in strengthening USP will eventually permit an unreservedly affirmative answer to your original question -- that the system for monitoring and protecting the quality of the nation's drug supply is working very well, indeed.

If you have any questions, I should be pleased to respond. Thank you.

THE UNITED STATES PHARMACOPEIA

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(301) 881-0666

DANIEL BANES, PH.D.
Director, Drug Standards Division

February 28, 1974

Mr. Benjamin Gordon
Staff Economist, Senate Select
Committee on Small Business
424 Russell Senate Office Building
Washington, D. C. 20510

Dear Mr. Gordon:

In response to your telephone call of 27 February 1974, I have perused the 67-page compilation on "Additional Requirements" submitted by the Department of Defense to the Subcommittee on Monopoly of the Senate Select Committee on Small Business. These documents, supplementing a similar list previously transmitted to you, comprise a catalog of about 500 drug products for which the Department of Defense is said to "develop definitive product specifications which often exceed official or commercial standards."

When I testified before the Subcommittee on Monopoly, I stated that in those few instances where the Department of Defense specifications have been considered scientifically significant and have served to strengthen the standards for a drug product, the United States Pharmacopeia has moved to adopt the modifications. In my testimony, I cited actual examples to illustrate that statement. The same observation holds for the supplementary listing now before us. It contains about 200 USP articles. Except for five or six articles, none of the so-called "definitive product specifications which exceed official standards" can be considered suitable candidates for adoption in the United States Pharmacopeia. From the standpoint of USP, the others are either irrelevant, trivial or superfluous.

The most frequently occurring entries under "Additional Requirements" are the phrases: "Classification of Defects" and "maximum unrefrigerated shipping time for items requiring refrigeration." Neither is germane to USP standard-setting.

Another commonly encountered "requirement" is "Free from sediment" for certain fluid drugs (e.g. Cinnamon Oil on page 1, Diphenhydramine Hydrochloride Elixir on page 2, etc.) which is said "to assure best production procedures and controls are utilized consistent with good manufacturing practices." This "additional requirement" is redundant; drugs in solutions by definition should be free from solids of all kinds, including sediments.

In many instances, the so-called "additional requirements" are trivial with respect to drug standardization, whatever their merit may be otherwise. Examples are the color of Ethinyl Estradiol Tablets and palatability of Meclizine Hydrochloride Tablets (page 17). These attributes may be of utility and importance to the consumer, but they are not properly subjects for strict USP standard-setting.

An example of a superfluous "additional requirement" is the test for loss on drying for Meclizine Hydrochloride Tablets (page 17). The Department of Defense states that this test is intended "to assure the stability of the product, in that excessive moisture may cause deterioration." To our knowledge, USP has received no scientific data to support this statement from either the Department of Defense or regulatory agencies, or from users or manufacturers of the product. In the absence of such supporting information, we would see no reason for adopting the proposed standard.

An "additional requirement" for Mannitol USP (page 38) is that it shall be free of boron because "the item is used in water chemistry control." USP is concerned with setting standards for articles to be utilized as drugs, not for any other purposes.

In my opinion, the documents submitted to you contain but few authentic examples of definitive product specifications that exceed present USP standards.

Sincerely yours,

Daniel Banes, Ph.D.

DB/ps

SYNTEX (U.S.A.) INC.
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DR. ALBERT BOWERS
PRESIDENT
(415) 855-6363

March 8, 1974

Senator Gaylord Nelson
Room 221
Old Senate Office Building
Washington, D.C. 20510

Dear Senator Nelson:

Although we have not yet seen a transcript of the March 5 hearings of the Senate Small Business subcommittee, we would like to take strong exception to a statement made concerning Syntex.

Our source is a Washington Post article on March 6 which said that "... Veteran Administration officials told Nelson yesterday about 'serious problems' recently with three companies. They said V.A. inspectors found 'bacterially contaminated' capsules at a Syntex plant".

The facts are that Syntex received empty capsules from a regular supplier. Routine Syntex inspection procedures indicated that these capsules were questionable. These questioned capsules were placed in quarantine and were not used in any products distributed or sold.

This was told to a V.A. inspector during a normal plant visit early in February. Far from evidencing a "serious problem", this situation demonstrated the effectiveness of Syntex quality control procedures in discovering and isolating questionable material received from an outside supplier.

We want the subcommittee to have this additional information, and we also request that the letter be included in the hearing record.

Yours sincerely,

Albert Bowers

AB:jb

AMERICAN PHARMACEUTICAL ASSOCIATION
The National Professional Society of Pharmacists

WILLIAM S. APPLE, Ph.D.
Executive Director

August 13, 1974

Mr. Benjamin Gordon
Staff Economist
Select Committee on Small Business
Monopoly Subcommittee
United States Senate
Room 424 - Old Senate Office Building
Washington, D. C. 20510

Dear Mr. Gordon:

During the February 21, 1974 hearings of the Subcommittee, you requested that we attempt to identify drug manufacturing firms which are frequently characterized as "schlock manufacturers."

This is to advise you that we asked our Academy of Pharmaceutical Sciences, which has been most verbal in challenging the Association's opinion that the quality of the nation's drug supply is very high, to have their members identify firms which they individually regard as warranting the characterization "schlock manufacturers."

This is to advise you that the Academy of Pharmaceutical Science leadership has declined to query its membership on the grounds that its members, which might have such information, did not wish to incur the risk of a libel suit by gratuitously disclosing that information in public. It has always been my understanding that any such information provided a Congressional Committee would not be actionable. It was their further opinion that such information should come directly from FDA.

I personally have met with the leadership of the APS on numerous occasions, during which generalized disparaging comments were made about the ability of some manufacturers to produce quality products. When I have asked them to name names, they have refused.

While we regret we are unable to furnish the Subcommittee with the information requested, we feel that your inquiry has served a useful purpose, namely to put everyone on notice that your Subcommittee expects those who question the quality of the nation's drug supply and FDA enforcement of the laws assuring that quality to come up with hard facts if they wish to have their charges seriously considered.

Sincerely,

William S. Apple

WSA:lf