NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Mepivacaine Hydrochloride Injection, NF, 2%, 20 cc Mepivacaine Hydrochloride Injection, NF, 1.5%, 30 cc Mepivacaine Hydrochloride Injection, NF, 1%, 30 cc Mepivacaine Hydrochloride Injection, NF, 1%, 50 cc	Classification of Defects Color Limits	See Explanatory Notes. See Explanatory Notes.
Nortriptyline Hydrochloride Capsules, NF, Equivalent to 25 mg. Nortriptyline Base, 100s	Classification of Defects	See Explanatory Notes.
Isoproterenol Hydrochloride Injection, USP, 0.2 mg, 1 cc, 5s	Color Limits Classification of Defects Leakage test for ampuls Additional Assay	See Explanatory Notes. See Explanatory Notes. See Explanatory Notes. This additional assay method was necessary since the fluorometric procedure is more specific for the isoproterenol molecule in that a trihydroxindole derivative is formed with intact isoproterenol.
Prednisolone Tablets, USP, 5 mg, 1000s	Moisture Content Classification of Defects	To assure the stability of the product, in that excessive moisture may cause deterioration. See Explanatory Notes.
Methyldopa Tablets, USP, 0.25 Gram, 100s	Hardness limits Classification of Defects Accelerated aging test	See Explanatory Notes. See Explanatory Notes. See Explanatory Notes.
Medroxyprogesterone Acetate Tablets, USP, 10 mg, 100s	Classification of Defects	See Explanatory Notes.

Kapco Inc.

Sodium Aminosalicylate Tablets

Major Deficiencies

1. Failure to provide adequate space for orderly placement of materials to minimize any risk of mix-ups between components.

Commingling of approved material, material with no approval sticker and in-process material with no indication of approval for use in the storage area for approved materials.

In addition, an affiliate company utilizes approximately 25% of the warehouse for general equipment and raw material storage.

2. Laboratory Control Deficiency

In complete testing of incoming raw materials.

Suppliers' protocols missing to substantiate material approved for use.

3. Production Control Deficiency

Lack of adequate control to ensure that only approved material is issued for manufacturing purposes.

4. Common loading platform for shipping and receiving is not arranged to prevent the commingling of incoming and outgoing material.

5. Unsanitary household practice.

Food is stored and eaten in the packaging room.

Richlyn Labs.

Major Deficiencies

1. Staffing Deficiency

Failure of one supervisor to have technical qualifications for the necessary supervisory functions. Another supervisor who is a chemist with pharmaceutical experience cannot allocate adequate time for supervision between operations of Richlyn and another affiliated company.

Inadequate laboratory supervision and technical review by chemist in charge.

Release of a batch which should have been rejected by the chief chemist based on test data indicates violation of quality assurance.

2. Laboratory Control Deficiency.

Incomplete and improper testing of raw material.

Failure to reject material in non-compliance with applicable specifications.

3. Production Control Deficiency

Absence of specific instructions on the Master Formula and production records for the manufacture of each item. Personnel manufacture in accordance with their experience rather than with delineated procedures. This may create non-uniformity of finished product.

Failure to record total granulation weight on batch production record in accordance with company requirements, thus recluding checks of theoretical yield against actual yield.

Absence of temperature recorder in drying oven to verify temperature used in drying granulation. Temperatures of all ovens varied although temperature control settings were the same.

4. Poor Housekeeping

Regular cleaning failed to remove drug residues or dirt accumulations on drying racks, walls, floors, containers tabletting machine and filter in air system supply heat to drying ovens, thus resulting in the possibility of cross contamination of product.

Exhaust fan in weighing room not screened, thus creating possibility of entrance of flies and other flying insects.

	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Hydrogen Peroxide Solution, USP, 3 % (30 cc.6 Grams)	Free from sediment	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	Color limits	See Explanatory Notes
	pH limits	The USP monograph has no specific requirement for pH. This requirement is to assure greater stability over the shelf life of the items.
	Preservative shall be present.	USP monograph states that a preservative "may be present". By our P. D. requiring the presence of a preservative, we are assuring greater stability of the item.
	Classification of Defects	See Explanatory Notes
Meglumine Iothalamate Injection, USP, 60%, 30 cc, 25s	Classification of Defects	See Explanatory Notes
Potassium Chloride Injection, USP, 2 Molar, 10 cc, 6s	Classification of Defects Color limits Leakage Tests for Ampuls	See Explanatory Notes See Explanatory Notes See Explanatory Notes
Nystatin Tablets, USP, Oral, 500,000 Units, 100s	Classification of Defects	See Explanatory Notes

[illegible]	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Potassium Phenoxymethyl Penicillin Tablets, USP, 400,000 Units, Individually Sealed, 100s	Classification of Defects Accelerated Aging Test Tighter lower limit for assay and an upper assay limit	See Explanatory Notes. See Explanatory Notes. The tighter lower limit for assay assures the best production procedures and controls are utilized and the restricted upper limit will preclude possibility of use of superpotent material. No upper assay limit given in regulations.
Potassium Phenoxymethyl Penicillin Tablets, USP, 800,000 Units, Individually Sealed, 100s		
Propantheline Bromide, Sterile, USP, 30 mg, 25s	Classification of Defects Solubility Time Limit Ultraviolet and infrared identity active ingredient	See Explanatory Notes. See Explanatory Notes. A more definitive identification for the active ingredient.
Propoxyphene Hydrochloride Capsules, USP, 65 mg, 500s	Classification of Defects	See Explanatory Notes.
Propoxyphene Hydrochloride Capsules, USP, 65 mg, Individually Sealed, 100s		
Menthol, USP, 1 oz (28.35 Gram)	Levorotatory	The Synthetic levorotatory form is subjected to more purification to eliminate stereoismers which may possibly differ in pharmacological action.
Nystatin Ointment, USP, 30 Grams	Leakage Test	To assure that the tubes of ointment do not leak.
Sodium Pentobarbital Capsules, USP, 100 mg, Individually Sealed, 25s	Classification of Defects	See Explanatory Notes.
Sodium Lactate Injection, USP, 1/6 Molar, 1000 cc, 6s	Classification of Defects	See Explanatory Notes.
Dioctyl Calcium Sulfosuccinate Capsules, NF	Classification of Defects Leakage Test	See Explanatory Notes. To assure that the liquid fill does not leak

Bell Pharmacal Corp.
Table Rock Labs. Division

Major Deficiencies

Surveyed and Rejected by the Veterans Administration.

STANLABS

Codeine Sulfate Tablets
Calcium Lactate Tablets

Major Deficiencies

1. Laboratory Control Deficiency

Absence of written laboratory test methods setting forth test procedures.

Incomplete monograph testing of raw materials.

Absence of in-house standards of finished product to provide uniformity of product. Examples: Company has no standard for hardness of compressed tablets indicating lack of quality of control. Further, firm uses Pfizer tester and Monsanto Tester. No correlation in hardness test values found between the two.

Incomplete testing on finished product.

2. Production Control Deficiency

Failure of Master Formula and Batch Production Record to be exact duplicate. Example: Batch Production Record specifies "Plasdone C" whereas the Master Formula indicates "Plasdone".

Failure to perform inspection of end item in accordance with established sampling plan and classification of defects, thus creating the possibility of non-uniformity of product.

Weighing area for raw material batch components adjacent to open receiving area to street. Flies and other insects accessible to contaminate raw materials.

Batch formulations ready for compression stored in reused fibre drums bearing identification of previous contents creates the possibility of product mix-up and mislabeling.

Reuse of fibre drums without new polyethylene liners creates the possibility of product contamination.

3. Defective overhead construction and openings in walls that permits contamination of products being manufactured.

4. Failure of Regular cleaning to remove drug residues from manufacturing equipment may result in cross-contamination. Drains in production area covered with slime.

ITEM	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Reserpine Tablets, USP, 0.25 mg, 1000s	Classification of Defects	See Explanatory Notes.
Isoniazid Tablets, USP, 0.3 Gram, 100s	Classification of Defects	See Explanatory Notes.
Isoniazid Tablets, USP, 100 mg, 100s	White Tablets	To limit deterioration which is evidenced by discoloration.
Pseudoephedrine Hydrochloride Syrup, NF, 30 mg per 5 cc, 1 pt (473 cc)	Taste/Palatability For Active Ingredient: Tighter Melting Range Tighter Specific Rotation	See Explanatory Notes. To reduce incidence of impurity isomers.
Pseudoephedrine Hydrochloride Tablets, NF, 30 mg, 100s	Classification of Defects For Active Ingredient: Tighter Melting Range Tighter Specific Rotation	See Explanatory Notes. To reduce incidence of impurity isomers.
Pyrimethamine Tablets, USP, 25 mg, 100s	Classification of Defects	See Explanatory Notes.
Promazine Hydrochloride Injection, NF, 50 mg per cc, 2 cc, 25s	Classification of Defects	See Explanatory Notes.
Prochlorperazine Suppositories, NF, 2.5 mg, 6s Prochlorperazine Suppositories, NF, 25 mg, 6s	Melting Point	To assure that the suppositories are made with a base which will melt within a specified time frame to release its medicament. No such requirement exists in the compendia.
	Accelerated Aging Test	See Explanatory Notes.
	Limits for Foreign Substances (Color, Unchlorinated Compound for Active Ingredient and 4-Chlorophenothiazine for Intermediate)	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.

ITEM	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Fibrobamate Tablets, USP, 0.4 Gram, 500s	Limits for Foreign Substances (chloride test, Residue on ignition) for active ingredient	To assure that impurities are detected that may arise from production procedures or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	Accelerated Aging Test	See Explanatory Notes
	Classification of Defects	See Explanatory Notes
Sodium Ethacrynate for Injection, USP, Lyophilized Equivalent to 50 mg of Ethacrynic Acid	Classification of Defects	See Explanatory Notes
	Solubility.Time Limit	See Explanatory Notes
Sodium Oxacillin Capsules, USP, Equivalent to 0.5 Gram of Oxacillin in each Capsule, 100s	Classification of Defects	See Explanatory Notes
	Weight Variation	The USP monograph and CFR do not specifically require compliance with weight variation for this item. Our requirement assures uniform quantity within limits and thus proper uniform dosage.
Propantheline Bromide Tablets, USP, 15 mg, 100s Propantheline Bromide Tablets, USP, 15 mg, 1000s	Classification of Defects	See Explanatory Notes
	Accelerated Aging Test	See Explanatory Notes
	Limits for foreign impurities (Completeness of solution and Infrared spectrum) for active ingredient	To assure that impurities are detected that may arise from production procedures or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.

32-814 (Pt. 24) O - 74 - 14

Kirkman Labs.

FSN 6505-110-4075 Bismuth Subcarbonate Tablets

Major Deficiences

1. Production Control Deficiency

Inadequate Master Formula and Batch Production Record. Lack of explicit instructions, precautions as to steps to be followed in preparation of the drug which may lead to non-uniformity of batches.

Operating personnel unaware of in-process test standards. Although in-process testing is conducted, it is not known when to take corrective action.

Use of city water instead of purified water in batch formulations. This may affect the purity of the product.

Lack of traceability of water used in batch formulations.

2. Housekeeping Deficiencies.

Potential for product contamination exists due to:

Absence of covers on hoppers of tabletting presses.

Failure of tabletting operators to wear suitable head covering to prevent the possibility of hair, dandruff from falling into the powder.

Insects may enter granulation in drying oven from the outside through oven exhause.

Strong Cobb Arner

FSN 6505-550-8464 Meprobamate Tablets

Major Deficiencies

New plant where bid item is to be produced is not yet in operation.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Thimerosol Tincture, NF, 1 pt (473 cc)	Free from Sediment	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
Thiamine Hydrochloride Injection, USP, 100 mg per cc, 10 cc	Classification of Defects Color limits	See Explanatory Notes. See Explanatory Notes.
Thiethylperazine Maleate Tablets, NF, 10 mg, 100s	Classification of Defects Hardness	See Explanatory Notes. See Explanatory Notes.
Oxyphenbutazone Tablets, NF, 100 mg, 1000s	Classification of Defects	See Explanatory Notes.
Ethosuximide Capsules, USP, 0.25 Gram, 100s	Classification of Defects	See Explanatory Notes.
Triamcinolone Acetonide Aerosol, NF, 0.0066%, 150 Grams	Spray delivery Moisture	To assure rate of delivery. To assure the stability of the product, in that excessive moisture may cause deterioration.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Sulfadiazine tablets, USP, 0.5 Gram, 1000s	Classification of Defects Limits for foreign substances (color, chloride and sulfate) for active ingredient	See Explanatory Notes. To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
Triamcinolone Diacetate Suspension, Sterile, NF, 40 mg per cc, 5 cc	Classification of Defects Particle size of Triamcinolone Raw Material	See Explanatory Notes. This requirement was added to control the particle size of the active ingredient in the long acting parenteral suspension. Particle size is related to the release rate. This requirement is not covered by the NF monograph.
	Pyrogen test	To assure that pyrogens are not present.
Tolbutamide Tablets, USP, 0.5 Gram, 200s	Classification of Defects	See Explanatory Notes.
Tolazamide Tablets, USP, 250 mg, 100 1000s	Classification of Defects Moisture	See Explanatory Notes. To assure the stability of the product, in that excessive moisture may cause deterioration.
Thimerosal Solution, NF, 1 pt (473 cc)	Color limits	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.

As is the custom the FDA is advised of all plant survey rejections when Quality Control and Housekeeping deficiencies are the cause of the rejection. The normal method is by mail. This was followed in the cases cited above except for the ICN (Strong Cobb Arner) rejection, since our telecons with the FDA revealed that they were aware of the relocation of the plant and the fact that they had not yet been registered or inspected by the FDA. Accordingly, no letter was forwarded.

Encl

Barr Labs.

Pyridoxine Hydrochloride Tablets
Dyphenhydramine Hydrochloride Tablets

Major Deficiencies

Plant Deficiencies

Incomplete raw material testing.

Production equipment not cleaned before and after use.

Live spider in drying oven.

Inadequate quarantine of raw material.

No Calibration program.

	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Spectinomycin Dihydrochloride, Sterile, Equiv to 2 Grams of Spectinomycin Spectinomycin Dihydrochloride, Sterile, Equiv to 4 Grams of Spectinomycin	Classification of Defects Solubility Time Limit Weight Variation	See Explanatory Notes. See Explanatory Notes. The CFR does not specifically require compliance with content uniformity for this item. Our requirement assures uniform quantity within limits and proper and uniform dosage.
Cyclophosphamide Tablets, USP, 50 mg, 100s	Classification of Defects Hardness Limits Moisture	See Explanatory Notes. See Explanatory Notes. To assure the stability of the product, in that excessive moisture may cause deterioration.
Tropicamide Ophthalmic Solution, USP, 1%, 15 cc	Free from Sediment Tighter Lower pH Limit	To assure the best production procedures and controls are utilized consistent with good manufacturing practices. To assure greater stability over the shelf life of the item.
Vincristine Sulfate for Injection, USP, 5 mg Vincristine Sulfate for Injection, USP, 1 mg	Classification of Defects Maximum Unrefrigerated Shipping Times for Items Requiring Refrigerated Storage	See Explanatory Notes. See Explanatory Notes.
Tolnaftate Solution, USP, 1%, 10 cc	APHA Color Free from Foreign Particles	To assure that impurities are detected that may arise from production procedures, or from changes in sources of material, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
Estrogens, Conjugated, For Injection, USP, Freeze-Dried, 25 mg	Classification of Defects Limits of: 17α-dihydroequilin 10.0-20.0% 17α-estradiol 3.0-5.0% Equilenins Max 15.0%	See Explanatory Notes. Without these limits pharmacologic testing may be required to assure therapeutic effect

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Tetracycline Hydrochloride for Injection, USP, 0.1 Gram	Classification of Defects	See Explanatory Notes.
	Solubility Time Limit	See Explanatory Notes.
	Weight Variation	The USP monograph and CFR do not specifically require compliance with content uniformity for this item. Our requirement assures uniform quantity within limits and thus proper and uniform dosage.
Tetracycline Hydrochloride for Injection, USP, Intravenous, 0.50 Gram	Classification of Defects	See Explanatory Notes.
	Solubility Time Limit	See Explanatory Notes.
	Weight Variation	The USP monograph and CFR do not specifically require compliance with content uniformity for this item. Our requirement assures uniform quantity within limits and thus proper and uniform dosage.
Tobucurarine Chloride Injection, USP, 3 mg per cc, 10 cc, 6s	Classification of Defects	See Explanatory Notes.
	Color Limits	See Explanatory Notes.
	Tighter Lower pH Limit	To assure greater stability over the shelf life of the item.
	Shall be Isotonic	To prevent hemolysis of red blood cells at the site of the injection.
Vitamin A Capsules, USP, 50,000 USP Units, 100s	Upper Assay Limit	To preclude possibility of use of super-potent material. No upper limit in USP. Fat soluble vitamins are stored in the body.
	Classification of Defects	See Explanatory Notes.
Perphenazine Tablets, NF, 5 mg, 500s	Classification of Defects	See Explanatory Notes.
Cyclophosphamide for Injection, USP, 100 mg, 12s	Classification of Defects	See Explanatory Notes.
	Solubility Time Limit	See Explanatory Notes.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Dienestrol Cream, NF, 0.01%, 2 3/4 oz (78 Gram)	pH	A pH is specified in order to assure greater stability over the shelf life of the item.
	Rabbit vaginal irritation test and shall produce no Cornification in vaginal smears of rats (on the formulation)	To assure that formulation does not cause irritation.
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets, NF, Individually Sealed, 100s	Classification of Defects	See Explanatory Notes.
Pralidoxime Chloride, Sterile, USP, 5 Grams	Tighter Assay Limits	More stringent assay limits to assure the best production procedures and controls are utilized, consistent with good manufacturing practices.
	Classification of Defects	See Explanatory Notes.
	Stability test (Accelerated Aging Test)	See Explanatory Notes.
	Color test, loss on drying, Elemental Analysis (C, H_2, N_2 Cl_2 O_2), Bromide, Iodide, Sulfate, and Neutralization Equivalent.	To provide tighter limits in order to assure the best production procedures and controls are utilized consistent with good manufacturing practices.
	Solubility Time Limit	See Explanatory Notes.
	Tighter Weight Variation	Our requirements assure more uniform quantity within limits and thus proper and uniform dosage.
Sodium Sulfobromophthalein Injection, USP, 50 mg per cc, 3 cc, 10s Sodium Sulfobromophthalein Injection, USP, 50 mg per cc, 7.5 cc, 10s	Classification of Defects	See Explanatory Notes.
	Toxicity test	To assure that the injection which is given intravenously is non-toxic.
	Double the current USP Pyrogen test dose	Retained the pyrogen test dose of USPXV.
	Leakage test for ampuls	See Explanatory Notes.
Methenamine Mandelate Tablets, USP, 0.5 Gram, 1000s	Classification of Defects	See Explanatory Notes.
	Bioavailability Test	Product Suitability.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Candicidin Suppositories, NF, Vaginal, 3 mg, 28s	Maximum unrefrigerated shipping times for items requiring refrigerated storage	See Explanatory Notes.
Candicidin Ointment, NF, Vaginal, 0.06%, 150 Gram	Maximum unrefrigerated shipping times for items requiring refrigerated storage	See Explanatory Notes.
Diphenhydramine Hydrochloride Capsules, USP, 25 mg, 30s	Classification of Defects	See Explanatory Notes.
Bisacodyl Tablets, NF, 5 mg, 1000s Bisacodyl Tablets, NF, 5 mg, Individually Sealed, 100s	Classification of Defects	See Explanatory Notes.
Pentaerythritol Tetranitrate Tablets, NF, 10 mg, 100s	Moisture Limits	To assure the stability of the product, in that excessive moisture may cause deterioration.
	Hardness	See Explanatory Notes.
	Color of Tablet	Due to nature of use of this drug for long term therapy color is considered a necessary factor for patient acceptance and patient assurance.
	Melting range for active ingredient IR for Extracted Petn Chromatographic Purity for Extracted Petn No Nitrates other than Petn	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	No Mannitol in Formulation	Interferes with Activity of Item.
Acetaminophen Elixir, NF, 0.12 Gram per 5 cc, 1 gal (3.78 liters)	Taste and Palatability	See Explanatory Notes.
	Accelerated aging test	See Explanatory Notes.
	Free p-aminophenol in Elixir	To limit a hydrolysis impurity which results from degradation.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Water, Purified, USP, Distilled, 1500 cc, 6s	Color Limits Sterility and Pyrogenicity	See Explanatory Notes. To assure proper requirements for a solution used as irrigating fluid.
Phenylephrine Hydrochloride Solution, USP, 1%, 1 pt	Free from particulation and sediment	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	Color Limits Tighter assay limits	See Explanatory Notes. To assure a tighter manufacturing control.
	Minimum limit for the quantity of preservative at time of delivery	To assure at least a minimum quantity of preservative will be present for stability of product.
	Formula specified	Obtained from R & D study to prevent ready deterioration.
Cholera Vaccine, USP, 20 cc	Classification of Defects Limit on Blood Group A and B Substances.	See Explanatory Notes. To avoid unwanted blood specific substances.
	Maximum unrefrigerated shipment time for refrigerated item	See Explanatory Notes.
Undecylenic Acid Ointment, Compound, NF, 28.35 Gram	Leakage for tubes	To assure that the tubes of ointments do not leak.
	Stability	To assure that the ointment will be usable after freezing and heating.
	Iodine number	To assure that the correct amount of double bonds are in the compound.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Phenylephrine Hydrochloride Solution, USP, 0.25%, 15 cc	Free from particulation and sediment	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices. See Explanatory Notes.
	Color Limits Bulk Solution shall have an adjusted pH and finished solution shall fall within specific pH limits	The USP monograph does not specifically require compliance with pH for this item. Our P.D. specifies a pH range in order to afford greater patient acceptance in pediatric use (Professional requirement).
	Tighter Assay Limits	To assure a tighter manufacturing control.
	Minimum limit for the quantity of preservative at time of delivery.	To assure at least a minimum quantity of preservative will be present for stability of product.
Meglumine Iodipamide Injection, USP, 52%, 20 cc	Classification of Defects	See Explanatory Notes.
Nitrofurantoin Oral Suspension, USP, 5 mg per cc, 16 fl oz (473)	Classification of Defects	See Explanatory Notes.
Antigen, Lymphogranuloma Venereum, USP, 1 cc	Each lot must be checked against known cases of Lymphogranuloma Venereum, and yield a positive skin response.	To assure that the antigen is specific for its intended use.
	Maximum unrefrigerated shipping time for refrigerated items.	See Explanatory Notes.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Xylometazoline Hydrochloride Solution, NF, 0.1%, 15 cc	Isotonic	To prevent irritation to the nasal membranes. See Explanatory Notes.
	Color limit pH	A pH range is not given in NF, thus a pH range is specified to assure greater stability over the shelf life of the item.
	Bacterial count	Bacteria limits to control the amount of viable microorganisms and to prohibit those organisms that should not be present in the product: This assures that undesirable contamination is not present in the product.
	Additional requirements of active ingredient more stringent limits of impurities (arsenic)	To provide tighter limits in order to assure the best production procedures and controls are utilized consistent with good manufacturing practices.
Xylometazoline Hydrochloride Solution, NF, 0.1%, 1 pt (473 cc)	Isotonic	To prevent irritation to the nasal membranes. See Explanatory Notes.
	Color limit pH	A pH range is not given in NF, thus a pH range is specified to assure greater solubility over the shelf life of this item.
	Bacterial Count	Bacteria limits to control the amount of viable microorganisms and to prohibit those organisms that should not be present in the product: This assures that undesirable contamination is not present in the product.
	Additional requirements of active ingredient more stringent limits of impurities (arsenic)	To provide tighter limits in order to assure the best production procedures and controls are utilized consistent with good manufacturing practices.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Dexamethasone Sodium Phosphate Injection, USP, Equivalent to 4 mg of Dexamethasone Phosphate per cc, 5 cc	Classification of Defects Color Limit	See Explanatory Notes. See Explanatory Notes.
Methylprednisolone Acetate Suspension, Sterile, NF, 40 mg per cc, 5 cc Methyprednisolone Acetate Suspension, Sterile, NF, 40 mg, 1 cc	Classification of Defects	See Explanatory Notes.
Lidocaine Hydrochloride Injection, USP, 1% with Epinephrine 1:100,000, 20 cc, 5s	Color Limits Classification of Defects	See Explanatory Notes. See Explanatory Notes.
Chloroquine Phosphate Tablets, USP, 0.5 Gram, 500s	Classification of Defects	See Explanatory Notes.
Quinidine Sulfate Tablets, USP, 0.2 Gram, Individually Sealed, 100s	Classification of Defects	See Explanatory Notes.
Acetaminophen tablets, NF, 0.325 Grams, 1000s	Disintegration (5 minutes) Free p-aminophenol in tablet Accelerated aging test Classification of Defects	Same disintegration time as Aspirin tablets. To limit hydrolysis impurity which results from degradation. See Explanatory Notes. See Explanatory Notes.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Blood Grouping Serum, Anti B, USP, Dried, Equivalent to 5 ml Blood Grouping Serum, Anti A, USP, Dried, Equivalent to 5 ml Blood Grouping Serum, Anti A, B, USP, Dried, Equivalent to 5 ml	Clear, free from particulate matter and sediment	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	Absence of false agglutinins or other reactions	To assure against false positive reactions.
	Higher Avidity Requirements	To assure a more potent reagent to reduce the possibility of error.
	Tighter Titer requirements	
	Certification by Blood Bank Center, Ft. Knox of final filled container	Requirement of military medical services which assures that each filling is tested and approved by their professional laboratory. FDA releases bulk lots; not necessarily filling lots.
	Maximum unrefrigerated shipping time for refrigerated material	See Explanatory Notes.
Blood Grouping Serum, Anti RH, USP, Equivalent to 5 cc	Clear, free from particulate matter and sediment	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	Absense of false agglutinins or other reactions	To assure against false positive reactions.
	Higher Avidity Requirements	To assure a more potent reagent to reduce the possibility of error.
	Tighter Titer requirements	
	Certification by Blood Bank Center, Ft. Knox of final filled container	Requirement of military medical services which assures that each filling is tested and approved by their professional laboratory. FDA releases bulk lots; not necessarily filling lots.
	Maximum unrefrigerated shippint time for refrigerated material	See Explanatory Notes.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Chlordiazepoxide Hydrochloride Capsules, USP, 10 mg, 500s Chlordiazepoxide Hydrochloride Capsules, USP, 5 mg, 500s Chlordiazepoxide Hydrochloride Capsules, USP, 25 mg, 500s	Classification of Defects More Stringent limits of impurities (Total lactam content)	See Explanatory Notes. To provide tighter limits in order to assure the best production procedures and controls are utilized consistent with good manufacturing practices.
Succinylcholine Chloride, Sterile, USP, 1 Gram Succinylcholine Chloride, Sterile, USP, 0.5 Gram	Classification of Defects Solubility time Limit Nitrogen Content Acute Toxicity	See Explanatory Notes. See Explanatory Notes. An additional indirect assay and identity test. To assure the product is non-toxic.
Succinylcholine Chloride Injection, USP, 20 mg per cc, 10 cc, 6s	Classification of Defects Color Limits Shall be isotonic Nitrogen Content Acute toxicity Maximum unrefrigerated shipping time for item items requiring refrigerated storage. Additional tests for active ingredient (Nitrogen content, acute toxicity)	See Explanatory Notes. See Explanatory Notes. To prevent hemolysis of red blood cells at site of the injection. As an additional indirect test for identity and assay. To assure the product is non-toxic. See Explanatory Notes. An additional assay and to assure the active ingredient is non-toxic.
Chlordiazepoxide Hydrochloride, Sterile, USP, 100 mg, 10s	Classification of Defects Leakage tests for ampuls Color Limits Maximum unrefrigerated shipping times for items requiring refrigerated storage	See Explanatory Notes. See Explanatory Notes. See Explanatory Notes. See Explanatory Notes.

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NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Xylometazoline Hydrochloride Solution, NF, 0.1%, 15 cc	Isotonic	To prevent irritation to the nasal membranes. See Explanatory Notes.
	Color limit pH	A pH range is not given in NF, thus a pH range is specified to assure greater stability over the shelf life of the item.
	Bacterial count	Bacteria limits to control the amount of viable microorganisms and to prohibit those organisms that should not be present in the product: This assures that undesirable contamination is not present in the product.
	Additional requirements of active ingredient more stringent limits of impurities (arsenic)	To provide tighter limits in order to assure the best production procedures and controls are utilized consistent with good manufacturing practices.
Xylometazoline Hydrochloride Solution, NF, 0.1%, 1 pt (473 cc)	Isotonic	To prevent irritation to the nasal membranes. See Explanatory Notes.
	Color limit pH	A pH range is not given in NF, thus a pH range is specified to assure greater solubility over the shelf life of this item.
	Bacterial Count	Bacteria limits to control the amount of viable microorganisms and to prohibit those organisms that should not be present in the product: This assures that undesirable contamination is not present in the product.
	Additional requirements of active ingredient more stringent limits of impurities (arsenic)	To provide tighter limits in order to assure the best production procedures and controls are utilized consistent with good manufacturing practices.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Dexamethasone Sodium Phosphate Injection, USP, Equivalent to 4 mg of Dexamethasone Phosphate per cc, 5 cc	Classification of Defects Color Limit	See Explanatory Notes. See Explanatory Notes.
Methylprednisolone Acetate Suspension, Sterile, NF, 40 mg per cc, 5 cc Methyprednisolone Acetate Suspension, Sterile, NF, 40 mg, 1 cc	Classification of Defects	See Explanatory Notes.
Lidocaine Hydrochloride Injection, USP, 1% with Epinephrine 1:100,000, 20 cc, 5s	Color Limits Classification of Defects	See Explanatory Notes. See Explanatory Notes.
Chloroquine Phosphate Tablets, USP, 0.5 Gram, 500s	Classification of Defects	See Explanatory Notes.
Quinidine Sulfate Tablets, USP, 0.2 Gram, Individually Sealed, 100s	Classification of Defects	See Explanatory Notes.
Acetaminophen tablets, NF, 0.325 Grams, 1000s	Disintegration (5 minutes) Free p-aminophenol in tablet Accelerated aging test Classification of Defects	Same disintegration time as Aspirin tablets. To limit hydrolysis impurity which results from degradation. See Explanatory Notes. See Explanatory Notes.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Scopolamine Hydrobromide Injection, USP, 0.5 mg, 1 cc, 12s	Classification of Defects	See Explanatory Notes.
	Leakage Test for Ampuls	See Explanatory Notes.
	Color Limits	See Explanatory Notes.
	Safety Test (mouse test)	To assure the material is non-toxic.
Sulfisoxazole Tablets, USP, 0.5 Gram, 1000s	Classification of Defects	See Explanatory Notes.
	IR identity of Active Ingredient in tablets-compared to USP standard	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	Moisture	To assure the stability of the product, in that excessive moisture may cause deterioration.
	X-Ray Diffraction	Insures that the particle size of the active ingredient in the finished tablet is optimal.
	Limits of foreign substances (Color of 10% solution, Chlorine NMT 100 PPM)	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
Soda Lime, USP, 2.1/2 lb (1.13 Kg)	Tighter Moisture	To assure optimum moisture at time of use.
	Tighter Hardness	This item is in a canister for use in the field.
Soda Lime, USP, 5 lb (2.27 Kg)	Tighter Moisture	To assure optimum moisture at time of use.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Pilocarpine Hydrochloride Ophthalmic Solution, USP, 1%, 15 cc Pilocarpine Hydrochloride Ophthalmic Solution, USP, 2%, 15 cc Pilocarpine Hydrochloride Ophthalmic Solution, USP, 4%, 15 cc	Shall contain suitable thickening agents - Viscosity limits specified Rabbit eye irritation test Chlorobutanol shall not be used in the solution	To assure contact of the active ingredient with the eye for maintenance of effect. Reduce potential for irritation to the eye. Chlorobutanol tends to break down and make the solution more acidic.
Ampicillin Capsules, USP, 0.25 Gram, 1000s Ampicillin Capsules, USP, 0.25 Gram, 100s Ampicillin Capsules, USP, 0.50 Gram, 100s	Classification of Defects	See Explanatory Notes.
Ampicillin for Oral Suspension, USP, Equivalent to 5.0 Grams of Ampicillin Ampicillin for Oral Suspension, USP, Equivalent to 3.75 Grams of Ampicillin Ampicillin for Oral Suspension, USP, Equivalent to 7.5 Grams of Ampicillin	Weight Variation	The USP monograph and CFR do not require compliance with content uniformity for this item. Our requirement assures uniform quantity within limits and thus proper and uniform dosage.
Aspirin Tablets, USP, 0.324 Gram, Individually Sealed, 100s	Classification of Defects Accelerated Aging Test Hardness Moisture content	See Explanatory Notes. See Explanatory Notes. See Explanatory Notes. To assure the stability of the product, in that excessive moisture may cause deterioration.
Codeine Sulfate Tablets, NF, 30 mg, 100s	Classification of Defects	See Explanatory Notes.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Dienestrol Cream, NF, 0.01%, 2 3/4 oz (78 Gram)	pH	A pH is specified in order to assure greater stability over the shelf life of the item.
	Rabbit vaginal irritation test and shall produce no Cornification in vaginal smears of rats (on the formulation)	To assure that formulation does not cause irritation.
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets, NF, Individually Sealed, 100s	Classification of Defects	See Explanatory Notes.
Pralidoxime Chloride, Sterile, USP, 5 Grams	Tighter Assay Limits	More stringent assay limits to assure the best production procedures and controls are utilized, consistent with good manufacturing practices.
	Classification of Defects	See Explanatory Notes.
	Stability test (Accelerated Aging Test)	See Explanatory Notes.
	Color test, loss on drying, Elemental Analysis (C, H_2, N_2 Cl_2 O_2), Bromide, Iodide Sulfate, and Neutralization Equivalent.	To provide tighter limits in order to assure the best production procedures and controls are utilized consistent with good manufacturing practices.
	Solubility Time Limit	See Explanatory Notes.
	Tighter Weight Variation	Our requirements assure more uniform quantity within limits and thus proper and uniform dosage.
Sodium Sulfobromophthalein Injection, USP, 50 mg per cc, 3 cc, 10s	Classification of Defects	See Explanatory Notes.
	Toxicity test	To assure that the injection which is given intravenously is non-toxic.
Sodium Sulfobromophthalein Injection, USP, 50 mg per cc, 7.5 cc, 10s	Double the current USP Pyrogen test dose	Retained the pyrogen test dose of USPXV.
	Leakage test for ampuls	See Explanatory Notes.
Methenamine Mandelate Tablets, USP, 0.5 Gram, 1000s	Classification of Defects	See Explanatory Notes.
	Bioavailability Test	Product Suitability.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Candicidin Suppositories, NF, Vaginal, 3 mg, 28s	Maximum unrefrigerated shipping times for items requiring refrigerated storage	See Explanatory Notes.
Candicidin Ointment, NF, Vaginal, 0.06%, 150 Gram	Maximum unrefrigerated shipping times for items requiring refrigerated storage	See Explanatory Notes.
Diphenhydramine Hydrochloride Capsules, USP, 25 mg, 30s	Classification of Defects	See Explanatory Notes.
Bisacodyl Tablets, NF, 5 mg, 1000s Bisacodyl Tablets, NF, 5 mg, Individually Sealed, 100s	Classification of Defects	See Explanatory Notes.
Pentaerythritol Tetranitrate Tablets, NF, 10 mg, 100s	Moisture Limits	To assure the stability of the product, in that excessive moisture may cause deterioration.
	Hardness	See Explanatory Notes.
	Color of Tablet	Due to nature of use of this drug for long term therapy color is considered a necessary factor for patient acceptance and patient assurance.
	Melting range for active ingredient	To assure that impurities are detected that may arise from production procedures, or from changes in sources of materials, or in the processing of the item. The presence of these impurities is inconsistent with good manufacturing practices.
	IR for Extracted Petn	
	Chromatographic Purity for Extracted Petn	
	No Nitrates other than Petn	
	No Mannitol in Formulation	Interferes with Activity of Item.
Acetaminophen Elixir, NF, 0.12 Gram per 5 cc, 1 gal (3.78 liters)	Taste and Palatability	See Explanatory Notes.
	Accelerated aging test	See Explanatory Notes.
	Free p-aminophenol in Elixir	To limit a hydrolysis impurity which results from degradation.

NAME	ADDITIONAL REQUIREMENTS	SIGNIFICANCE
Digoxin Tablets, USP, 0.25 mg, Individually Sealed, 100s	Classification of Defects	See Explanatory Notes.
Insulin, Isophane, Suspension, USP, U-100, 10 cc	Classification of Defects	See Explanatory Notes.
Insulin, Zinc, Suspension, USP, U-100, 10 cc	Maximum Unrefrigerated Shipping Time for Items Requiring Refrigerated Storage	See Explanatory Notes.
Insulin Injection, USP, U-100, 10 cc		
Methenamine Mandelate Oral Suspension, USP, 0.5 Gram per 5 cc, 8 fl oz	Taste/Palatability Test	See Explanatory Notes.

REPLY TO QUESTION 1A OF DSA CAMERON STATION MESSAGE - R271751Z FEB 74

At one point in Mr. Feinberg's 8 November speech a list of Meprobamate suppliers as taken from the Blue Book was presented on the screen. The narrative indicated that ten of the firms were rejected as a result of plant visits. There was no indication that these rejections were for Meprobamate Tablets alone. In fact not all of these firms are bidders for Meprobamate Tablets.

Surveys are listed below along with the dates of rejection and notification to FDA. A summary of the major deficiencies is attached:

Company	Product	Date of Rejection	Date FDA Advised
Barr Labs.	Diphenhydramine HCl Pyridoxine HCl Meprobamate	July 73 October 73	25 July 73 25 October 73
Kirkman Labs.	Bismuth Subcarbonate	July 73	12 July 73
ICN (Strong Cobb Arner)	Meprobamate	June 73	June 73
Zenith	Meprobamate	June 73	29 June 73
American Quinine (Natcon)(Napp)	Propoxyphene HCl	April 73	3 May 73
Bell Pharmacal Corp.	No Specific Product	February 73	February 73
Stanlabs.	Codeine Sulfate Calcium Lactate	May 68	September 68
Bowman	Sodium Fluoride	March 67	March 67
Fellows (Kapco)	Sodium Aminosalicylate	July 66	July 66
Richlyn	No Specific Product	February 66	April 66

As is the custom the FDA is advised of all plant survey rejections when Quality Control and Housekeeping deficiencies are the cause of the rejection. The normal method is by mail. This was followed in the cases cited above except for the ICN (Strong Cobb Arner) rejection, since our telecons with the FDA revealed that they were aware of the relocation of the plant and the fact that they had not yet been registered or inspected by the FDA. Accordingly, no letter was forwarded.

Encl

Barr Labs.

Pyridoxine Hydrochloride Tablets
Dyphenhydramine Hydrochloride Tablets

Major Deficiencies

Plant Deficiencies

Incomplete raw material testing.

Production equipment not cleaned before and after use.

Live spider in drying oven.

Inadequate quarantine of raw material.

No Calibration program.

Barr Labs.

Meprobamate Tablets, USP.

Major Deficiencies

1. Laboratory Control Deficiency.

Absence of testing of raw materials.

Company does not perform specific identity test to assure material is what it purports to be. (Company relies on suppliers' protocol).

Incomplete monograph testing(suppliers' protocol) of components for DPSC.

Failure to incorporate changes in USP XVIII in test procedures as part of the firm's test procedures of the end item. Example: Dissolution and assay procedures were not performed in accordance with changes reported in the "Fifth Interim Revision to USP XVIII".

Failure to document compliance of in-process testing with written specification requirements.

2. Production Control Deficiency

Failure to record lot numbers of all raw materials used in the production of "crude" Meprobamate on the batch production record.

Failure to identify equipment used in a manufacturing step.

Tabletting operations of as many as 6 different products conducted in a single room at one time without benefit of structural separations between machines creates the potential of cross contamination.

Improper use of hot air ovens during drying operations. All doors of the 12 ovens open at the same time presents the possibility of cross contamination of material in the different ovens.

Failure to provide an appropriate procedure to minimize the hazard of contamination of material in trays to be dried or which have been dried from air borne contaminants.

Barr Labs.

Meprobamate Tablets, USP.

Major Deficiencies

3. Lack of a dust control system.

Collected powder present on overhead beams and tops of other manufacturing equipment such as dryers and ovens.

4. No record on verification of regular cleaning of equipment and no documentation to assure that drug residues have been removed to avoid cross contamination.

Kirkman Labs.

FSN 6505-110-4075 Bismuth Subcarbonate Tablets

Major Deficiences

1. Production Control Deficiency

Inadequate Master Formula and Batch Production Record. Lack of explicit instructions, precautions as to steps to be followed in preparation of the drug which may lead to non-uniformity of batches.

Operating personnel unaware of in-process test standards. Although in-process testing is conducted, it is not known when to take corrective action.

Use of city water instead of purified water in batch formulations. This may affect the purity of the product.

Lack of traceability of water used in batch formulations.

2. Housekeeping Deficiencies.

Potential for product contamination exists due to:

Absence of covers on hoppers of tabletting presses.

Failure of tabletting operators to wear suitable head covering to prevent the possibility of hair, dandruff from falling into the powder.

Insects may enter granulation in drying oven from the outside through oven exhause.

Strong Cobb Arner

FSN 6505-550-8464 Meprobamate Tablets

Major Deficiencies

New plant where bid item is to be produced is not yet in operation.

Zenith Labs.

FSN 6505-550-8464 Meprobamate Tablets

Major Deficiencies

1. Production Control Deficiency.

   Improper testing schedule for in-process hardness of tablets.

2. Laboratory Control Deficiency.

   Improper testing of active ingredient and end item.

3. Improper Control of Raw Material.

   Commingling of drums of raw material with empty drums for discard.

   Presence of 2 different lot numbers on drum of raw material.

   Drum of raw material labeled "Ascorbic Acid" and "Starch".

   Non-released material commingled with approved material in the release storage area.

NAPP Chemical Co(Subcontractor) to Natcon. (American Quinine)

FSN 6505-958-2364 Propoxyphene Hydrochloride Capsules

Major Deficiencies

1. Laboratory control Deficiency

Incomplete testing of material.

Lab work not initialled by analyst.

2. Production Control Deficiency.

Each step of manufacturing process shown on batch production record is not initialled by operator performing operations and verifying individual.

3. Rusty drying trays which create the potential for product contamination.

Commingling of approved and untested raw material.

4. Poor Housekeeping.

Sweating pipes in storage area over raw material creating the possibility of contamination of raw materials.

Dust on raw material containers which may lead to product contamination.

Open window in work area not screened.

Broken receiving door leading to outside of building.

Bell Pharmacal Corp.
Table Rock Labs. Division

Major Deficiencies

Surveyed and Rejected by the Veterans Administration.

STANLABS

Codeine Sulfate Tablets
Calcium Lactate Tablets

Major Deficiencies

1. Laboratory Control Deficiency

Absence of written laboratory test methods setting forth test procedures.

Incomplete monograph testing of raw materials.

Absence of in-house standards of finished product to provide uniformity of product. Examples: Company has no standard for hardness of compressed tablets indicating lack of quality of control. Further, firm uses Pfizer tester and Monsanto Tester. No correlation in hardness test values found between the two.

Incomplete testing on finished product.

2. Production Control Deficiency

Failure of Master Formula and Batch Production Record to be exact duplicate. Example: Batch Production Record specifies "Plasdone C" whereas the Master Formula indicates "Plasdone".

Failure to perform inspection of end item in accordance with established sampling plan and classification of defects, thus creating the possibility of non-uniformity of product.

Weighing area for raw material batch components adjacent to open receiving area to street. Flies and other insects accessible to contaminate raw materials.

Batch formulations ready for compression stored in reused fibre drums bearing identification of previous contents creates the possibility of product mix-up and mislabeling.

Reuse of fibre drums without new polyethylene liners creates the possibility of product contamination.

3. Defective overhead construction and openings in walls that permits contamination of products being manufactured.

4. Failure of Regular cleaning to remove drug residues from manufacturing equipment may result in cross-contamination. Drains in production area covered with slime.

STANLABS

Codeine Sulfate Tablets
Calcium Lactate Tablets

Major Deficiencies

5. Failure to louvers attached to exhause fan in the manufacturing ares to close, thus permitting the entrance of flies and other insects.

6. Improper control and handling of raw materials.

Failure to store raw materials under conditions to prevent their decomposition and deterioration and/or becoming contaminated in storage. Material stored in warm, moist basement near boiler room. Floors in disrepair. Poor lighting exists and flammable finished goods stored near boiler presents safety hazard.

Receiving area for raw material is adjacent to open receiving area adjacent to street.

Sampling of raw material is done in dirty, dusty atmosphere creating the possibility of contamination of the open contaimers with foreign airborne matter.

Failure to provde adequate space for the orderly placement of materials to minimize any risk of mix-ups Ex. Commingling of rejected and hold material in the Drug Abuse Finished Goods Storage Area with finished and approved products.

7. Absence of calibration program for test equipment.

8. Absence of a stability testing program.

Bowman-Braun Pharmaceutical

Sodium Fluoride Tablets

Major Deficiencies

1. Production Control Deficiency

a. Failure to record of theoretical yield against actual yield and actual yield at various stages of processing.

b. Failure to maintain equipment used for manufacture in a clean and orderly manner to exclude the drug from contamination from previous and current production that might affect the safety, identity, strength, quality or purity of the drug. Examples are:

Tape on tablet filler, counting machine filling spout and other associated parts had accumulation of caked material and the presence of powder of a previous run.

Coating of pink dust on the structural braces of exhaust system and dust and caked material on outside surfaces of coating pans.

Presence of various colored tablets behind tape protector attached to drive of tablet sifter.

c. Uncovered vessel during manufacturing process creates the potential for cross contamination.

2. Laboratory Control Deficiency

Incomplete testing of components and finished product.

Incomplete laboratory records.

3. Lack of a stability testing program.

No data available to determine minimum shelf life of finished product.

4. Inadequate calibration program of test equipment(gages, seals, thermometers).

5. Box of rat poison on same shelf side by side with cans of Aspirin.

6. Inadequate dust control system.

Miscellaneous equipment in mixing area, wall clocks, air conditioner, mixers were dusty.

Kapco Inc.

Sodium Aminosalicylate Tablets

Major Deficiencies

1. Failure to provide adequate space for orderly placement of materials to minimize any risk of mix-ups between components.

Commingling of approved material, material with no approval sticker and in-process material with no indication of approval for use in the storage area for approved materials.

In addition, an affiliate company utilizes approximately 25% of the warehouse for general equipment and raw material storage.

2. Laboratory Control Deficiency

In complete testing of incoming raw materials.

Suppliers' protocols missing to substantiate material approved for use.

3. Production Control Deficiency

Lack of adequate control to ensure that only approved material is issued for manufacturing purposes.

4. Common loading platform for shipping and receiving is not arranged to prevent the commingling of incoming and outgoing material.

5. Unsanitary household practice.

Food is stored and eaten in the packaging room.

Richlyn Labs.

Major Deficiencies

1. Staffing Deficiency

Failure of one supervisor to have technical qualifications for the necessary supervisory functions. Another supervisor who is a chemist with pharmaceutical experience cannot allocate adequate time for supervision between operations of Richlyn and another affiliated company.

Inadequate laboratory supervision and technical review by chemist in charge.

Release of a batch which should have been rejected by the chief chemist based on test data indicates violation of quality assurance.

2. Laboratory Control Deficiency.

Incomplete and improper testing of raw material.

Failure to reject material in non-compliance with applicable specifications.

3. Production Control Deficiency

Absence of specific instructions on the Master Formula and production records for the manufacture of each item. Personnel manufacture in accordance with their experience rather than with delineated procedures. This may create non-uniformity of finished product.

Failure to record total granulation weight on batch production record in accordance with company requirements, thus recluding checks of theoretical yield against actual yield.

Absence of temperature recorder in drying oven to verify temperature used in drying granulation. Temperatures of all ovens varied although temperature control settings were the same.

4. Poor Housekeeping

Regular cleaning failed to remove drug residues or dirt accumulations on drying racks, walls, floors, containers tabletting machine and filter in air system supply heat to drying ovens, thus resulting in the possibility of cross contamination of product.

Exhaust fan in weighing room not screened, thus creating possibility of entrance of flies and other flying insects.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

THURSDAY, FEBRUARY 21, 1974

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:15 a.m., in room 6202, Dirksen Senate Office Building, Senator Gaylord Nelson [chairman of the subcommittee] presiding.

Present: Senator Nelson.

Also present: Chester H. Smith, Staff Director and General Counsel; Benjamin Gordon, Staff Economist; and John O. Adams, Minority Counsel.

Senator NELSON. Our first witness this morning will be Dr. William Apple, Executive Director of the American Pharmaceutical Association.

You may go ahead and present your statement. The committee is very pleased to have you here this morning.[1]

STATEMENT OF DR. WILLIAM S. APPLE, EXECUTIVE DIRECTOR OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, ACCOMPANIED BY DR. EDWARD G. FELDMANN, ASSOCIATE EXECUTIVE DIRECTOR FOR SCIENTIFIC AFFAIRS; AND CARL ROBERTS, COUNSEL

Dr. APPLE. Thank you, Mr. Chairman. I am Dr. William S. Apple, Executive Director of the American Pharmaceutical Association. I am accompanied by Dr. Edward G. Feldmann, Associate Executive Director for Scientific Affairs, and our Counsel, Mr. Carl Roberts.

Before Dr. Feldmann presents our specific comments on the subject matter requested in your invitation for APhA testimony, we feel that it is most important first to make the following general comments.

Senator Nelson, APhA wants the Congress to know that no one has a greater interest than the pharmacist in clearing up the doubts and suspicions that have been propagated in an obviously organized campaign questioning the safety and integrity of prescription drugs

[1] See information beginning at page 10724.

dispensed in the United States. The pharmacist's interest stems primarily from the fact that the pharmacist knows how important the medication is to the patient and the pharmacist has to look the patient or a member of his family in the eye. The pharmacist has no vested economic self-interest in the price the manufacturer charges for his drug products because the pharmaceutical service system provides that the pharmacist be reimbursed what the pharmacist pays for the drug product. On the other hand, the pharmacist does have an obvious professional objective in providing patients with effective and safe medication at reasonable prices.

No subject investigated by your subcommittee in the almost 7 years of your extensive work is, from the pharmacist and patient point of view, more important than the hearings you are now holding. More than two billion prescriptions are being dispensed annually—more than five million daily—and the patients who take these prescriptions have a right to expect their government to resolve the question of how much confidence can be placed in the medicines their pharmacists dispense.

APhA as the national professional society for all pharmacists has no ax to grind for anybody, but the patient and his pharmacist. The pharmacist does not care whether a drug product is made and marketed by a large firm or a small firm, as long as the pharmacist can be assured of the product's safety and efficacy. APhA knows that high quality prescription drugs can be and are fabricated by manufacturers of all sizes.

APhA also knows that the hallmark of quality is not derived by giving a product a euphonious brand name. And we have watched with interest the development of so-called "branded generics" by such fine firms as Lilly, Lederle, SKF and Upjohn.

Simply stated, the situation in our country today is that one agency of the Federal Government says that you can depend on the quality of the Nation's drug supply, and another agency of the same Government would like you to believe otherwise. Regardless of how this controversy is resolved, APhA is sick and tired of having the finest drug supply in the world under a constant cloud of suspicion. It was bad enough when only the pharmacist was the target of this propaganda, but now prescribers and patients are asking the pharmacist for assurance.

APhA believes the country can ill afford further delay in putting the issue to rest.

Thank you, Mr. Chairman. I will be glad to answer questions now or after Dr. Feldmann submits his testimony.

Senator NELSON. Well, when you refer to "another agency of the same government," you are referring to the Defense Department?

Dr. APPLE. Mr. Chairman, I am saying that HEW—the Food and Drug Administration—says the drug supply is good, and the Department of Defense has been casting clouds over the Nation's drug supply for the last several years with statements made by some of their spokesmen.

Senator NELSON. Well, the same thing is true, is it not, of the Pharmaceutical Manufacturers Association in respect to generics?

In other words, they repeatedly said, sometimes subtly, more frequently not so subtly, that you can only trust the big brand name companies, of which most all of them are members of the PMA, is that not so?

Dr. APPLE. I would certainly have to agree that that is the thrust of their propaganda.

Senator NELSON. I thought it was interesting. You say that the APhA "also knows that the hallmark of quality is not derived by giving a drug product a euphonious trade name, and we have watched with interest the development of so-called 'branded generics' by such fine firms as Lilly, Lederle, SKF and Upjohn."

I found interesting a recent report from the FDC reports—frequently called the Pink Sheet—of July 16, 1973, which states that:

> Squibb, Pfizer and Wyeth have recently joined SKF, Robins and Parke-Davis as purchasers of antibiotics and other generic dosage forms from Mylan a private formula manufacturer in Morgantown, West Virginia. Mylan's private formula sales to major drug manufacturers jumped to $4,800,000 in fiscal year 1973 ending March 31 from $2,200.000 a year earlier.
>
> Emerging as Mylan's top major pharmaceutical marketing customer in fiscal year 1973, Squibb purchased $1.3 million erythromycin in the first year it bought anything from the Morgantown private formula manufacturer. Mylan is sole supplier for Squibbs' erythromycin. introduced in 1972.
>
> A Squibb spokesman said the company decided to use Mylan rather than processing erythromycin itself because of the "difficult technology involved." Mylan is one of the few companies capable of making the product, the Squibb spokesman said.

Well, I think that is rather interesting, since their own association keeps attacking the generics as not being of the same quality as the trade name products. And here you have Squibb saying that this little company which hardly anybody has heard of has the difficult technology to master this, and I think we ought to lay to rest this propaganda campaign that the Pharmaceutical Manufacturers Association and the DOD have been carrying on.

Dr. APPLE. Mr. Chairman, if I could comment on that. We tried to lay that issue to rest. Our association has a policy encouraging legislation that would reveal the actual identity of the fabricator of the dosage form on the label, as well as the identity of the distributor. That legislation has been enacted in the State of California and more recently in the State of Kentucky.

There is an effort by the Pharmaceutical Manufacturers Association now in California to have that legislation amended, and I regret to say that it has already passed one House of the California legislature.

For the record, I can give you the information that California was able to gather under prevailing regulations of this so-called "Crown Statute." And I would particularly like to call to your attention an editorial which appeared in the November 1973 California Pharmacist, in which the editor asked, "It is difficult to understand why the drug industry is fearful of having the pharmacist and physician know who really makes their drug products. PMA consistently maligns small manufacturers by suggesting their products may not be of adequate quality. Yet, they are attempting to deny the pharmacist the informa-

tion that would be helpful to him in determining who actually makes these products."

Senator NELSON. Yes, we would receive that editorial and the other information for the record.

[Testimony resumes at page 10173. The information referred to follows:]

NOVEMBER 1973 issue of CALIFORNIA PHARMACIST

Editorial

WHAT KIND OF GAMES ARE BEING PLAYED?

During the last week of the 1973 Legislative Session, the Pharmaceutical Manufacturers Association (PMA) decided on taking up a bill, AB 1535, introduced on April 24, 1973, at the request of the drug industry. The purpose of this bill is to eliminate the requirement of AB 1404 to place the name of the manufacturer of the finished dosage form on the drug label [illegible] product advertising.

The California Pharmaceutical Association, with the support of the California Medical Association, was successful in passing AB 1404 in 1971. The purpose of this legislation is to assist the physician and the pharmacist in knowing who actually manufactured the drug product being prescribed and dispensed to the patient.

The legislation, signed into law in 1971 by Governor Reagan, had passed the Legislature by a nearly unanimous vote. For two years the drug industry was successful in delaying implementation of AB 1404 through their constant instigation of misleading statements and a general smoke screen that hampered the Department of Health's efforts in adopting the necessary implementing regulation. Subsequently, the regulation to implement AB 1404 also was passed by a unanimous vote of the Board of Health.

When the industry was unable to defeat the bill and the regulation, they endeavored to gain CPhA's support to permit the manufacturer to merely file the required information as to the actual manufacturer of the drug product with the Department of Health. CPhA refused, inasmuch as it was recognized that this was a mere subterfuge on the part of PMA, to withhold the information from the practitioner. The State of California does not have the funds to serve as a data bank for the industry nor would such information on file in Sacramento be of any assistance to a pharmacist at the time that he elects to purchase or dispense a drug product.

Failing to gain CPhA's support, the drug industry has attempted to get the Legislature, via AB 1535, to buy their filing concept. They have amassed the efforts of their three Sacramento lobbyists and all of the resources that PMA can bring to bear to overturn AB 1404.

Their tactics at this 11th hour must be questioned.

Why did they endeavor on September 10th, the last week of the '73 Legislative Session, to have AB 1535 considered when it had been on file in the Committee since April 24th?

Inasmuch as the regulation which implements AB 1404 requires the name to appear on the label by June 1, 1974, what was the purpose of taking up AB 1535 on September 10th since it couldn't become effective, even if passed, until January 1, 1975?

Just as AB 581, the drug product selection bill, was taken off calendar a week before it was to be heard in the Senate Business and Professions Committee, similar strange incidences were occurring with respect to AB 1535 in September.

It is difficult to understand why the drug industry is fearful of having the pharmacist and physician know who really makes their drug products.

PMA consistently maligns small manufacturers by suggesting their products may not be of adequate quality; yet, they are attempting to deny the pharmacist the information that would be helpful to him in determining who actually makes those products.

It is equally difficult to determine why the Department of Health reversed itself at the 11th hour and switched from an oppose to a neutral position on AB 1535.

The PMA endeavored on September 10th to create the illusion that too much confusion surrounded AB 1404; no one but the industry, however, seems to be confused.

CPhA, under the provisions of the regulation, has written and obtained information with respect to the actual manufacturer which has readily been provided by many manufacturers and distributors as witnessed by the report contained in this and the October issue of the *California Pharmacist*.

What are the rest attempting to conceal and what kind of games are being played?

The Assembly Health Committee did not succumb to the PMA tactics on September 10th and refused to report the bill out of Committee. What will happen next January when the Committee reconvenes?

It will be well for you to make certain that your legislator knows that AB 1404, as it was enacted, is appropriate and helpful legislation and the subterfuge attempted by PMA through AB 1535 is not in the best interest of the profession or the public.

—RCJ

Retain for future reference

OCTOBER 1973 issue of CALIFORNIA PHARMACIST

SOME MANUFACTURERS DISCLOSE SOURCES OF SUPPLY

The last issue of the *California Pharmacist* (September, 1973, page 5) reported the implementation of regulations which require pharmaceutical manufacturers to disclose the name and place of business of the manufacturer who produces the finished dosage form of their products. The regulation, effective July 28, 1973, provides that manufacturers must either include the names of the mixer of the final ingredients and the encapsulator or tabulator in the product's labeling and advertising material; or provide this information in response to the written or oral request of any physician, pharmacist, or their professional associations.

In an effort to supply information to the profession, the California Pharmaceutical Association requested the identity of the manufacturer who mixed the final ingredients and encapsulated or tableted the finished dosage forms of products manufacturered or distributed by over fifty different companies. The results of these requests, mailed on the 15th and 16th of August, are compiled in the following table. At the time of publication, over one month past the date of writing to the manufacturers, many firms have not complied with the Association's request for information.

Under the provisions of these regulations (Section 10386 of Title 17 of the California Administrative Code), failure to respond to requests for the identity of the manufacturer of the finished dosage form shall result in the products of the firm failing to respond being deemed misbranded. Those companies who have not responded to the Association's requests are being sent a final notice which will precede the institution of legal proceedings against non-complying firms.

Pharmacists who have not been provided information as to the identity of the manufacturer of any prescription drug as provided for in California law, should notify the CPhA offices so that appropriate action may be taken.

The following list indicates the replies received at this office as of October 1, 1973. "Acknowledged request" indicates that the distributor has advised CPhA of the receipt of the request but has not supplied the name of the manufacturer of the final dosage form prior to press time.

DISTRIBUTOR	MANUFACTURER[1]	DATE REPLIED
AMPICILLIN TRIHYDRATE 250 mg Capsules		
American Pharmaceutical Co.	**No Reply**	
American Quinine Products	Zenith Labs., Inc. (Northvale, NJ)	8-29-73
B. F. Ascher & Co., Inc.	International Labs., Inc.[2] (Mayaguez, Puerto Rico)	9-07-73
Ayerst Laboratories	Beecham-Massengill Pharm.[3] (Piscataway, NJ)	9-05-73
Beecham-Massengill Pharm.	Beecham, Inc.	9-27-73
Bristol Laboratories, Div. of Bristol-Myers Co.	Bristol Labs. (E. Syracuse, NY)	8-29-73
Coastal Pharmaceutical Co.	**No Reply**	
Columbia Medical Company	Biocraft Labs. (E. Paterson, NJ)	9-05-73
Consolidated Midland Corp.	Reid Provident [4] or Zenith Labs., Inc.	8-21-73
ICN Pharmaceuticals, Inc. Strong Cobb Arner	**No Reply**	
Parke, Davis & Company	Replied[13]	9-19-73
Perepac Pharmaceutical Co.	**No Reply**	
Rachelle Laboratories, Inc.	International Labs.[5] (Atlanta, GA)	8-24-73
Sherry Pharm. Co., Inc.	**No Reply**	
Smith Kline & French, Labs.	**No Reply**	
E. R. Squibb & Sons, Inc.	E. R. Squibb & Sons, Inc.	8-31-73
Stayner Corporation	International Labs. (Atlanta, GA)	8-20-73
Towne, Paulsen & Co., Inc.	International Labs. (Atlanta, GA)	8-27-73
	John D. Copanos & Co., Inc. (Baltimore, MD)	
	Biocraft Labs. (E. Paterson, NJ)	
West-ward, Inc.	**No Reply**	
Wolins Pharmacal Corp.	Biocraft Labs.	9-06-73

DISTRIBUTOR	MANUFACTURER[1]	DATE REPLIED
AMPICILLIN ANHYDROUS		
Wyeth Laboratories	Wyeth Labs. (Philadelphia, PA)	8-24-73
BROMPHENIRAMINE MALEATE		
—Elixir (Dimetane)		
A. H. Robins Company	A. H. Robins Company (Richmond, VA)	8-27-73
—Sustained Release Tablets (Dimetane Extentabs)		
A. H. Robins Company	ICN Pharmaceuticals Strong Cobb Arner (Cincinnati, OH)	8-27-73
—Sustained Release Tablets with phenylephrine and phenylpropanolamine (Dimetapp Extentabs)		
A. H. Robins Company	ICN Pharmaceuticals Strong Cobb Arner (Cincinnati, OH)	8-27-73
DEXAMETHASONE 0.75 mg Tablets		
CIBA Pharmaceutical Co.	**No Reply**	
Consolidated Midland Corp.	Danbury Pharmacal[4] or Cord Laboratories acknowledged request	8-21-73 8-20-73
Merck Sharp & Dohme Div. of Merck & Co., Inc.	Organon, Inc.	8-23-73
Organon, Inc.	Schering Corp.	9-18-73
Schering Corp.	**No Reply**	
Sherry Pharm. Co., Inc.	USV Pharmaceutical Corp.	8-31-73
USV Pharmaceutical Corp.	Zenith Labs., Inc. (Northvale, NJ)[6]	8-20-73
Zenith Laboratories, Inc.		

(Continued on page 8)

(Continued from page 7)

DISTRIBUTOR	MANUFACTURER[1]	DATE REPLIED
DONNATAL Tablets		
A. H. Robins Company	A. H. Robins Company (Richmond, VA)	8-27-73
ERYTHROMYCIN BASE 250 mg Tablets		
Eli Lilly & Company	Eli Lilly & Company (Indianapolis, IN)	8-30-73
The Upjohn Company	The Upjohn Company	8-30-73
ERYTHROMYCIN STEARATE 250 mg Tablets		
Abbott Laboratories	Abbott Labs.[6]	8-24-73
American Quinine Products	Zenith Labs., Inc. (Northvale, NJ)	8-29-73
Bristol Laboratories, Div. of Bristol-Myers Company	Bristol Laboratories (E. Syracuse, NY)	8-29-73
Columbia Medical Company	Zenith Labs., Inc. (Northvale, NJ)	9-05-73
Mallinckrodt Pharmaceuticals	**No Reply**	
Parke, Davis & Company	Replied[13]	9-19-73
Sherry Pharm. Co., Inc.	**No Reply**	
Smith Kline & French Labs.	**No Reply**	
Towne, Paulsen & Co., Inc.	Mylan Pharmaceuticals (Morgantown, WV)	8-29-73
West-ward, Inc.	**No Reply**	
Wyeth Laboratories	Mylan Pharmaceuticals[7] (Morgantown, WV)	8-24-73
Zenith Laboratories, Inc.	Zenith Labs., Inc.[6] (Northvale, NJ)	8-20-73
FENFLURAMINE 20 mg Tablets		
A. H. Robins Company	A. H. Robins Company (Richmond, VA)	8-27-73
GLYCERYL GUAIACOLATE Syrup		
A. H. Robins Company	A. H. Robins Company (Richmond, VA)	8-27-73
HEPARIN SODIUM 1000 Units/cc Injection		
Abbott Laboratories	Abbott Laboratories[6]	8-24-73
Century Pharmaceuticals, Inc.	Medwick Laboratories, Inc. (Chicago, IL)	8-29-73
Consolidated Midland Corp.	Elkins-Sinn or Medical Chemicals[4]	8-27-73
Eli Lilly & Company	Eli Lilly & Company (Indianapolis, IN)	8-30-73
Medwick Laboratories, Inc.	**No Reply**	
Organon, Inc.	Organon, Inc.	8-27-73
Parke, Davis & Company	Replied[13]	9-19-73
Robinson Laboratories, Inc	**No Reply**	
Towne, Paulsen & Co., Inc.	Medwick Laboratories, Inc. (Melrose Park, IL)	8-27-73
The Upjohn Company	The Upjohn Company	8-30-73
Wyeth Laboratories	Wyeth Laboratories (Philadelphia, PA)	8-24-73
HYDROCHLOROTHIAZIDE 50 mg Tablets		
Geigy Pharmaceuticals Div. of Ciba-Geigy Corp.	**No Reply**	
Merck Sharp & Dohme Div. of Merck & Co., Inc.	acknowledged request	8-20-73
Wolins Pharmacal Corp.	Zenith Labs., Inc.	9-06-73
L-DOPA 250 mg Capsules		
Eaton Laboratories, Div. Morton-Norwich Products, Inc.	Eaton Laboratories, Inc. (Norwich, NY)	8-23-73
Roche Laboratories, Div. Hoffmann-LaRoche, Inc.	Roche Laboratories (Nutley, NJ)	8-21-73

DISTRIBUTOR	MANUFACTURER[1]	DATE REPLIED
MEPROBAMATE 200 & 400 mg Tablets		
American Pharmaceutical Co.	**No Reply**	
American Quinine Products	Zenith Labs., Inc. (Northvale, NJ)	8-29-73
Barr Laboratories, Inc.	Barr Labs., Inc. (Northvale, NJ)	8-20-73
Columbia Medical Co.	Zenith Labs., Inc.	9-05-73
ICN Pharmaceuticals, Inc. Strong Cobb Arner	**No Reply**	
Kirkman Laboratories[9]	**No Reply**	
McKesson Laboratories, Div. Foremost-McKesson, Inc.	**No Reply**	
Parke, Davis & Company	Replied[13]	9-19-73
Purepac Pharmaceutical Co.	**No Reply**	
Richlyn Laboratories, Inc.[8]	Richlyn Labs., Inc. (Philadelphia, PA)	9-05-73
Sherry Pharm. Co., Inc.	**No Reply**	
Stanlabs, Inc.	**No Reply**	
Smith Kline & French Labs.	**No Reply**	
Stayner Corp.	Zenith Labs., Inc. (Northvale, NJ)	8-20-73
Towne, Paulsen & Co., Inc.	Towne, Paulsen & Co., Inc. (Monrovia, CA)	8-27-73
Wallace Pharmaceuticals Div. of Carter-Wallace, Inc.	Carter-Wallace, Inc. (Cranbury, NJ)	8-20-73
Wolins Pharmacal Corp.[8]	Heather Drug Co., Inc.	9-06-73
Wyeth Laboratories	Wyeth Labs. (Philadelphia, PA)	8-24-73
Zenith Laboratories, Inc.	Zenith Labs., Inc.[6] (Northvale, NJ)	8-20-73
PENICILLIN V POTASSIUM 250 mg Tablets		
ICN Pharmaceuticals, Inc. Strong Cobb Arner	**No Reply**	
Lederle Laboratories, Div. of American Cyanamid Company	Lederle Laboratories	8-24-73
Eli Lilly & Company	Eli Lilly & Company[8] (Indianapolis, IN)	8-21-73
A. H. Robins Company	Biocraft Laboratories (E. Paterson, NJ)	8-27-73
Robinson Laboratory, Inc.	**No Reply**	
Sherry Pharm. Co., Inc.	**No Reply**	
E. R. Squibb & Sons, Inc.	E. R. Squibb & Sons, Inc.	8-29-73
Towne, Paulsen & Co., Inc.	Mylan Pharmaceuticals Inc. (Morgantown, WV)	8-27-73
	John D. Copanos & Co., Inc. (Baltimore, MD)	
West-ward, Inc.	**No Reply**	
McKesson Laboratories, Div. Foremost-McKesson, Inc.	**No Reply**	
Pfizer Laboratories, Div. Pfizer, Inc.	**No Reply**	
Purepac Pharmaceutical Co.	**No Reply**	
PREDNISONE 5 mg Tablets		
American Pharmaceutical Co.	**No Reply**	
Barr Laboratories, Inc.	Barr Labs., Inc. (Northvale, N.I)	8-20-73
Columbia Medical Co.	Blue Cross Products (Brooklyn, NY)	9-05-73
First Texas Pharm., Inc.	First Texas Pharm., Inc. (Dallas, TX)	8-23-73
ICN Pharmaceuticals, Inc. Strong Cobb Arner	**No Reply**	
Kirkman Laboratories	**No Reply**	
McKesson Laboratories, Div. Foremost-McKesson, Inc.	**No Reply**	

DISTRIBUTOR	MANUFACTURER[1]	DATE REPLIED
Merck Sharp & Dohme Div. of Merck & Co., Inc.	acknowledged request	8-20-73
Ormont Drug & Chemical Co., Inc.	**No Reply**	
Parke, Davis & Company	Replied[13]	9-19-73
Purepac Pharmaceutical Co.	**No Reply**	
Richlyn Laboratories, Inc.	Richlyn Labs., Inc. (Philadelphia, PA)	9-05-73
Rowell Laboratories, Inc.	Rowell Labs., Inc. (Bandette, MN)	8-23-73
Schering Corporation	Schering Corp.	9-18-73
Stanlabs, Inc.	**No Reply**	
Stayner Corporation	Stayner Corporation (Berkeley, CA) or Zenith Labs., Inc.[4] (Northvale, NJ)	8-20-73
Towne, Paulsen & Co., Inc.	Towne, Paulsen & Co., Inc. (Monrovia, CA)	8-27-73
The Upjohn Company	The Upjohn Company	8-30-73
USV Pharmaceutical Corp.	USV Pharm. Corp.	8-31-73
West-ward, Inc.	**No Reply**	
Wolins Pharmacal Corp.	Zenith Labs., Inc. and Phoenix Labs.	9-06-73
Zenith Laboratories, Inc.	Zenith Labs., Inc.[6]	8-20-73
PROPOXYPHENE HCl 65 mg		
American Quinine Products	Zenith Labs., Inc. (Northvale, NJ) and Natcon Chemical Co., Inc. (Plainview, NY)	8-29-73
Barr Laboratories, Inc.	Barr Labs., Inc. (Northvale, NJ)	8-20-73
Columbia Medical Company	Richlyn Labs., Inc.	9-05-73
Lederle Laboratories, Div. of American Cyanamid Company	Lederle Labs.	8-24-73
Rachelle Laboratories, Inc.	Rachelle Labs., Inc. (Formerly by Cord Labs., Detroit, MI)[5]	8-21-73
Richlyn Laboratories, Inc.	Richlyn Labs., Inc. (Philadelphia, PA)	9-05-73
Smith Kline & French Labs.	**No Reply**	
Towne, Paulsen & Co., Inc.	Anabolic Inc. (Irvine, CA)	8-27-73
West-ward, Inc.	**No Reply**	
Wolins Pharmacal Corp.	Richlyn Labs., Inc. and Bolar Labs.	9-11-73
Zenith Laboratories, Inc.	Zenith Labs., Inc. (Northvale, NJ)[6]	8-20-73
PROPOXYPHENE HCl 65 mg COMPOUND		
Lederle Laboratories, Div. of American Cyanamid Co.	Lederle Labs.	8-24-73
Smith Kline & French Labs.	**No Reply**	
Towne, Paulsen & Co., Inc.	Caribe Chemical Company (St. Croix, US Virgin Islands)	8-27-73
West-ward, Inc.	**No Reply**	
Wolins Pharmacal Corp.	Caribe Chemical Co. and Mylan Laboratories	9-06-73
RESERPINE 0.25 mg Tablets		
Eli Lilly & Company	Eli Lilly & Company (Indianapolis, IN)[8]	8-21-73
RIFAMPIN 300 mg Capsules		
CIBA Pharmaceutical Co.	**No Reply**	
Dow Pharmaceuticals, The Dow Chemical Company	Dow Pharmactuticals[10]	8-28-73

DISTRIBUTOR	MANUFACTURER[1]	DATE REPLIED
TETRACYCLINE HCl 250 mg Capsules		
American Pharmaceutical Co.	**No Reply**	
American Quinine Products	Zenith Labs., Inc. (Northvale, NJ)	8-29-73
Barr Laboratories, Inc.	Barr Labs., Inc.[11]	8-20-73
Bristol Laboratories, Div. Bristol-Myers Company	Bristol Labs.[12] (E. Syracuse, NY)	8-29-73
Columbia Medical Company	Richlyn Labs, Inc. (Philadelphia, PA)	9-05-73
Dow Pharmaceuticals, The Dow Chemical Company	Dow Pharmaceuticals[10]	8-28-73
First Texas Pharm., Inc.	International Labs, Inc. (Mayaguez, Puerto Rico)	8-27-73
ICN Pharmaceuticals, Inc. Strong Cobb Arner	**No Reply**	
Ketchum Laboratories, Inc.	Replied[13]	8-29-73
Lederle Laboratories, Div. of American Cyanamid Co.	Lederle Labs.	8-24-73
McKesson Laboratories, Div. Foremost-McKesson, Inc.	**No Reply**	
Parke, Davis & Company	Replied [13]	9-19-73
Pfizer Laboratories, Div. of Pfizer, Inc.	**No Reply**	
Purepac Pharmaceutical Co.	**No Reply**	
Rachelle Laboratories, Inc.	Rachelle Labs., Inc.[6]	8-21-73
Richlyn Laboratories, Inc.	Richlyn Labs., Inc. (Philadelphia, PA)	9-05-73
A. H. Robins Company	Mylan Pharmaceutical Co. (Morgantown, WV)	8-27-73
Sherry Pharm. Co., Inc.	**No Reply**	
Smith Kline & French Labs.	**No Reply**	
E. R. Squibb & Sons, Inc.	E. R. Squibb & Sons, Inc.	8-29-73
Stayner Corporation	Rachelle Labs., Inc. (Long Beach, CA)	8-20-73
Towne, Paulsen & Co., Inc.	Towne, Paulsen & Co., Inc. (Monrovia, CA) Rachelle Labs., Inc. (Long Beach, CA) Mylan Pharmaceuticals Inc. (Morgantown, WV)	8-27-73
The Upjohn Company	The Upjohn Company	8-30-73
West-ward, Inc.	**No Reply**	
Wolins Pharmacal Corp.	Heather Drug Co., Inc. and Mylan Labs.	9-06-73
Wyeth Laboratories	Mylan Pharmaceuticals (Morgantown, WV)	8-24-73
TRIMETHOBENZAMIDE HCl 250 mg Capsules		
Beecham-Massengill Pharm.	Beecham, Inc.[14]	

FOOTNOTES

[1]In this table, manufacturer is defined as that company who mixed the final ingredients and tableted or encapsulated the finished dosage form of a pharmaceutical product.

[2]Discontinued distribution, January, 1973.

[3]An NDA is held by the distributor, who also specifies the manufacturing procedures and observes the plant monthly.

[4]Second manufacturer listed is a back-up supplier.

[5]Plans to discontinue distribution when present stocks are exhausted.

[6]Distributor states they *completely* manufacture the product.

[7]Release is subject to the distributors quality control.

[8]Distributed by Dista Products Co., Division of Eli Lilly & Company in some areas.

[9]400 mg Tablets only.

[10]Manufactured by The Dow Chemical Company, Dow Pharmaceuticals or its wholly-owned Virgin Islands Company.

[11]Barr Laboratories is awaiting FDA approval.

[12]Includes both tetracycline HCl and phosphate complex.

[13]Clarification of response requested by CPhA.

[14]As of September 27, 1973.

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Retain for future reference

MANUFACTURER DISCLOSURES — PART II

This article is provided as part of the Association's continuing efforts to furnish the profession with meaningful information on the actual sources of manufacture of pharmaceutical products. The October issue of the *California Pharmacist* contained the first of a series of compilations of drug products distributed by various pharmaceutical firms identifying the manufacturer of the finished dosage form, and this issue includes similar information received since October 1, 1973.

The Association has requested the information contained in this and the previous article pursuant to Section 10386 of Title 17 of the California Administrative Code which was published in the September, 1973, *California Pharmacist*. Several firms have failed to comply with the California law ignoring CPhA's initial and final requests for the identity of the manufacturer of various products distributed by these firms. The names of those firms failing to respond to CPhA's final notice will be reported in the next issue of the CPhA Journal. Under the provisions of the regulations the failure of these manufacturers to respond results in their products being deemed misbranded. This matter will be brought to the attention of the Food and Drug Section of the State Department of Health for action.

The following table reflects the most recent information supplied by the firms distributing the specified products. Those companies who have not yet provided the information requested by CPhA are indicated as **No Reply**. The table also indicates that several firms have advised the Association of the receipt of the request for information "Acknowledged Request" but at press time have not responded with the specified data.

DISTRIBUTING FIRM	MANUFACTURER[1]
AMITRIPTYLINE HCl 25 mg Tablets	
Merck Sharp & Dohme, Division of Merck & Co., Inc. (ELAVIL®)	Merck Sharp & Dohme (West Point, PA)[2]
AMPICILLIN TRIHYDRATE 250 mg Capsules	
American Pharmaceutical Company	Acknowledged Request[3]
Coastal Pharmaceutical Company	**No Reply**
ICN Pharmaceuticals, Inc.	International Laboratories (Atlanta, GA)[2]
Parke, Davis & Company	Replied[3]
Purepac Pharmaceutical Company	Acknowledged Request[3]
Sherry Pharmaceutical Co., Inc.	Zenith Laboratories, Inc. (Northvale, NJ)[2]
Smith Kline & French Laboratories	Bristol Laboratories[4] (E. Syracuse, NY)[2]
Stanlabs, Inc.	Whiteworth Pharmaceuticals, Inc. (McLean, VA)[2]
West-ward, Inc.	Zenith Laboratories, Inc.[7]
CHLORPROMAZINE HCl 25 & 50 mg Tablets	
Purepac Pharmaceutical Company	Acknowledged Request[3]
DEXAMETHASONE 0.75 mg Tablets	
Ciba Pharmaceutical Company	Pharmaceuticals Division of Ciba-Geigy Corp. (Summit, NJ)[2]
Merck Sharp & Dohme Div. of Merck & Co., Inc.	Merck Sharp & Dohme
Sherry Pharmaceutical Company, Inc.	Danbury Pharmacal (Danbury, CN)[2]
DIGOXIN 0.25 mg Tablets	
Progress Laboratories, Inc.	**No Reply**
Purepac Pharmaceutical Company	Rondex Laboratories[5] (Guttenburg, NJ)[2]

DISTRIBUTING FIRM	MANUFACTURER[1]
ERYTHROMYCIN STEARATE 250 mg Tablets	
Mallinckrodt Pharmaceuticals (QIDMYCIN®)	Mylan Pharmaceuticals, Inc. (Morgantown, WV)[2]
Parke, Davis & Company	Replied[3]
Sherry Pharmaceutical Company, Inc.	Mylan Pharmaceuticals, Inc.
Smith Kline & French Laboratories (SK-ERYTHROMYCIN®)	Mylan Pharmaceuticals, Inc.[4]
West-ward, Inc.	Zenith Laboratories, Inc.[7]
HEPARIN SODIUM 1000 Units/cc Injection	
Medwick Laboratories, Inc.	Medwick Laboratories, Inc. (Melrose Park, IL)
Parke, Davis & Company	Replied[3]
Progress Laboratories, Inc.	**No Reply**
Robinson Laboratory, Inc.	Acknowledged Request
HYDROCHLOROTHIAZIDE 50 mg Tablets	
Geigy Pharmaceuticals Division of Ciba-Geigy Corp.	Pharmaceuticals Division of Ciba-Geigy Corp.
Merck Sharp & Dohme, Division of Merck & Co., Inc. (HYDRODIURIL®)	Merck Sharp & Dohme
INDOMETHACIN 25 & 50 mg Capsules	
Merck Sharp & Dohme, Division of Merck & Co., Inc. (INDOCIN®)	Merck Sharp & Dohme
MEPROBAMATE 200 & 400 mg Tablets	
American Pharmaceutical Company	Acknowledged Request[3]
ICN Pharmaceuticals, Inc.	ICN Pharmaceuticals, Inc. (Cincinnati, OH)[2]
Kirkman Laboratories, Inc.	Barr Laboratories, Inc. (Northvale, NJ)[2]
McKesson Laboratories, Div. Foremost-McKesson, Inc. (KESSO-BAMATE®)	McKesson Laboratories (Fairfield, CT)[2]
Parke, Davis & Company	Replied[3]
Purepac Pharmaceutical Company	Purepac Pharm. Co. (Elizabeth, NJ)[2]
Robinson Laboratory, Inc.	Acknowledged Request

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DISTRIBUTING FIRM	MANUFACTURER[1]
MEPROBAMATE (cont)	
Sherry Pharmaceutical Company, Inc.	Zenith Laboratories, Inc.
Smith Kline & French Laboratories	Smith Kline & French Laboratories[4] (Philadelphia, PA)[2]
Stanlabs, Inc.	Stanlabs, Inc. (Portland, OR)[2]
METHYLDOPA 250 mg Tablets	
Merck Sharp & Dohme, Division of Merck & Co., Inc. (ALDOMET®)	Merck Sharp & Dohme
PAPAVERINE HCl 150 mg Capsules	
Purepac Pharmaceutical Company	Rondex Laboratories[5]
PENICILLIN V POTASSIUM 250 mg Tablets	
ICN Pharmaceuticals, Inc.	Zenith Laboratories
McKesson Laboratories, Div. Foremost-McKesson, Inc. (KESSO-PEN-VK®)	John D. Copanos & Company, Inc. (Baltimore, MD)[2]
Pfizer Laboratories, Div. Pfizer, Inc.	John D. Copanos & Company, Inc.
Progress Laboratories, Inc.	**No Reply**
Purepac Pharmaceutical Company	Rondex Laboratories[5]
Robinson Laboratory, Inc.	Acknowledged Request
Sherry Pharmaceutical Company, Inc.	Mylan Pharmaceuticals, Inc.
Stanlabs, Inc.	Biocraft Laboratories (E. Paterson, NJ)[2]
West-ward, Inc.	Biocraft Laboratories[8]
PENTAERYTHRITOL TETRANITRATE 10 & 20 mg Tablets	
Stanlabs, Inc.	Stanlabs, Inc.
PENTOBARBITAL SODIUM 100 mg Capsules	
Stanlabs, Inc.	Stanlabs, Inc.
PHENFORMIN HCl	
Geigy Pharmaceuticals Division of Ciba-Geigy Corp. (DBI® 25 mg Tablets)	K-V Pharmaceutical Company (St. Louis, MO)[2]
Geigy Pharmaceuticals Division of Ciba-Geigy Corp. (DBI-TD® 50 & 100 mg Capsules)	K-V Pharmaceutical Company
PHENOBARBITAL 30 mg Tablets	
Purepac Pharmaceutical Company	Rondex Laboratories[5]
Stanlabs, Inc.	Stanlabs, Inc.
PREDNISONE 5 mg Tablets	
American Pharmaceutical Company	Acknowledged Request[3]
ICN Pharmaceuticals, Inc.	ICN Pharmaceuticals, Inc.
Kirkman Laboratories, Inc.	Kirkman Laboratories, Inc. (Portland, OR)[2]
McKesson Laboratories, Div. Foremost-McKesson, Inc.	McKesson Laboratories
Merck Sharp & Dohme, Division of Merck & Co., Inc. (DELTRA®)	Merck Sharp & Dohme
Ormont Drug & Chemical Company, Inc.	Ormont Drug & Chemical Company, Inc. (Englewood, NJ)[2]
Parke, Davis & Company (PARACORT®)	Replied[3]
Progress Laboratories, Inc.	**No Reply**
Purepac Pharmaceutical Company	Rondex Laboratories[5]
Robinson Laboratory, Inc.	Acknowledged Request
Stanlabs, Inc.	Stanlabs, Inc.
West-ward, Inc.	West-ward, Inc. (Bronx, NY)[2]

DISTRIBUTING FIRM	MANUFACTURER[1]
PROBENECID 500 mg Tablets	
Merck Sharp & Dohme, Div. of Merck & Co., Inc. (BENEMID®)	Merck Sharp & Dohme
PROPOXYPHENE HCl 65 mg	
Progress Laboratories, Inc.	**No Reply**
Smith Kline & French Laboratories	Smith Kline & French Laboratories[4]
West-ward, Inc.	West-ward, Inc.
PROPOXYPHENE HCl 65 mg COMPOUND	
Progress Laboratories, Inc.	**No Reply**
Smith Kline & French Laboratories	Mylan Pharmaceuticals, Inc.[4]
West-ward, Inc.	Caribe Chemical Co.[7] (St. Croix, US Virgin Islands)
RESERPINE 0.25 mg Tablets	
Progress Laboratories, Inc.	**No Reply**
Purepac Pharmaceutical Company	Rondex Laboratories[5]
Robinson Laboratory, Inc.	Acknowledged Request
Stanlabs, Inc.	Stanlabs, Inc.
RIFAMPIN 300 mg Capsules	
Ciba Pharmaceutical Company	Pharmaceuticals Division of Ciba-Geigy Corp.
SECOBARBITAL SODIUM 100 mg Capsules	
Stanlabs, Inc.	Stanlabs, Inc.
TETRACYCLINE HCl 250 mg Capsules	
American Pharmaceutical Company	Acknowledged Request[3]
ICN Pharmaceuticals, Inc.	ICN Pharmaceuticals, Inc.
Ketchum Laboratories, Inc.	Replied[3]
McKesson Laboratories, Div. Foremost-McKesson, Inc. (KESSO-TETRA®)	McKesson Laboratories
Parke, Davis & Company (CYCLOPAR®)	Replied[3]
Pfizer Laboratories, Div. of Pfizer, Inc. (TETRACYN®)	Pfizer, Inc. (New York, NY)[2]
Progress Laboratories, Inc.	**No Reply**
Purepac Pharmaceutical Company	Rondex Laboratories[5]
Robinson Laboratory, Inc.	Acknowledged Request
Sherry Pharmaceutical Company, Inc.	Heather Drug Company, Inc. (Cherry Hill, NJ)[2]
Smith Kline & French Laboratories	Mylan Pharmaceuticals, Inc.[4]
Stanlabs, Inc.	Heather Drug Company, Inc.
West-ward, Inc.	West-ward, Inc.
THEOPHYLLYINE 130 mg — EPHEDRINE 24 mg — PHENOBARBITAL 8 mg	
Stanlabs, Inc.	Stanlabs, Inc.
THYROID 60 mg Tablets	
Purepac Pharmaceutical Company	Rondex Laboratories[5]
TRIMETHOBENZAMIDE HCl 250 mg Capsules	
Beecham-Massengill Pharmaceuticals	Hoffman-LaRoche[6]

FOOTNOTES
[1]In this table, manufacturer is defined as the producer of the finished dosage form which includes mixing the final ingredients and tableting or encapsulating the finished dosage form of a pharmaceutical product.
[2]Place of business of manufacturers are only listed the first time the name of the firm appears.
[3]Clarification of response requested by CPhA.
[4]Product inspected by the distributor prior to release of the drug.
[5]Rondex is a wholly owned subsidiary of Purepac Pharmaceutical Company.
[6]Listed in error as Beecham, Inc. in the October report. Beecham, Inc. intends to manufacture this product pending approval from the FDA.
[7]Product subject to distributor's quality control procedures prior to release.
[8]Distributor states that distribution of this product has been discontinued.

Mr. GORDON. Were there cases of the companies refusing to tell who actually manufactured the product, or did they disclose everything?

Dr. APPLE. Mr. Gordon, I cannot say that they refused. But as of the compilations in November and December—October and November, rather—there were a number of firms that had not responded to the request for the information. In the article, the tables here show the actual date replied. In a number of instances there are blanks—actually it states "no reply."

Mr. GORDON. What about these statements that Mr. Feinberg has been making about the rejection rate on DOD plant inspection is 45 percent, and the rejection rate on precontract award sample inspections is 42 percent?

The FDA explained what that meant yesterday.

Do you have any comments on that?

Dr. APPLE. Well, Dr. Feldmann may later on. He has studied the tables, and I have not. I can make this general observation. My concern when I hear a statement that 45 percent of the manufacturers have been rejected—I am interested in what the universe is, because it would be like my going up to Walter Reed Hospital or Bethesda Naval Hospital and going into the VD ward and then walking out of there and saying that 90 percent of the patients have venereal disease. Well, sure they do in the VD ward. But this does not characterize the total universe of patients in that hospital. So I think these statements that you cited are grossly misleading, and they are intended to be inflammatory and cast suspicion on the Nation's drug supply.

This is not to say that every firm meets the criteria. But I am saying that these are generalizations that we have been trying to find some documentation for.

Mr. GORDON. Well, you have the documentation. We gave it to you.

Dr. APPLE. Well, Dr. Feldmann will comment on that. He has studied that material. I have not, Mr. Gordon.

Mr. GORDON. All right.

Senator NELSON. Our next witness will be Dr. Feldmann, Associate Executive Director for Scientific Affairs of the American Pharmaceutical Association.

Go ahead, Dr. Feldmann.

Dr. FELDMANN. Thank you, Mr. Chairman. I am Edward G. Feldmann of the American Pharmaceutical Association.

You have requested that we discuss the views of the APhA 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 appears in my prepared statement. To save time I will not read it. But it addresses itself to the fact that the Association shall publish a compendium of standards and specifications known as the "National Formulary", and also will promote the safe use of drugs by taking certain steps as an Association in cooperation with other organizations to assure drugs of the highest quality.

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 professions most capably and if the public is to be best served with pharmaceutical products which are both effective and safe. I have appended to my statement as submitted an exhibit A, which is an illustration of an article from the 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. I have appended exhibit B to my statement as submitted, which is a tearsheet from the 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. And I have provided you with several examples of those.

Furthermore——

Senator NELSON. May I ask a question there?

Dr. FELDMANN. Yes, sir.

Senator NELSON. When did your organization become aware of the digoxin problem?

Dr. FELDMANN. Well, there have been two so-called problems involved with digoxin. One of these pertained to content uniformity, and the other an indication that there is a bioavailability problem involved with the product.

We became aware of the matter of the content uniformity problem in the late 60's, and as was testified to yesterday by Commissioner Schmidt, the USP adopted a content uniformity test, after which the FDA implemented it via a certification program in their St. Louis facility to batch certify digoxin.

More recently there has been indication that there is a problem involved with the bioavailability of the product. This came to the public eye with the so-called "Lindenbaum study", which was published in the "New England Journal of Medicine" along about late 1971. This has resulted again in USP taking action to adopt a dissolution test, which has been adopted by way of a recent interim

revision announcement. And again, the FDA has been implementing that, as was testified to by Commissioner Schmidt.

Now, in the DPSC material that DOD supplied to you, they indicate in answer to your question—about when did they become aware of this, question 15(d)—they indicate that they learned of the problem in 1965. But they do not say what the problem was. They do not identify it in any way.

You also asked them about whether they supplied information about this to the FDA, and they responded there is no record on this. Their explanation is that this was before the so-called Intergovernment Professional Advisory Council, or IPAD, was fully operational.

I find this a little puzzling, because further on in their same response under 15(d), they say that they were regularly supplying such information—for at least several other products that are listed—going back to May of 1961; they supplied information in 1961, 1962, 1963 and so forth. So I do not quite understand that as an explanation.

Senator NELSON. Well, there is another contradiction, it seems to me, and that is, the Intergovernmental Professional Advisory Council on Drugs was established in July 1963, 2 years before the Department of Defense said they discovered problems with digoxin.

The other question is, why do you need an intergovernmental advisory council anyway; if you found some serious defect in a drug you would think that the agency would feel the responsibility forthwith, if it were a matter of any consequence, to notify the Food and Drug Administration.

Would you not?

Dr. FELDMANN. Well, I would think that it is desirable by whatever mechanism you choose to use to have exchange of information, whether it is this intergovernmental council or some other mechanism.

I would be more apt to question how effectively this particular operation has worked to achieve that intended purpose. The indications I have gotten are that for the most part information has been irregularly exchanged, and where it has, it has been largely provided to the DPSC, rather than the reverse being the case.

Senator NELSON. Well, since the DOD does not recite what the problem was, we do not know whether it involved a question of bioavailability or a question of product uniformity or neither.

Dr. FELDMANN. Correct.

I would also expand on my earlier statement to indicate to you that whether or not they informed FDA—and they apparently have no record—certainly they did not inform the professions. They did not inform the APhA, who, as I have indicated just in my immediate preceding testimony, has over the years made an effort to disseminate such information to the professions—to alert the professions, particularly pharmacy, but also the health professions in general, when to be alert to a potential problem or to take note of it.

And I think it is most unfortunate that they have not seen fit to make such information available, if indeed they have had it.

Senator NELSON. Please go ahead.

Dr. FELDMANN. 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: 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; 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; 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; 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 the establishment of a bioavailability project whereby, in an efficient and coordinated manner, 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: The association has collaborated with efforts of the California Pharmaceutical Association in supporting the so-called Crown bill and regulations for its implementation. This is what Dr. Apple referred to just a few moments ago in response to one of your questions about requiring the name of the actual manufacturer or fabricator on the product label.

This is an important piece of information to assist practitioners in making quality judgments relative to that article.

And the association endorsed and cooperated with the Food and Drug Administration and the U.S. Pharmacopeia in a type of grassroots 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.

FDA Commissioner Schmidt's statement yesterday mentioned, as a single example of this, the fact that a pharmacist in the course of his practice noted the problem with respect to the novelty container used for nitroglycerin tablets.

Senator NELSON. Is that the plastic container case?

Dr. FELDMANN. Yes, right. The pan shaped container.

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, 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.

Mr. GORDON. May I interrupt for just a moment?

This is to Dr. Apple. What is a "schlock" manufacturer?

This word "schlock" is used especially by the big firms.

Dr. APPLE. I would have to describe it in the field of pharmaceuticals; it is certainly a derogatory euphemism, frequently employed by industry propagandists to describe a small firm which concentrates on producing drug products which are in the public domain.

I suppose the inference is that such a firm cuts corners, at least the way the term is used. That is, that these firms, schlock manufacturers, cut corners on quality; they cut corners on meeting the legal standards; and that they are in business to make a fast buck.

I do not know of any.

Senator NELSON. Any such manufacturers?

Dr. APPLE. Mr. Chairman, I cannot identify any particular manufacturer that meets this description.

Mr. GORDON. Actually, that word is also onomatopoeic. In the sense it is an invidious word. It is supposed to engender hostility toward a person who can be identified by that word.

Now, I notice that the APhA Academy of Pharmaceutical Sciences says that there is a considerable amount of "schlock" manufacturing going on in this country.[1]

Does the APhA have any facts to support this?

Dr. APPLE. Mr. Gordon, we have not received from any member of the association, and we have not read anywhere, where any firm has been identified this way. We do not know the identify of such firms.

I agree with you that the term is frequently used, especially in speeches at pharmacy meetings. It is used frequently in discussions.

[1] See page 10758.

It has crept into the literature. I regret that it has even crept into some of the comments by eminent scientists in our field who tend to use this euphemism without identifying anyone.

Mr. GORDON. Well, is it possible for you to send a letter to the academy members to find out exactly what evidence they have on this particular subject, and perhaps submit it to the Committee for our records?

Dr. APPLE. Yes, it is possible. We would be glad to do it. We would like to know who they are as well as the committee does. Yes, we will do it if you wish.

Mr. GORDON. Thank you.

Senator NELSON. Please go ahead.

Dr. FELDMANN. I would simply add to Dr. Apple's statement that we would welcome having the identity of these firms brought out for us, because if we were aware of them, the association would feel it is incumbent upon us to make pharmacists aware of them; that was the purpose of my exhibit A in this testimony, where I showed that in the past, going back to 1960 when there was a problem of this nature and the association became aware of it, we took the action necessary to make pharmacists aware of it also.

Senator NELSON. I suspect you will not find any evidence. We have been taking testimony for 7 years on this question, and those who make that kind of a criticism have yet in 7 years to come up with any specific evidence. So I think reasonable persons can conclude that it is a propaganda campaign based on no substance whatsoever.

Dr. APPLE. Well, Mr. Chairman, you asked the question at the February 1 hearings at the Subcommittee on Health from Dr. Cavallito. I do not know if you received any response to that yet.

Senator NELSON. No, we have not. We have asked questions of some of these people that are 7 years old and we have not gotten a response yet, though they promised that they would give us one. I know the mail is running slow, but——

Dr. FELDMANN. I will continue.

Such implications and allegations appear to run contrary to information available to us from other sources. And these are the implications and allegations made by the DPSC spokesmen. 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 that the existing standards and specifications may not be generally adequate; or that the existing standards and specifications, while being adequate, are not being adequately enforced.

With respect to the former possibility, we note that then—Brig. Gen. George J. Hayes of the Medical Corps, U.S. Army, Principal Deputy Assistant Secretary of Defense, had testified before your subcommittee, Mr. Chairman, on February 3, 1971, and in his prepared statement—again, I will not read the entire quote that is reproduced here. But I would specifically call your attention at the top of page 8 to where he says,

> We cannot procure competitively without generic specification. Our standards are basically those of the USP and the NF, 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.

So, as General 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 lightweight 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.

Senator NELSON. Have these suggested deficiencies ever been delineated by the DOD?

Dr. FELDMANN. I am sorry, Mr. Chairman?

Senator NELSON. Have they ever described what the deficiencies were?

Now, the statement by General Hayes does not suggest any deficiencies whatsoever.

All he is saying is that they use the compendial standards. That is all we have ever heard specifically, and that is that in the handling of products overseas there may be circumstances which would be quite different from handling products within the boundaries of the United States. They may have to be hauled into a jungle and be there a month or two or three in a humid climate, which does not exist here. They may be taken into the Arctic under circumstances which do not exist here, and that, therefore—understand them to be saying—we require in some circumstances certain specifications for packaging, handling, that would not be necessary in this country.

But I have not seen any description of any deficiencies in the drug products themselves from a medical or therapeutic standpoint. Have you?

Dr. FELDMANN. Getting information from the DPSC has been a very tortuous task, Mr. Chairman. It is very difficult to get information from them. I have seen very little except for these statements that were referred to earlier about so many percent of unnamed drug manufacturers, so many percent of drug products.

Now, in the information that you mentioned a moment ago that you obtained from DPSC, and which you provided to me prior to our appearance here today to examine, one section did ask them, under question 15(e)——

Senator NELSON. Under which one?

Dr. FELDMANN. Fifteen (e).

You quoted—a statement made by Mr. Feinberg, "We develop definitive product specifications which often exceed official or commercial standards." You asked them to please name each product for which such specifications have been developed, the significance for each product of these extra requirements, and the medical purpose served by these extra requirements.

I examined the answer that they provided, and there are a number of drugs which are either in the USP or the NF listed in their response. Knowing that Dr. Banes will be testifying later, I will not address myself to the USP drugs. But there are four NF articles that are listed in their response.

One of these is Glyceryl Guaiacolate syrup NF. This is cough syrup, an expectorant. They list three additional tests. One of these is a "taste palatability test." Well, the matter of taste is a subjective matter, Mr. Chairman, at least in my opinion. This can be a matter of preference for the patient, but I would hardly say that this falls into a critical medical consideration.

They have a so-called "accelerated aging test."

Senator NELSON. Accelerated aging?

Dr. FELDMANN. Yes, which simply means that the product is subjected to intensified environmental conditions to see whether it will stand up. Well, the NF specification is such—the "general notices" in the NF require—that an article meet the standards during its entire shelf-life. So this is, in a sense, really already covered by the NF monograph.

They then have a requirement for "color value, specific gravity and refractive index." Well, in our opinion, Mr. Chairman, in the opinion of the official compendia, the NF and USP, these types of specifications are totally inappropriate. They are appropriate for an active ingredient, something that will go into the formulation, to ascertain its purity; but to apply to a formulation which is a mixture of ingredients, they are inappropriate. It would appear that such specifications may be largely geared or skewed around one particular formulation.

Senator NELSON. Well, that is the issue or suspicion, to use a more accurate description, of what may be going on. That is to say that they may be taking a drug, in this case a cough syrup, and deciding they want to buy it from a particular manufacturer, so they take all of the manufacturers' specs and then ask for a bid, and there is

only one manufacturer who can meet it. Else why, or how, would they ever be able to decide what the specific gravity ought to be? They could decide what the specific gravity ought to be, and then ask for bids and find out that there is no manufacturer in America that produces one with that specific gravity. So I suspect what they actually do is to take a cough syrup and then test the specific gravity and the other aspects of taste and so forth and then write a spec and ask for bids. And what you have done is eliminate all of the competition.

Whether that is intentional or not, that would be the effect, would it not?

Dr. FELDMANN. Yes, it would appear to be, Mr. Chairman. I am not in a position to be able to draw a conclusion from these things, but I can certainly supplement what you have said with some rather dramatic examples, if you would care to have me do so.

Senator NELSON. We would like to have them for the record.

Dr. FELDMANN. I might simply mention several descriptions, purchase descriptions, which are the only things that we have gotten from DPSC prior to the material you supplied to me. I will be happy to submit approximately a half dozen or a dozen of these chosen simply at random from their listings, but they cover various things, such as optional rotation, specific gravity, very narrow pH limits and so forth.

Beyond this, however, they have some other very strange specifications. For instance, under ethynodiol diacetate with mestranol tablets, they require that the shape of these tables shall be pentagonal, which is a rather unusual specification, I would think.

Senator NELSON. Do they identify the manufacturer who can meet that spec?

Dr. FELDMANN. No, and I am not able to, Mr. Chairman.

Senator NELSON. Can you see any therapeutic service or therapeutic benefit from the shape of the tablet?

Dr. FELDMANN. I am not aware of any, Mr. Chairman.

Senator NELSON. If you hear of any, would you please let us know?

Dr. FELDMANN. Under dimenhydrinate tablets, they require that the uncoated tablet shall be yellow in color. Well, this would be logical if the drug substance itself were yellow, but the USP XVIII description of this says that it is a white, crystalline, odorless powder. So, again, the fact that these tablets must be yellow in color would seem to be rather a peculiar requirement.

Similarly, the same can be said about ethinyl estradiol tablets, which, again, state that the sugar-coated tablet shall be light tan in color, and the article itself is coloreless.

But I think that one that is really the epitome here is doxepin hydrochloride capsules, which specify that the capsules shall have a pink body and a blue cap.

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 issue a correction that under the assay the word lincomycin is deleted, and substitute clindamycin.

This would suggest to me that the specifications may, or must have been written from a draft that had a specific company's drug name in originally, and they forgot to delete it in one case.

Mr. GORDON. We are going to get those for the record, are we not?

Dr. FELDMANN. Yes.

I think that any doubt is removed when one goes to clomiphene citrate tablets, in which it states a trade name at the beginning of their bid specification: "shall be the William S. Merrell Company's Clomid tablets, and in addition shall comply with." I do not see how such a bid specification can go out to multiple bidders, or can be competitively bid upon.

Senator NELSON. That is one way to insure that you get only one bid.

Please go ahead.

Dr. FELDMANN. 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 certain assay limits which they claim are higher or will insure greater adherence to a 100 percent of label claim. In fact, their specification does permit assay at not less than 93 percent up to 90 days, whereas the NF limits are a minimum of 90 percent for the entire shelf-life of the article.

Senator NELSON. What is the shelf-life?

Dr. FELDMANN. Whenever it is offered for dispensing to the patient—in other words, whenever it is in the channels of distribution.

Senator NELSON. How can you have a definition of shelf-life like that? There is some termination date.

Dr. FELDMANN. The manufacturer would need to state an expiration date if he is not confident or sure that it will maintain its potency under the normal conditions of storage—or as stated on the label, if there are special conditions of storage. If it will deteriorate to an extent that it would fall below the standard, then it is up to him to recall the product and remove it from the channels of distribution.

Senator NELSON. Well, does the manufacturer know what the shelf-life of the product is in all cases?

Dr. FELDMANN. I do not know whether he does or not, Mr. Chairman. This should be a factor in his being permitted to market a drug. In other words, this would be a responsibility which a manufacturer should assume.

Senator NELSON. Well, does the label show it, the shelf-life?

Dr. FELDMANN. Those products which are expected to possibly deteriorate or which might be expected to deteriorate would carry an expiration date, or should carry an expiration date, which would indicate a point or a date beyond which the integrity of the product could not be assumed.

Senator NELSON. Well, then, the specification, if I understood you correctly, of the compendia is higher than the specification of the DOD in this case.

Dr. FELDMANN. In our opinion, it is at least as good. That is correct.

The third item that they list is an ophthalmic ointment, containing three antibiotics. And since this is an antibiotic, it is covered by the FDA's certification regulations, and the compendia do not provide separate standards for those in addition to FDA's, so this would not be higher than compendia standards.

Mr. GORDON. If this is a form 6 drug, that is an antibiotic subject to batch testing, the requirements are set by the FDA. And, as I understand it, additional requirements cannot be set up by the DPSC. Is that correct?

Dr. FELDMANN. I am afraid I cannot answer that question. Perhaps the FDA would be able to. I am afraid I cannot.

Mr. GORDON. Because if they batch test it, they have to meet certain FDA requirements.

Dr. FELDMANN. I would think if they meet the FDA requirements, I know of no case where additional requirements above and beyond those should be necessary for an article marketed in this country for public consumption.

The final example that they listed for you. Mr. Chairman, is hyaluronidase for injection, which they list that they have certain color limits. The NF states that the article shall be colorless, which in essence is saying the same thing.

Senator NELSON. The National Formulary says that?

Dr. FELDMANN. Yes, the NF states that it shall be colorless.

DPSC also states a solubility time limit, which, again, the National Formulary requires that the article completely dissolve in solution; and DPSC lists a content uniformity test.

Now, this may, on the surface, appear to be a substantial added requirement, above and beyond the NF requirement. Well, as it so happens, back in the late 1960's, I had correspondence at that time, when I was director of the National Formulary, with personnel in the DPSC. And in three pages, I tried to explain to them that a content uniformity test in this particular case was entirely superfluous, that the assay and the other provisions of the monograph were such that they assured content uniformity of the article.

And, again, Mr. Chairman, I would be pleased to submit this correspondence for your record.

Senator NELSON. If you would.

[Testimony resumes at page 10217. The information referred to follows:]

AMERICAN PHARMACEUTICAL ASSOCIATION
The National Professional Society of Pharmacists

February 25, 1974

Honorable Gaylord Nelson
United States Senator
Senate Select Committee on Small Business
Room 424
Old Senate Office Building
Washington, DC 20510

Dear Senator Nelson:

During the hearings of the Monopoly Subcommittee on February 21, I referred to a number of documents or matters of information in the course of my testimony. You requested that I submit copies of pertinent material to you for the Subcommittee record.

On this basis, I am herewith enclosing the following items:

a. Copies of letters dated September 30, 1969 and October 8, 1969 which I sent (in my capacity at the time as Director of the National Formulary) to Defense Personnel Support Center (DPSC) staff. In particular, I quoted during my testimony from the latter half of the first paragraph which appears on page three of the September 30 letter and which explains to the DPSC staff the fact that a weight variation test and a content uniformity test in the case of Hyaluronidase for Injection would be meaningless and redundant.

b. Copies of pertinent pages of "Defense Medical Purchase Discription" documents issued by DPSC. These include identification of the drug dosage forms involved, as well as the specific requirements or specifications which I quoted in my testimony as being -- in my opinion and based upon knowledge available to me -- unnecessary and meaningless from a medical or drug quality standpoint. These examples were cited in the context of the discussion relative to examples of DPSC requirements which serve to eliminate competition among bidders by being structured in a manner that they describe a single manufacturer's particular drug product.

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CABLE ADDRESS: AMPHARMA

c. A list of dates and meeting information relative to the Intra-Governmental Professional Advisory Council on Drugs and Devices (IPADD) -- working group on specifications and quality control of drugs of which Mr. Max Feinberg is chairman. During my testimony I referred to the fact that this Committee has met less and less frequently and that meeting minutes were not issued for the past two meetings.

I believe this provides all of the supplemental information you requested from me during the February 21 hearing. In the event that additional information or documents are desired, I shall be pleased to attempt to provide them.

Sincerely,

Edward G. Feldmann

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

EGF:ehb

Enclosures

"DPSC" - File

→ See page 3

September 30, 1969

Mr. Thomas C. Filoccia
Drug and Chemical Unit
Technical Services Branch
Defense Personnel Support Center
2800 South 20th Street
Philadelphia, PA 19101

Dear Mr. Filoccia:

I am responding to your communication dated August 8, 1969, (DPSC-ATTS-2 :rag) with which you enclosed a draft, which, when published in final form, would become part of Federal Standard No. 148a.

While your letter requested that our reply be sent within 30 days, I would note for the record that my associate in the NF office, Mr. Durward Dodgen, has telephoned you and Mr. Cattler on this matter several times during the past month. During these discussions, he was informed that our comments would be welcomed and duly taken into account even though they did not reach you until this date.

A principal reason for the delay in our response can be attributed to our effort to edit or revise your draft based upon our knowledge of the NF monographs involved, the pertinent NF General Test chapters involved, and the basis for each of these as well as their proper application and interpretation. Our efforts in this regard have not been particularly successful, however, since we are not certain that our redraft of your proposed specification will necessarily achieve the precise results which you intend. Consequently, we are forced to conclude that it would be simplest to provide you with an explanation of the basis of the NF standards and leave it to you to utilize or apply this information as you see fit in developing your own specifications.

The basic approach of the NF with respect to sterile solids is comparable and consistent with our approach to other dosage forms including tablets and capsules.

In the case of sterile solids having diluents present (these are identified by monograph titles reading "_____ _____ for Injection"), the sterile solid is required to comply with the monograph ruberic tolerance which provides limits, compliance with which is determined through the Assay utilizing a pooled sample of a number of containers. In the case of these monographs, moreover, the article must comply with a specification in the monograph concerning either weight variation or content uniformity.

In the case of sterile solids which are available in strengths of 50 mg. or less of active ingredient, it is our policy to require compliance with the content uniformity specification for sterile solids, as detailed beginning on page 796 of NF XIIII page proof. (The procedure employed will be specified as either Method I or Method II, depending on whether the Assay procedure can be utilized or whether a special procedure is called for.) If the article is such that no strength or size is available in quantities of 50 mg. or less of the active ingredient, it is then presumed that the major portion of the substance present is the active ingredient, and the weight variation test (combined with the Assay) provides adequate assurance of homogeneity of the sterile solid. In such cases, therefore, the monograph will specify compliance with the weight variation test for sterile solids, which appears on page 902 of NF XIIII page proof.

In the case of sterile solids which have no diluents present (these are identified with monograph titles reading "Sterile _____"), the approach is slightly different. As in the case of the other sterile solids, a rubric definition is provided with specified tolerances. Since the article is the pure drug, only prepared and packaged in sterile form, the Assay virtually without exception is identical to the Assay for the drug substance and the tolerances are comparably based upon a sample obtained from the pooled contents of a number of containers. With respect to vial to vial differences, however, the approach in the case of these sterile solids is somewhat different. The article has no diluents or added substances whatever and, as a consequence, the weight variation test provides a reliable index of vial to vial homogeneity without necessitating any more sophisticated analytical approach than simply weighing the contents. As a consequence, such monographs include the specification for the weight variation test. This in itself, however, is not sufficient to assure with certainty the suitability of the article, since the weight variation test requires compliance with the average net weight rather than with a labeled quantity. For this reason, the weight variation test in NF monographs for sterile solids without diluents provides to specify that the mean net weight so determined is within specific percentage tolerances of the labeled amount. The specific range is specified in the individual monographs rather than in the General Tests section to take into account the fact that depending upon the nature of the product, its size, etc., the tolerances specified might need to vary from one monograph to another. This, of course, is analogous to stating the tolerances in all other monographs in the individual monograph rubric definitions.

The above constitute the general policies involved in drafting the respective monographs for NF sterile solids. Exceptions may be made on an individual basis for justified reasons. I am enclosing with this letter a tabulation of NF XII sterile solids and NF XIII sterile solids, which may be of interest to you. The NF XII sterile solids do not include the content uniformity test because this was newly introduced in the case of this dosage form in NF XIII. There is only one inconsistency in this NF XII tabulation, in that Chlordiazepoxide Hydrochloride for Injection should be entitled Sterile Chlordiazepoxide Hydrochloride. As initially marketed, this article included diluents. By the time the monograph was completed, however, the article available contains no added substances but has separate diluents. Consequently, the monograph title should have been revised accordingly, although the monograph definition and the content of the monograph is all satisfactory. In the case of NF XIII sterile solids, the articles are all consistent with our policies with the apparent exception of the monographs Sterile Chymotrypsin and Hyaluronidase for Injection. However, there are special circumstances pertaining to each of these articles which require them to be exceptions to the general policies. These revolve about the fact that both are enzyme products, with peculiar problems associated with the non-homogeneity of enzymes. You will note that in each case (NF XIII page proof, page 169 and page 347), the Assay directives call for conducting the Assay on individual vials of the article rather than pooled samples. As a consequence, weight variation tests are meaningless and the Assay itself amounts to content uniformity.

I trust that the information provided above will be helpful to you in revising your specifications. My principal desire has been to indicate the basis for the NF approach to these monographs and to point out that the approach followed not only provides adequate assurance of suitable standards and specifications, but that the standards and specifications for this type of dosage form are consistent with other dosage forms such as tablets and capsules.

In particular, we find the proposed wording under item 86.4.2. to be especially objectionable and would recommend that appropriate changes be incorporated. We would further recommend that comparable changes be incorporated in section 86.4.3 of the proposed amendment to Federal Standard No. 1d2a be considered.

Sincerely yours,

Edward G. Feldmann, Ph.D.
Director

EGF:pal
Enclosure

October 8, 1969

Mr. Max Feinberg
Defense Personnel Support Center
Directorate of Medical Material
2800 South 20th Street
Philadelphia, PA 19101

Dear Max:

On September 30, 1969, I sent a letter to Mr. Fileccia embodying an explanation of the NF approach to providing standards and specifications for sterile solids.

I have now received a copy of your letter dated October 1, 1969, addressed to Dr. Miller, in further connection with this subject (your reference DPSC-ATTN-24:kmc). By and large, the documents enclosed with your October 1 letter restate the DPSC viewpoint as previously expressed and as reflected in the draft document which Mr. Fileccia had transmitted for review and comment. As such, I will not reiterate the NF viewpoint in these areas, but would simply refer you to my September 30 letter.

There is, however, one new point which is introduced in the enclosures to your October 1 letter which had not arisen before and concerning which I have, therfore, not previously commented. This is the matter of sterile solids with added substances which are lyophilized in the final container and for which the NF provides an exemption from compliance with the Content Uniformity Test, as noted in the enclosure which accompanied your letter.

Please note that there are several conditions embodied in the NF exemption which are not specifically mentioned in your discussion of this exemption. These conditions are: (a) that the article was prepared from a true solution; (b) that the lyophilization process be performed in the final container; and (c) that the label must carry a statement to this effect in order for the exemption from this Content Uniformity requirement. Finally, while an article meeting these three conditions is then exempt from the Content Uniformity requirement, you will note that the NF specification then states that the preparation is required to meet the Weight Variation Test for sterile solids.

This exemption was adopted only after careful consideration by the NF Board and appropriate study of the manufacturing procedures utilized within the pharmaceutical industry. This study convinced the National Formulary that such an exemption would be entirely appropriate and would adequately assure suitable potency, homogeneity, and related standards of quality. If the conditions exist which would qualify a product for this exemption, one is

assured of a homogenous distribution of the active ingredient, since it is initially in the form of a true solution. The Weight Variation requirement, combined with the assay and rubric definition, then provide complete assurance of the satisfactory quality of the lyophilized material in the individual final containers.

Consequently, it is our opinion that thereiis no basis for the statement in the third paragraph of your enclosure which reads "DPS feels the above standards are inadequate." (Incidentally, the sentence which immediately follows this quoted sentence does not appear to make sense as it reads--it would appear that the word "not" was left out of the second clause in this sentence.)

I trust these additional comments will be helpful to you in preparing your Amendments to the Federal Standard for Parenterals.

With kind regards,

Sincerely,

Edward G. Feldmann, Ph.D.
Director

EGF:pal
Enclosure

MODIFICATION NO. 3
DATE: 21 April 1972

MODIFICATION TO DEFENSE MEDICAL PURCHASE DESCRIPTION

This modification forms a part of Defense Medical Purchase Description No. 3, dated 28 May 1970, and covers the following item to the extent specified herein:

Federal Stock No.	Item Identification
6505-926-8985	DEXTROMETHORPHAN HYDROBROMIDE AND GLYCERYL GUAIACOLATE SYRUP, 4 fl oz (118 cc)

Page 2:

3.1.9 Optical rotation. Delete in its entirety. There in no substitute paragraph.

Page 5:

4.3.2 Assay (dextromethorphan hydrobromide in the finished preparation). Line 8, delete "282 mu" and substitute "278 mu."

Page 7:

5.2.1 Immediate containers. Add the following new subparagraph:

"(j) the following or similar statement: 'A precipitate may form in the syrup on exposure to freezing temperatures. On warming the precipitate should redissolve. In the event it does not redissolve, discard the syrup.'"

Page 8:

5.4.2 "Intermediate package" and "5.4.3 "Exterior container." - Delete "STORE IN A COOL PLACE (50° - 80° F.)" and substitute:

"STORE AT CONTROLLED ROOM TEMPERATURE (59° - 86° F.)."

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6505-926-8985 (P. D. No. 3)

3.1.3.3 Alcohol. The finished preparation shall assay to contain not less than 1.1 percent and not more than 1.7 percent ethyl alcohol, by volume, when determined as specified in 4.3.3.

3.1.4 Identity. The retention time for the glyceryl guaiacolate extracted from the syrup shall be the same as the retention time of Glyceryl Guaiacolate N.F. Standard when determined as specified in 4.3.1.

A copy of the standard graph shall be kept on file at the Defense Personnel Support Center for use if samples are submitted.

3.1.5 Color. The finished preparation shall have a range of 55 to 65 percent transmittance when determined as specified in 4.3.5, using a 10 percent solution of the syrup.

3.1.6 pH. The pH of the finished preparation shall be between 2.00 and 3.00 at 25° C., when determined potentiometrically, using the U.S.P. method.

3.1.7 Specific gravity. The specific gravity of the finished preparation shall be not less than 1.235 and not more than 1.255 at 25° C., when determined using a pycnometer, hydrometer, or specific gravity balance.

3.1.8 Refractive index. The finished preparation shall have a refractive index of not less than 1.4300 and not more than 1.4400, when determined at 25° C., using an Abbe Refractometer or equivalent instrument giving comparable results.

3.1.9 Optical rotation. A 20 percent solution of the preparation shall have an optical rotation not less than +85° and not more than +100° when determined using a 100 mm tube and a sodium light source. Multiply the observed rotation by 10.

3.1.10 Flavor and palatability. The finished syrup shall be mentholated, cherry vanilla flavored, and shall be palatable and pleasant to the taste with no unpleasant after-taste. Not later than the time specified for opening of bids or receipt of proposals, the offeror shall submit to the contracting offices six (6) individually packaged samples (each containing 4 fl oz) of Dextromethorphan Hydrobromide and Glyceryl Guaiacolate Syrup, representative of the product which the offeror proposes to furnish. Two (2) samples will be subjected to panel testing for a determination of palatability (see 4.3.6 - Palatability test). The remaining samples will be used by cognizant Government inspection and quality assurance activities for determining compliance of supplies furnished hereunder with the palatability requirement. Approval as to palatability of any sample submitted by the offeror will not constitute approval of the sample as to any other requirement of this specification.

SCIENTIFIC AUG 31 1972

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 6	DATE 17 May 1972

FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-261-7246	ETHINYL ESTRADIOL TABLETS, USP, 0.02 mg, 500s	Bottle

Shall be Ethinyl Estradiol Tablets, USP, and shall be in accordance with all applicable requirements of Federal Standard Fed. Std. No. 140a, dated October 30, 1966, and Amendment-1, 25 March 1970 and as specified herein.

S2. Classification. Shall be type I, class 2, style A, grade 1.

S5.2 The following additional requirements and tests are added to this paragraph:

Shall be sugar coated tablets containing 0.02 mg of Ethinyl Estradiol per tablet, within the applicable assay limits for the tablets.

S6.4.2. Color. The sugar coated tablets shall be light tan in color.

Not more than 6 months shall have elapsed from date of manufacture until delivery to the Government.

PREPARATION FOR DELIVERY

Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-00186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, and as specified herein:

Immediate containers. Shall comply with the following classification:

GROUP A CLASS 1 TYPE e STYLE 2 GRADE 1

CLOSURE A, B, or F SEAL A or B

Labeling. Labeling shall be in accordance with the requirements of the Federal Food, Drug and Cosmetic Act, and shall include the information required below:

Immediate containers. Each immediate container label shall bear the following information. However, the information is not required to appear in the sequence indicated.

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DPSC FORM 2087 OCT 68

REPLACES DMSC FORM T-4120/11, MAR 64, WHICH WILL BE USED UNTIL DEPLETED

12 B

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 5	DATE 22 June 1972
FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-116-9660	DIMENHYDRINATE TABLETS, USP, 50 mg, 100s	Bottle

FILE

Shall be Dimenhydrinate Tablets, U.S.P., and shall be in accordance with all applicable requirements of Federal Standard No. 1405, dated 30 October 1966, and Amendment-1, dated 2[illegible] March 1970, and as specified herein:

3.2. Classification. Shall be type I, class 1.

3.2.2 The following additional requirements are added to this paragraph:

Shall be tablets containing 50 mg of Dimenhydrinate, within the applicable assay limits for the [illegible].

3.4.3 Uncoated tablets. Tablets shall be yellow in color.

3.4.7 Scoring. Tablets shall be scored.

PREPARATION FOR DELIVERY

Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-[illegible], dated 15 May 1969, and Amendment-1, dated 27 October 1969, and as specified herein:

Immediate containers. Shall comply with the following classification:

[illegible] UP A	[illegible] 1	TYPE [illegible]	STYLE 2 GRADE 1 or 2
CLOSURE A, [illegible], or [illegible]			SEAL A or B

Labeling. Labels shall be in accordance with the requirements of the Federal Food, Drug and Cosmetic Act, and shall include the information required below:

Immediate containers. Each immediate container label shall bear the following information. However, the information [illegible] required to appear in the sequence indicated:

(a) The item name designated as "DIMENHYDRINATE TABLETS, U.S.P."

(b) The quantity of active ingredient designated as "50 mg"

(See additional label information on page 2)

DPSC FORM 2087 OCT 65

REPLACES DMAC FORM [illegible]-20/11 MAR 64, WHICH WILL BE USED UNTIL DEPLETED.

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 2	DATE 29 April 1971
FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-935-6836	ETHYNODIOL DIACETATE WITH MESTRANOL TABLETS, 63s	Box

FILE

1. SCOPE

1.1 This specification covers Ethynodiol Diacetate with Mestranol Tablets, 63s.

2. APPLICABLE DOCUMENTS

2.1 Unless otherwise indicated, the issue in effect on date of invitation for bids or request for proposals of the specifications and standards referenced in the body of this specification shall apply to the extent specified herein. These documents may be obtained as directed by the contracting officer.

3. REQUIREMENTS

3.1 Material. Shall be Ethynodiol Diacetate with Mestranol Tablets and shall be in accordance with all applicable requiremements of Fed. Std. No. 1l0a, dated 30 October 1966, and Amendment-1, dated 25 March 1970, and as specified herein:

S2. Classification. Shall be tyne I, class 1.

Shall be suitable for use as an oral contraceptive.

S3.3 The following additional requirements and tests are added to this paragraph:

Each tablet shall contain the following:

Ethynodiol Diacetate- - - - - - - - 1.0 mg
Mestranol - - - - - - - - - - - - - 0.1 mg

The tablets shall assay to contain between 93.0 percent and 107.0 percent of the labeled strength of Ethynodiol Diacetate, and between 90.0 percent and 115.0 percent of their labeled strength of Mestranol, when assayed as specified in 4.3.1.

The Ethynodiol Diacetate powder used in the manufacture of the tablets shall be in accordance with the tests, standards, and requirements of the U.S.P., including any supplements or revisions thereto.

The Mestranol powder used in the manufacture of the tablets shall be in accordance with the tests, standards, and requirements of the U.S.P. and, in addition, shall comply with the following:

Methoxyl (radical). Shall contain not less than 9.75 percent and not more than 10.25 percent of methoxyl (radical) when assayed by an appropriate, reproducible method.

6505-935-5836 (P. D. No. 2)

All other ingredients used in the manufacture of the tablets shall comply with S5.1.

S6.4.2 Color. Uncoated tablets shall be white.

S6.4.5 Shape. The tablets shall be pentagonal.

S6.4.9 Disintegration and solubility. Tablets shall meet the requirements of the U.S.P. tablet disintegration test for uncoated tablets in not more than 15 minutes.

S6.4.10.1 Uncoated tablets. Tablets shall meet the requirements of the Weight Variation Test for Tablets, as set forth in the U.S.P., including any supplements or revisions thereto.

4. QUALITY ASSURANCE PROVISIONS

4.1 Supplier responsibility for inspection. Unless otherwise specified in the contract or purchase order, the supplier is responsible for the performance of all inspection requirements as specified herein. Except as otherwise specified in the contract or order, the supplier may use his own or any other facilities suitable for the performance of the inspection requirements specified herein, unless disapproved by the Government. The Government reserves the right to perform any of the inspections set forth in the specification where such inspections are deemed necessary to assure supplies and services conform to prescribed requirements.

4.1.1 Records of examinations and tests performed by or for the contractor shall be maintained by the contractor and made available to the Government, upon the Government's request, at any time, or from time to time, during the performance of the contract and for a period of 3 years after delivery of the supplies to which such records relate.

4.1.2 No company supplying any ingredient(s) to the contractor will be considered an acceptable facility for the performance of any inspection requirements specified herein.

4.2 Sampling and inspection. The classification of defects as shown in Fed. Std. No. 140a shall be applicable.

MODIFICATION NO. 1
DATE: 20 March 1972

MODIFICATION TO DEFENSE MEDICAL PURCHASE DESCRIPTION

This modification forms a part of Defense Medical Purchase Description No. 4, dated 10 August 1970, and covers the following item to the extent specified herein:

Federal Stock No.	Item Identification
6505-817-2279	CHLORPROPAMIDE TABLETS, USP, 0.25 Gram, 250s

Page 1:

At top of page, in the block headed "Item Identification" add the following:

POTENCY
60 Months

In the first paragraph, delete the last line in its entirety and substitute:

"1966, and Amendment-1, dated 25 March 1970, and as specified herein."

Under "S5.2" - In the first paragraph, delete "hypoglyclycemic agent" and substitute "hypoglycemic agent."

Under "PREPARATION FOR DELIVERY" - "Immediate containers" - Delete "CLOSURE G" and substitute "CLOSURE B or G"

Add "SEAL A or B (for CLOSURE B only)."

Page 2:

Under "Labeling" - "Immediate containers" - Delete subparagraph (f) in its entirety and substitute:

"(f) the expiration date."

Page 3:

Under "Marking:"

"Intermediate package" - Delete last sentence entirely and substitute: "Type I Shelf-Life markings as specified in MIL-STD-129 shall be shown."

"Exterior container. Delete last sentence entirely and substitute: "Type I Shelf-Life markings as specified in MIL-STD-129 shall be shown."

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 4	DATE 10 August 1970

FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-817-2279	CHLORPROPAMIDE TABLETS, USP, 0.25 Gram, 250s	Bottle

Shall be Chlorpropamide Tablets, U.S.P., and shall be in accordance with all applicable requirements of Federal Standard Fed. Std. No. 140a, dated 30 October 1966, together with the options and additions stated herein:

S2. Classification. Shall be type I, class 1.

Shall be suitable for use as an oral hypoglyclycemic agent in the treatment of uncomplicated diabetes mellitus of the stable, mild or moderately severe nonketotic, maturity-onset type.

S5.2 The following additional requirements and tests are added to this paragraph:

Shall be tablets containing 250 mg of chlorpropamide /1-(p-chlorobenzenesulfonyl) 3-propylurea/ per tablet, within the applicable assay limits for the tablets.

S6.4.2 Color. Uncoated tablets shall be mottled blue.

S6.4.5 Shape. Tablets shall be "D" shaped.

S6.4.7 Scoring. Tablets shall be scored.

PREPARATION FOR DELIVERY

Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-00186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, together with the deletions or additions as indicated herein:

Immediate containers. Shall comply with the following classification:

GROUP A CLASS 1 TYPE e STYLE 2 GRADE 1 or 2

CLOSURE G

DPSC FORM 2087 OCT 68

REPLACES DMSC FORM T-4120/11, MAR 64, WHICH WILL BE USED UNTIL DEPLETED

SCIENTIFIC JUN 23 1972 B/8

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 1	DATE 11 April 1972

FEDERAL STOCK NO.	ITEM IDENTIFICATION	POTENCY	UNIT
6505-408-8935	DOXEPIN HYDROCHLORIDE CAPSULES, Equivalent to 25 mg of Doxepin, 100s	36 Months	Bottle

1. SCOPE

1.1 This specification covers Doxepin Hydrochloride Capsules, Equivalent to 25 mg of Doxepin, 100s.

2. APPLICABLE DOCUMENTS

2.1 Specifications and standards. Unless otherwise indicated, the issue in effect on date of invitation for bids or request for proposals of the specifications and standards referenced in the body of this specification shall apply to the extent specified herein. These documents may be obtained as directed by the contracting officer.

3. REQUIREMENTS

3.1 Material. Shall be Doxepin Hydrochloride Capsules containing Doxepin Hydrochloride equivalent to 25 mg of Doxepin, and shall be in accordance with all applicable requirements of Interim Federal Standard Int. Fed. Std. No. 00285, dated 21 July 1971, and as specified herein:

S2. Classification. Shall be type I, size No. 3, shape a, grade A, class 1.

Shall be suitable for use as a psychotherapeutic agent.

S6.2.2 Color. Capsules shall have a pink body and a blue cap.

S6.2.6 Disintegration and solubility. Shall disintegrate in not more than 15 minutes, when tested using the U.S.P. apparatus and procedure for disintegration testing of uncoated tablets, using Simulated Gastric Fluid, T.S, as the immersion fluid. For the purpose of this test, complete disintegration is defined as that state in which any residue of the capsule remaining on the screen is a soft mass having no recognizable capsule shape.

S6.2.7 Moisture content. Shall contain not more than 9.0 percent moisture when determined using the Karl Fischer method for water determination, as specified in the U.S.P.

S6.2.9 Weight variation. Shall comply with the U.S.P.Weight Variation Test for Capsules. In addition, the capsules shall comply with the U.S.P. Content Uniformity Test for Capsules when determined as specified in 4.3.1.1.

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DPSC FORM 2087 OCT 68

REPLACES DMSC FORM T-4130/11, MAR 64, WHICH WILL BE USED UNTIL DEPLETED

MODIFICATION NO. 1
DATE: 19 November 1971

MODIFICATION TO DEFENSE MEDICAL PURCHASE DESCRIPTION

This modification forms a part of Defense Medical Purchase Description No. 1, dated 26 August 1971 and covers the following item(s) to the extent specified herein:

Federal Stock No.	Item Identification
6505-159-4892	Clindamycin Hydrochloride Hydrate Capsules, Equivalent to 150 mg of Clindamycin, 100s

Page 1

3.1 Material. Delete third from last word in paragraph and substitute "as".

3.1.1 Assay. Delete the work "Lincomycin" and substitute "Clindamycin". (Upjohn Company "Lincocin")

Page 2

3.2.2 Unfilled capsules. Delete second line and substitute ". . . manufacture of the finished product shall conform to . . ."

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 1	DATE 26 August 1971

FEDERAL STOCK NO.	ITEM IDENTIFICATION	POTENCY	UNIT
6505-159-4892	CLINDAMYCIN HYDROCHLORIDE HYDRATE CAPSULES, Equivalent to 150 mg of Clindamycin, 100s	24 Months	Bottle

1. SCOPE

1.1 This purchase description covers Clindamycin Hydrochloride Hydrate Capsules, Equivalent to 150 mg of Clindamycin.

2. APPLICABLE DOCUMENTS

2.1 Specifications and standards. Unless otherwise indicated, the issue in effect on date of invitation for bids or request for proposals of the specifications and standards referenced in the body of this specification shall apply to the extent specified herein. These documents may be obtained as directed by the contracting officer.

3. REQUIREMENTS

3.1 Material. Shall be Clindamycin Hydrochloride Hydrate Capsules, equivalent to 150 mg of clindamycin Base. Shall be suitable for use an an antibiotic.

Shall conform to the applicable regulations for the Certification of Antibiotics and Antibiotic-Containing Drugs as promulgated by the Food and Drug Administration, U. S. Department of Health, Education, and Welfare. Each lot shall be certified by the F.D.A. In addition to complying with the F.D.A. regulations, the finished capsules shall comply with the following requirements:

3.1.1 Assay. The capsules shall assay to contain not less than 90.0 percent and not more than 120.0 percent of the required amount of Lincomycin, when assayed in accordance with the applicable F.D.A. procedure.

3.1.2 Weight variation. The finished capsules shall comply with the requirements of the U.S.P. Weight Variation Test for Capsules.

3.1.3 Identification. The retention time of the clindamycin peak of the sample preparation in the assay is identical, within experimental error, to that of the Clindamycin Hydrochloride Hydrate Reference Solution.

3.1.4 Filled capsules. The filled capsules shall be uniform and free from manufacturing or other defects, such as, cracks, dents, splits, specks, etc.

SSC-1 M

DPSC FORM 2087 OCT 65

REPLACES DMSC FORM T-4120/11, MAR 64, WHICH WILL BE USED UNTIL DEPLETED.

DATE: 28 June 1972

APPROVED NEW DRUG APPLICATION REQUIRED

The supplier of any item(s) listed below must possess, at time of award of contract for such item(s), a New Drug Application which has been approved by the Food and Drug Administration.

FSN	Item Identification
6505-181-7678	CLOMIPHENE CITRATE TABLETS, 50 mg, 30s

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DEFENSE MEDICAL PURCHASE DESCRIPTION	NSN	DATE 4 November 1970
FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-181-7678	CLOMID TABLETS, 50 mg, 30s	Package

Shall be The Wm. S. Merrell Company's "CLOMID TABLETS" and, in addition, shall comply with the following:

Each tablet shall contain 50 mg of Clomiphene Citrate.

Shall be supplied 30 tablets as specified herein.

Not more than 6 months shall have elapsed from the date of manufacture to the date of delivery to the Government.

PREPARATION FOR DELIVERY

Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-00186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, and as specified herein:

Immediate containers (foil packet). Shall comply with the following:

Each tablet shall be packaged in a hermetically sealed, aluminum foil packet.

Labeling. Labeling shall be in accordance with the requirements of the Federal Food, Drug, and Cosmetic Act, and shall include the information required below:

Immediate containers. Each immediate container (packet) shall be permanently and legibly marked with the lot or control number.

Unit packages. Each unit package shall bear the following information. However, the information is not required to appear in the sequence indicated:

(a) labeling information in accordance with commercial practice

(b) the item name designated as "CLOMIPHENE CITRATE TABLETS"

(See additional labeling information on page 2)

DSSC-1 M

DPSC FORM 2087 (REPLACES DMSC FORM T-4120/11, MAR 64, WHICH WILL BE USED UNTIL DEPLETED)

February 15, 1974

Intra-Governmental Professional Advisory Council on Drugs and Devices (IPADD), Working Group on Specifications and Quality Control of Drugs

10-6-70	Working group reactivated
	[redacted]
10-27-70	Meeting (Washington)
12-4-70	Meeting of Subcommittee on Plastic Containers (Washington)
2-16-71	Meeting of Subcommittee on NDA's (Washington)
3-17-71	Meeting (Washington)
8-12-71	Meeting (Washington)
5-25-72	Meeting (Washington)
10-17-72	Meeting (Philadelphia); [redacted] (no minutes issued)
9-24-73	Meeting (Perry Point); [redacted] (no minutes issued)

740215

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

February 22, 1974

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

Dear Dr. Feldmann:

Thank you very much for your very valuable contribution to our hearings on government procurement of drugs.

In order to complete the hearing record on this subject, it would be greatly appreciated if you would send us a detailed analysis of the Department of Defense data which our staff has submitted to you for your study.

Kindest personal regards.

Sincerely,

GAYLORD NELSON
Chairman
Subcommittee on Monopoly

AMERICAN PHARMACEUTICAL ASSOCIATION
The National Professional Society of Pharmacists

February 25, 1974

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

Dear Senator Nelson:

This will respond to your letter of February 22, requesting that I analyze and comment upon the information submitted to the Senate Subcommittee on Monopoly by the Department of Defense, as per your request to them dated January 17, 1974.

I will restrict my comments to those subject areas in which I feel qualified, and I will not comment upon such aspects as the budgetary and fiscal matters, relative allocation of personnel, and so on. For purposes of ready reference, I have organized my review of the DOD response in the following areas which I will comment upon in turn: (a) plant inspections, (b) product testing, (c) problem drugs, and (d) specifications.

a. Plant Inspections

DOD's response to your question 1 reveals that DPSC, in fact, surveys only about 10% of their prospective contractors and that this 10% is the result of a conscious selection process. In other words, DPSC has already concluded that the remaining 90% constitute prospective contractors which are fully capable -- in the judgment of DPSC -- of performing satisfactorily under the terms of the proposed contracts.

Therefore, combining this information with the "45% rejection rate" for fiscal year 1973 -- mentioned in DOD's answer to question 15(a) -- results in a true rejection rate of only 4.5% of all prospective contractors; that is, fully 95.5% of the contractors submitting a bid during fiscal year 1973 were judged by DPSC to be capable to perform under the terms of the proposed contracts.

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Under your question 15(b) to DOD, you requested the names of the firms, the dates of the "gross violations," whether or not they were reported to FDA, etc., and the exact description of the violation. Further elaboration was requested under your question 15(c). Although DOD's response under 15(a) stated that during FY 1973 there were 97 rejections based upon plant inspections, DOD did not provide you with the specific information you requested relative to these 97 cases; instead, as stated on page 11 of their response, they simply provided "examples" without comment as to how these examples were chosen by them. Since there is no indication that DOD selected these examples purely at random, and since your request was couched in terms of the "gross violations," it is logical to assume that the examples they provided to you were actually the most extreme or serious violations among the 97 identified during FY 1973.

Turning to the list of violations supplied by DOD as "examples," it will be noted that there is a total of 12 entries for FY 1973. Certain comments can be made based upon inspection of the information provided relative to these 12 entries:

-- The nature of the violations is such that they are essentially technical in nature, and are minor and/or easily correctable. (Your hearing record indicates that an FDA spokesman has characterized them as "relatively trivial.")

-- Of the 12 entries, Zenith Laboratories of Northdale, New Jersey, is listed twice, thereby reducing the number of plants to a total of 11.

-- Of these 11 plants, 3 are located in Puerto Rico and one is located in England.

-- There appears to be no correlation between these 11 plants and the size or "reputation" of the company involved; 5 out of the 11 examples appear to be plants operated by member firms of the Pharmaceutical Manufacturers Association (the PMA has approximately 130 member firms) while 6 out of 11 are not PMA member firms. (There are probably several thousand drug companies operating in the United States which are not members of the PMA.)

b. Product Testing

The DOD answer to your question 3 reveals that it is their practice to make a preliminary determination of what drug products should be subjected to laboratory analysis in contrast to those which can be judged suitable without such

testing. The DOD response specifically reveals that only 5% of the drug products obtained based upon contracts awarded are, in fact, subjected to laboratory testing -- the remaining 95% are judged satisfactory based upon other DOD information. Combining this response with the information provided in the second paragraph of DOD's answer to your question 15(a) -- in which they give the ratio of drug samples rejected to drug samples tested -- the composite true rejection rate in terms of total drug samples involved, amounts to less than 2.5% (that is, 42% of the 5% increment). In other words, over 97.5% of all drug product samples offered are judged satisfactory by DOD-DPSC.

No breakdown was provided by DOD relative to the 136 cases which they recommended for rejection during FY 1973; therefore, no comments can be offered relative to the severity of the alleged product deficiency or upon the appropriateness of the finding on which the rejection was based.

c. Problem Drugs

In your question 15(d) to DOD, you requested specific information relative to findings made by DPSC personnel, as well as action taken by DPSC personnel, concerning problems pertaining to digoxin tablets. You also asked DOD to name the "many other examples" referred to by a DPSC spokesman, along with other specific information pertaining to these "examples."

During my testimony before the Subcommittee on February 21, I commented specifically concerning apparent inconsistencies or peculiarities in the DOD response pertaining to digoxin tablets; since comments on this matter are already part of the hearing record, I shall not repeat them here.

With respect to the "other examples," DOD's response mentions that such information has been obtained through two sources; namely, the "published literature" and "complaint reports received by DPSC." Concerning the published literature, they cited two examples (one of which, incidentally, is published by the American Pharmaceutical Association, the organization which I represented in my testimony before the Subcommittee). Such publications are generally available, and anyone having an interest in drug quality could be expected to be as familiar with them as the DPSC spokesman. Consequently, this does not represent any special information source beyond what is widely available and already known to FDA, the official compendia, and health professionals involved in procuring or selecting drug products.

The "complaint reports received by DPSC," as tabulated in the DOD response, listed only a total of 6 drugs -- it is a matter of personal opinion as to whether this relatively small number truly constitutes "many other examples." Moreover, examination of these 6 items reveals the following:

-- Most of the complaints are rather old and, in fact, only one (November 16, 1973, regarding Cortisone Acetate Tablets) has been made since July 1971 -- fully two and one-half years prior to your request to DOD. Indeed, the latest complaint concerning Thyroid Tablets was in October 1961, and the latest complaint concerning Diphenylhydantoin Sodium Capsules was in May 1966. This paucity of complaints suggests that few drug problems either have occurred in recent years, or remain today.

-- The first 4 complaints relative to Nitrofurantoin Tablets were filed in 1961 and 1962; since USP XVII, published in 1965, identifies this drug as still being under patent as of 1965, it would appear that the article was available only from the single manufacturer who held the patent -- and at least these initial "complaints" would have pertained to that company's product.

-- There is no indication in the DOD response as to the nature of the specific problems or complaints associated with the 6 drugs listed. For example, to my knowledge, the only publicized problem which has come to light relative to Nitroglycerin Tablets pertained to the packaging of the article. Consequently, even among these six drugs, one or more "examples" listed in the DOD response may very well not be "bioavailability problems" in the sense that this term is usually used.

d. Specifications Provided

Your question 15(e) requested DOD to provide information to document the DPSC claim that they "develop definitive product specifications which often exceed official or commercial standards."

In the DOD response they provided a listing of drug articles along with the additional DPSC requirements and their explanation. During my testimony before the Subcommittee on February 21,

I commented in detail concerning the four articles appearing on their list which are recognized in the current National Formulary. Consequently, I will not repeat those comments here. Moreover, following my testimony, Dr. Daniel Banes testified on behalf of the USP, and during his appearance before the Subcommittee Dr. Banes offered his views relative to comparing the DPSC "additional requirements" with the specifications in the current USP. Hence, I also will not comment here on the so-called additional DPSC specifications for the USP articles.

* * * * * *

I trust that the above comments will provide you with the analysis and evaluation desired by the Subcommittee. If I can be of any further assistance, or if you desire clarification relative to any of my comments, I shall be happy to cooperate.

Sincerely,

Edward G. Feldmann

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

ehb

AMERICAN PHARMACEUTICAL ASSOCIATION
The National Professional Society of Pharmacists

February 27, 1974

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

Dear Senator Nelson:

This will respond to your request that I supplement my letter to you of February 25, 1974, with a review and analysis of the second increment of information sent to you by the Department of Defense.

In view of the fact that this information was only recently received in this office, coupled with the fact that you have requested my response promptly, my analysis of necessity has had to be both concise and relatively general. In the event that a more detailed response -- even on an item-by-item basis -- is desired, I will undertake to provide such an effort at your additional request.

Turning to the specific material provided by DOD, the data under "tab A" and "tab B" all appear to pertain to matters about which I did not comment in my February 25 analysis. Consequently, I have no comments relative to these sections. On the other hand, the information provided under "tab C" does contain supplemental information relative to one question about which I had commented earlier; namely, question 15(e), in which you had requested that DOD-DPSC name the products for which additional specifications have been developed by them, and that they indicate the significance and purpose of these extra requirements.

In essence, the DOD in its original response dated January 30, had provided a representative sampling of drug items along with the so-called "additional requirements" they have developed and applied to these drug items. In testifying before the

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Subcommittee on February 21, I reviewed the NF articles included in this sample that they provided, and I offered my general conclusions. Later that same day, Dr. Daniel Banes testified on behalf of the USP, and he offered a very similar assessment and opinion with regard to the USP articles in that sample listing.

Based upon my review of the current material submitted by DOD as its second increment of information, I have concluded that the general assessment I presented on February 21, can be applied with little, if any, modification to the entire list of NF items which the DOD has just submitted.

-- The overwhelming majority of so-called "additional requirements" are identified in the DOD list as "classification of defects," as defined and explained in the explanatory notes which accompanied their January 30 letter. This "requirement" is desirable or perhaps necessary for contractual purposes. This does not constitute a standard of quality in the usual sense; therefore, while such a requirement may be useful for administrative purchasing purposes, it should not be considered as, nor confused with, quality specifications.

-- A very substantial number of the other "additional requirements" are of such a nature that they may contribute to the elegance or aesthetics of the product, but they have no apparent relevance from the standpoint of medical value or safety of the article.

-- A very significant number of so-called "additional requirements" are already covered in the overall NF standards and specifications -- either in the pertinent monograph, related monograph for the active ingredient, or in some other section of the NF pertaining to general product specifications. (A list of selected examples, along with comments, is appended to this letter for illustrative purposes.)

-- And finally, there are a few "additional requirements" which are not currently specified in the National Formulary for the pertinent drug items. In most of these cases, it is not apparent that such additional requirement is either necessary or serves a meaningful

purpose; however, without any supportive information or explanation from DOD, it is impossible to make a judgement that they do or do not serve a useful purpose. However, I would emphasize that at most, these represent a very few isolated incidences and that they probably total less than 2% of the so-called "additional requirements" listed by DOD in connection with the complete listing of NF items.

* * * * *

I trust these comments will be of assistance to you in your evaluation of the material submitted by DOD.

Sincerely,

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

ehb

Enclosure

February 27, 1974

Comments on "Additional Requirements" listed by DOD/DPSC regarding selected National Formulary (NF) articles, appearing in second increment of DOD response to Senator Nelson's request of January 17, 1974. These comments prepared by Edward G. Feldmann, Ph.D., American Pharmaceutical Association.

[Note: The listing submitted by DOD was not page numbered, nor were items in alphabetical order. These comments are presented on drug items in the same order that they appeared on the DOD listing.]

Name	Additional Requirement	Comment (EGF)
Chloral Betaine Tablets, NF, 0.50 Gram, 30s	Additional test requirement for the active ingredient (Melting Range)	Melting Range of Chloral Betaine cannot be determined either with accuracy or consistency due to inherent nature of compound. Hence, inappropriate as a standard or specification. Therefore, it is in the NF monograph, but is given under the heading of "Description" to distinguish from an enforceable standard.
Cyproheptadine Hydrochloride Tablets, NF, 4 mg, 100s	Free Hydrochloric Acid	There is no reason to expect any free hydrochloric acid to be present, and even if there were, it would be a micro-quantity since there is only a total of 4 mg of active ingredient per tablet. Moreover, in light of the composition of gastric fluid there is no medical purpose served by this limit.
Aspirin, Phenacetin, and Caffeine Tablets, NF	Moisture Content	The NF monograph provides a test and limit for the deterioration product which would result from any moisture present. This is a more meaningful standard in judging the quality of the product.

Name	Additional Requirement	Comment (EGF)
Benzonatate Capsules, NF, 100 mg, 100s	Identity	The NF monograph specifies two identity tests and both of them are quite specific. Additional tests for this purpose are redundant.
Ammonia Spirit, Aromatic, NF, 1/4 pt	Removal torque for closure on immediate container	The NF monograph specifies packaging in a "tight container" which is defined in the General Notices, and which provides adequate protection for the product.
Hydralazine Hydrochloride Tablets, NF, 25 mg, 100s	Weight Variation	The NF monograph includes a Content Uniformity test, which is even more precise than the Weight Variation test, making it superfluous for this item.
Methylprednisolone Sodium Succinate for Injection, NF, Equivalent to 1 Gram of methylprednisolone	Content Uniformity	Contrary to DPSC statement, the NF monograph does require compliance with Content Uniformity specification.
Methylprednisolone Sodium Succinate for Injection, NF, Equivalent to 40 mg of methylprednisolone	Content Uniformity	(ditto; see above)
Methylprednisolone Sodium Succinate for Injection, NF, Equivalent to 125 mg of methylprednisolone	Content Uniformity	(ditto; see above)
Soap, Green, NF, 25 lb	Vegetable Oil (Cottonseed Oil, Corn Oil, or Soya Bean Oil)	NF monograph does require use of a suitable vegetable oil, and specifically excludes coconut oil or palm kernel oil. Additional requirement is redundant.

Name	Additional Requirement	Comment (EGF)
Phenazopyridine Hydrochloride Tablets, NF, 0.1 Gram, 100s	Additional identity test	NF monograph specifies two identity tests, both of which are quite specific. Additional identification tests are redundant.
Undecylenic Acid Ointment, Compound, NF, 28.35 Gram	Iodine Number	NF monograph for the active ingredient does include such a test and specification. NF requires all dosage forms to be prepared with active ingredients complying with their pertinent standards. Hence, this specification is redundant here.

Dr. FELDMANN. In other words, it makes a nice little piece of added window dressing, but it adds nothing to the integrity of the article.

Senator NELSON. Would you please explain what you mean, the content uniformity is assured? In what way is it assured?

Dr. FELDMANN. It is assured in this particular case because the assay provides—let me just—I will not read the three pages of the letter, but let me read just a couple of pertinent sentences from my response.

> In the case of the NF XIII sterile solids, the articles are all consistent with our policies, with the apparent exception of the monographs for Sterile Chymotrypsin and Hyaluronidase for Injection. However, there are special circumstances pertaining to each of these articles which require them to be exceptions to the general policies. These revolve about the fact that both are enzyme products, with peculiar problems associated with the non-homogeneity of enzymes.
>
> You will note that in each case the Assay directives call for conducting the Assay on individual vials of the article rather than pooled samples.

So the assay, as it is done in each particular case, is to take individual unit vials. Therefore, a content uniformity test, which is also to take individual unit vials, is simply duplicative of the assay.

Senator NELSON. I see.

Go ahead.

Dr. FELDMANN. Returning to page 9, Mr. Chairman.

If such as 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 APA'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 it was promulgated in the Federal Register. Again, this effort failed to elicit the kind of information we seek.

And I have provided you, Mr. Chairman, with copies of our correspondence as exhibits F and G.

Mr. Chairman——

Mr. GORDON. Dr. Feldmann, this is rather puzzling in view of the statement the DPSC makes that: "A close working relationship exists between DPSC and the personnel of the FDA, the U.S. Pharmacopeia and the National Formulary." Here you are unable to get information from them, and they claim you have a very close working relationship.

What is the explanation?

Dr. FELDMANN. I think that largely, Mr. Gordon, this depends upon how one defines "a close working relationship." It is true that we have had contact with them when we have sought information; they have at times provided it to us, such as the purchase specifications, which they have made generally available to all bidders, so that this was not unusual information. But other than that, they have not provided us with much information and, certainly, none of the information that I have just described here—namely, where they have encountered problems, and what drugs they have encountered problems with, and so forth.

We have made a practice of trying to supply them with information. I note in yesterday's testimony of Commissioner Schmidt he mentioned any number of areas that FDA has provided information to the DPSC and DOD. Again, unfortunately, there has been little response, very little—it has been sort of a one-way street.

This organization mentioned earlier, this Intra-Governmental Professional Advisory Council on Drugs and Devices, has a working group on specifications and quality control of drugs. This working group is chaired by Mr. Feinberg of DPSC, and the meetings of this group have been progressing with less and less frequency. They have had only one meeting in over the last year and a half. There have been no minutes issued from these, at least from the last couple of meetings.

I do not know how else I can characterize this, Mr. Chairman, but I think that the idea of "a close working relationship," perhaps is a subjective evaluation, but I think it may be a bit exaggerated here.

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—be 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 you committee would certainly render an equally beneficial service by exposing the truth of the matter.

Thank you, Mr. Chairman.

Senator NELSON. You state on page 9 that you made in 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 promul-

gated in the Federal Register dated September 6, 1973. Again, this effort failed to elicit the kind of information we seek. Then you say "See correspondence appended as exhibits F and G."

I have not looked at that correspondence.

Are you saying that your request, that their answer was unresponsive to your request?

Dr. FELDMANN. Yes, I am, Mr. Chairman. This was one of a number of requests we have made. We have made other requests we have asked the DPSC people, following their statements that there is so much percent of manufacturers that are deficient and so much percent of products, if they would provide us with such information. And on this, nothing was forthcoming to us.

We used this route that I mentioned—as provided for in the Federal Register—to ask for a list of such manufacturers, and their response was, "we have no list."

I am gratified that you have been more successful than we have been. It has been as difficult as pulling teeth to get an answer out of these people, or to pull something out of them.

Senator NELSON. They said to you they had no such list?

Dr. APPLE. Oh, yes.

Senator NELSON. That is hard to believe that they developed some statistics on rejection, but they do not keep any track of who the manufacturers were.

Dr. FELDMANN. They told us that, "please be advised that such lists are not developed or maintained by the DPSC or the Defense Supply Agency; thus we cannot respond to your request for such information."

This is in Colonel Kimerer's letter to me dated October 18, 1973, which is exhibit G, the first paragraph of that letter.

Mr. ADAMS. Dr. Feldmann, I just want to clear up a couple of points, if I may. Thank you, Mr. Chairman.

In your response to one of the Chairman's questions you read from some DPSC or DOD bid specification sheets?

Dr. FELDMANN. Yes, sir.

Mr. ADAMS. These specifications were circulated, and perhaps continue to be circulated, supposedly requesting competitive bids?

Dr. FELDMANN. I would assume that that is the purpose of them, yes, sir.

Mr. ADAMS. Am I to understand, further, that these sample specifications in at least one instance, contain the name of a particular drug manufacturer, and in another case the brand name of a particular drug, followed by an amendment to the bid specification, replacing the brand name with the generic, non-proprietary name?

Dr. FELDMANN. Yes, sir, that is correct on both counts.

Mr. ADAMS. As to the drug list supplied by DPSC, which you previously commented on, I understand that list contains at least a portion of DPSC's list of drugs for which they have additional specifications. Do you recall listing the additional specifications from the list of drugs the Committee supplied to you, which the Committee received from DPSC?

Dr. FELDMANN. Yes, sir. This is not the bid specifications, but rather the material supplied to the Committee; yes, sir.

Mr. ADAMS. Now, in no case were there an additional specification that dealt with the safety or efficacy of a drug mentioned in your opinion?

Dr. FELDMANN. I addressed myself only to those drugs that are recognized in the National Formulary. I deferred response to those in the USP. With respect to those in the National Formulary, in my opinion, approximately half of the aspects referred to were matters that are not of a medical significance. In other words, color—excuse me—taste, and specific gravity, things of this nature, for the formula.

Now, concerning the other half, that could be regarded as having a medical significance, or a quality significance, I concluded that there were none of those requirements which were not adequately covered by the existing National Formulary specifications; so that indeed, there were no specifications among those listed by the DPSC in their response, which would have led one to believe that the product would thereby be of a higher quality, or would need to be of a higher quality, in order to meet their standard than if it simply met the NF standard.

Mr. ADAMS. Limiting yourself simply to that list, would it be fair to say that making an additional requirement dealing with taste, color, and shape would yield a higher bid price?

Dr. FELDMANN. That they would warrant a higher bid price?

Mr. ADAMS. That is correct.

Dr. FELDMANN. Unless I were to see some specific reason for it, that I am presently unaware of—in my opinion, no, it would not warrant a higher bid price.

Mr. ADAMS. As to the other list, the bid specifications, I just want to make sure I understand it correctly, in the cases where the Government orders drugs under their generic name, it is generally less expensive than ordering drugs under a brand name.

Is that an accurate generalization? I realize there may be some exceptions?

Dr. FELDMANN. It is my understanding that all DPSC bids are made under the generic name, so that all of the specifications, therefore, are titled by the generic name. The Chairman drew a conclusion from some of this information, as I interpret it, that the specifications could be designed in such a way that only one product would meet all of those. I just take note of that conclusion.

Mr. ADAMS. Thank you, Mr. Chairman.

Senator NELSON. On February 1, Dr. Edwards, commenting on the issue in general—and I think he also was commenting on the bioavailability question—stated before the Health Subcommittee of the Labor and Public Welfare Committee:

> Nevertheless, based upon present knowledge, I believe that with very few exceptions, any drug prescribed in this country, will give the same therapeutic results as any other chemically equivalent product. . . . we regard this issue as limited, well-recognized, and manageable.

What would be your observation about that statement by Dr. Edwards?

Dr. FELDMANN. I'll ask Dr. Apple to respond to it first.

Dr. APPLE. Basically, the association supports that observation by Dr. Edwards. We went into considerable detail at the Senate Subcommittee on Health on that subject. We do recognize there are drugs that are subject to inequivalency. We are doing a great deal of work, through both our Academy of Pharmaceutical Sciences and our Academy of General Practice, to try and identify actual problem drugs.

As I indicated in my testimony on February 1, we cannot support negative hypotheses with regard to this subject. There are some people who want to refer continuously to probabilities—of things that may happen. Today, it is commonly recognized among scientists that we may have, 15, 20 or some such drug entities of that magnitude that are subject to this problem. Other scientists talk about the probability of there being 70 of them, or 80 of them. We have got to deal with the real world, because our pharmacists are dispensing real drugs to real patients every day.

I recognize the value of this scientific exercise, on the part of people who are interested in this, and we encourage them to pursue that type of scientific investigation. But I do not think it can be used to characterize the present status of the Nation's drug supply, or the quality of the Nation's drug supply? In other words, Mr. Chairman, I would say that I cannot think of a pharmacist who would knowingly and wantonly dispense a bad drug to a sick person.

Senator NELSON. Well, is not the truth of the matter really that the Pharmaceutical Manufacturers Association is not really saying that we do not have high-quality drugs in this country; nor is the DOD. The Pharmaceutical Manufacturer's Association will say that we have got the finest drugs anyplace on earth, manufactured by our members. What they are really trying to say, or are saying, is something quite different; that you cannot trust anybody who does not make brand names.

Is that not the heart of the matter? They are not attacking the quality of the production of their members, but what they are attacking is those who do not carry a brand name, those who compete under a generic label at a much cheaper price. Is that not what they are really doing?

Dr. APPLE. Mr. Chairman, there are times when I do not know what they are attacking, because they make 95 percent of the Nation's drug supply, and I cannot think it through on the basis of brand or generic name, because some of their manufacturers—PMA members—also make generic-labeled products. Likewise, in the other 5 percent, you have a number of firms that produce products under brand names.

Now, you get on a juxtaposition here that just does not make sense, if you try to rationalize it out in any way, shape or form. On the one hand, you cannot claim to be producing 95 percent of

the Nation's drug supply, and you cannot be claiming that we make high-quality drugs. And on the other hand, say there is someone else who makes bad drugs. Well, who are they, and what percent? They have to fall within that 5 percent, or less than 5 percent, and we want to know who they are. We do not believe it, frankly, Mr. Chairman.

Dr. FELDMANN. Mr. Chairman, I would like to add a little bit to what Dr. Apple has said here. I think it goes beyond simply the brand name versus generic name aspect that they are attempting to muddy the waters with. I think that they have attempted, in a type of psychological warfare, almost, to create a climate of distrust, so that the individual practitioner—and this is especially true of the practitioner who might have an opportunity to choose between different company's products—would be fearful of making his own decision.

In other words, you could have three or four brand name articles, but they do not even want the pharmacist to be able to select among those. So they have created an atmosphere of fear, of concern, so that the guy is afraid to make a choice, because he thinks he is taking a chance. So I think this really is at the heart of the matter.

Incidentally, in Dr. Apple's response a minute ago—I believe he meant to say that some people have said there is a *potentiality* that there might be 70 drugs involved in this matter, and he inadvertently said *probability;* this is just to correct that record.

Mr. GORDON. Where did you get that number, 70?

Dr. FELDMANN. I believe Dr. Cavallito mentioned it in his testimony before Senator Kennedy, and you will recall that we tried to emphasize, following his testimony, that in each case, he did qualify his statements by saying, *potential* bioequivalence problems, *potential* inequivalency.

Now, there is a great deal of difference between "potential" problems and actual problems, and I think that that is a distinction that all of us, and particularly your committee, Mr. Chairman, must not overlook. What has, in fact, been the record; what has, in fact, been the number of therapeutic failures; how many drugs, actually, will present a problem; and once a problem has been identified, continue to represent a problem? And that has not been adequately corrected, and is not just ancient history now?

Senator NELSON. I think the testimony was yesterday on the question of bioavailability, that there were perhaps 12 or 13 cases of such problems. As a general proposition, the same compound, the same salt, and the same dosage form will produce the same result therapeutically, with limited exceptions which have been discovered. I suppose there will be some in future dates. But it is a limited, manageable problem.

Would that be a correct statement of the issue?

Dr. FELDMANN. I think that that would represent our assessment of it, Mr. Chairman; yes, sir.

Mr. GORDON. You mentioned that the Pharmaceutical Manufacturers Association's members manufacture 95 percent of the drugs.

Are you sure that the proper statement is that they market 95 percent of the drugs? You know that a large number of drugs which are marketed by the big companies are produced by smaller companies.

Dr. APPLE. Mr. Gordon, I can get you the exact quote. Wait a moment—I may have it here. I think they use the word "produce," where I use the word "manufacture," where you are using the word "market."

Mr. GORDON. I recall, in the early part of our hearings, the Geigy Co., for example—before they even built a plant in the United States did not manufacture any drugs in this country. They just bought them from small companies, put their own label on them. I think during the Kefauver hearings, it was disclosed that—I think it was Parke, Davis—manufactured only about 20 percent of the items they marketed. So I am just wondering if the 95 percent—maybe they say produce—but I am wondering if that is really what they mean.

Dr. APPLE. I do not recall that the term has ever been defined by PMA, but let me just say, in the context of testimony presented to State legislatures and to the Congress, the term is used in a context in which, I think, the average listener would at least gain the impression that they are saying that our members are responsible for 95 percent of the Nation's drug supply. They do not characterize it finely. I can get the exact wording for the record. I think it is produce. I could be wrong there, but I would rather submit it.

Now, as to what it means, I would have to agree with you. It does not say that they—it does not imply that they are the actual fabricators. It says imply that they take final responsibility for the quality of the product going out under their label, and I think that is important.

[Testimony resumes at page 10230. The information referred to follows:]

PMA PRESCRIPTION DRUG INDUSTRY FACTBOOK, 1973

The PMA

The Pharmaceutical Manufacturers Association is a non-profit scientific, professional and trade organization. Its active membership comprises 115 firms that are principally engaged in the manufacture of prescription pharmaceutical and biological products; these are primarily promoted to medical and dental practitioners licensed by law to administer and prescribe them and are dispensed by licensed pharmacists. Financial support is derived mainly from dues based on the annual sales volume of member firms.

Membership in PMA is voluntary, and consists predominantly of manufacturers that produce ethical pharmaceuticals for their own label and who also are engaged in a significant research effort. The present members account for approximately 95 percent of U.S. sales of prescription and over-the-counter "ethical" products, as well as half of the free world's supply of such medicines.

PMA was founded in 1958. It is the successor to the American Association of Pharmaceutical Chemists, organized in 1907 and renamed the American Pharmaceutical Manufacturers' Association in 1922; and to the National Association of Manufacturers of Medicinal Products, founded in 1912 and called the American Drug Manufacturers Association after 1916.

PMA is governed by a 30-member Board of Directors, one-third of whom are elected each year at an annual meeting of the membership. There cannot be more than one Board member from any one firm and two new members must be selected each year. The Association's work is facilitated by ten functional units, known as Sections; these are composed of representatives of member firms and organizations who work closely with the permanent staff on numerous projects. The staff of PMA is organized into five major divisions: Research and Planning; Legal; Scientific and Professional Relations; Public Relations and International.

The Industry At A Glance

Sales and Growth	
Total domestic and overseas sales of ethical drugs (human & veterinary) by U. S. firms: 1970	$6.9 billion
1971	7.4 billion
Forecast — 1972: (estimate)	8.1 billion
Earnings (Manufacturers), 1971	
On Sales	9.5%
On Net Worth	17.9%
Employment, 1971	
In the United States	142,970
Overseas	97,650
Total	240,620
Price Levels	
Government wholesale (manufacturers level) price index for ethical pharmaceutical products (1967 = 100)	
1970	99.2
1971	98.8
Research and Development	
Expenditures:	
1971	$684 million
1972 (budgeted)	$728 million
Scientific and Technical Manpower	11,310
Productivity: New Single Chemical Entities introduced to the U. S. Prescription Market from:	
1940-1971	898
1972	14
International Operations, 1971	
Foreign Sales	$2.4 billion
Health Care Industry, 1969	
Personnel	23.8 million
National Health Expenditures	
Fiscal 1971	$75 billion

PMA PRESCRIPTION DRUG INDUSTRY FACTBOOK 1973.

Industry Structure

Periodically, the government analyzes industrial concentration based upon the Commerce Department's "Census of Manufactures" data. According to the latest report, published in 1967, 1,130 establishments produce pharmaceutical preparations. (As defined, an "establishment" is a statistical concept which itemizes each plant location as a separate entity. This differs from a "firm", in that a firm may include two or more divisions of the same corporation.)

Data gathered by the U. S. Treasury Department (again, 1967 is the most recent year reported) indicate that individual corporations filing "drug and pharmaceuticals" corporate returns numbered 1,265. Not all of these firms, however, made prescription pharmaceuticals.

Table 3 provides a breakdown of market shares for companies in various sales size groups, as compiled from PMA surveys.

The PMA estimates that perhaps 600-700 firms in the United States produce prescription products. Many of these firms are quite small. PMA represents 115 manufacturers, both large and small, who

Table 3. U.S. Market Shares by Sales Size Group, 1970

Firm Sale Size (millions)	Total Sales By Group (millions)	Percent of Domestic Market	Number of Companies
$200 & over	$1,793	38.1%	6
$100-$200	1,244	26.5	9
$50-$100	775	16.5	11
$25-$50	350	7.5	10
Less than $25	538	11.4	[5]
	$4,701	100.0%	

(5) All other companies.

account for approximately 95 percent of the prescription products sold in the United States, and an estimated 50 percent of total free-world output.

The prescription pharmaceutical industry is not dominated by any one firm. In 1971, the largest firm's share of the U. S. ethical market was only seven percent. The 10 leading firms accounted for 51 percent of the total. Each of 37 companies had an ethical product volume totaling $30 million or more. Nineteen firms had sales of more than $100 million; 15 had sales which exceeded $200 million. During the year, an additional firm joined the ranks of the $300 million-and-over group, bringing the number of firms in that category to seven.

The asset size of firms in the "drugs and medicines" industry is reported periodically by the Internal Revenue Service. This informa-

Table 4. Drug Manufacturing Corporations by Asset Size, 1968

Assets	Number of Companies	(Dollars-add 000)
$100 million or more	21	6,161,697
From 50 million to 99 million	3	244,868
From 5 million to 49 million	39	629,505
From 50,000 to 4.9 million	901	268,239
From zero to 50,000	440	—
Zero assets	18	—
All corporations	1,422	$7,508,292

tion is summarized above. These figures are not comparable to those in Table 3, since the IRS definitions are based upon a broader definition of "drug" company than PMA employs. However, as shown in Table 4, the majority of the firms had assets in 1968 (the most recent year for which statistics have been compiled) of less than $5 million.

Taxes

Total taxes paid by the prescription pharmaceutical industry in 1970 declined for the first time in the history of the PMA survey of member firms' operations. The $828 million in such outlays was 5 percent less than that in 1969. U. S. federal taxes, which had risen by 25 and 15 percent respectively in 1968 and 1969, dropped from

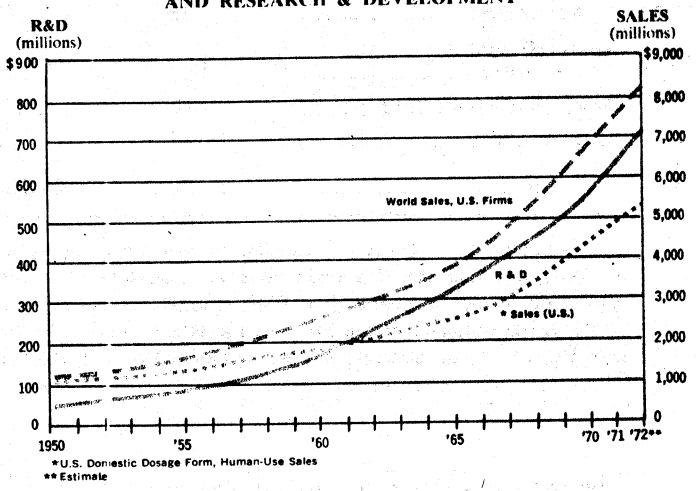
PMA, "Annual Survey Report '71-72: Pharmaceutical Industry Operations Research and Development Activity

FOREWORD

Each year the PMA surveys its member firms' sales, operations, research and development expenditures, employment and R&D manpower. These data are then compiled into a report which reflects the prescription and over-the-counter ethical pharmaceutical industry for that year. The 1971 survey is the 13th in a series of reports which began in 1959. The report is intended to provide information which will be useful to industry executives, financial analysts, educators, and other interested groups.

The PMA is a non-profit trade association and represents 115 pharmaceutical firms that provide about 95 percent of the ethical drugs in the United States and about 50 percent of the world supply. The cooperation of member firms in providing data for this survey is gratefully acknowledged.

GROWTH PICTURE OF ETHICAL DRUG SALES AND RESEARCH & DEVELOPMENT



*U.S. Domestic Dosage Form, Human-Use Sales
** Estimate

PMA, PRESCRIPTION DRUG INDUSTRY FACT BOOK 1968

A Few Words About PMA

The Pharmaceutical Manufacturers Association is a non-profit scientific, professional and trade organization. Its active membership comprises 136 firms principally engaged in production of prescription drugs—those which are primarily promoted to practitioners licensed by law to administer and prescribe them, and dispensed by licensed pharmacists.

Membership is voluntary. The present members account for upwards of 95 per cent of U.S. sales of products of the "ethical" type.

PMA was founded in 1958. It is the successor to the American Association of Pharmaceutical Chemists, organized in 1907 and renamed the American Pharmaceutical Manufacturers' Association in 1922; and to the National Association of Manufacturers of Medicinal Products, founded in 1912 and called the American Drug Manufacturers Association after 1916.

Objectives

1. To encourage consistently high standards of potency, quality and purity for pharmaceutical and biological products for the cure, mitigation, treatment, prevention or diagnosis of disease.

2. To encourage research toward development of new and better medicinal products, better facilities and methods for the pharmacological and clinical evaluation of them, and safer methods for their manufacture, packaging and transportation.

3. To disseminate information, to and on behalf of the pharmaceutical industry, on governmental regulations and policies and other subjects of interest to the industry.

4. To work constantly and closely, on a very broad front, with other professional associations or groups in the health field, with allied industries and with governmental authorities for the advancement of medical science.

(Continued inside back cover)

Senator NELSON. Well, I think quite clearly they market 95 percent, but since they also purchase from generic manufacturers, the latter are also producing some percent of that 95 percent. Up until about a year ago, there was not any bulk meprobamate produced in the United States. All was imported into the country. Domestic manufacturers merely put it into tablet form and then put it into bottles. Carter-Wallace, the marketer of Miltown, produced the drug neither in bulks or finished form, but merely put its own label on it. I ask that a speech on this subject be inserted in the record at the appropriate place. So it would be interesting to have the statistics. I suspect the reason they are trying to upset the Crown law in California is it might be a good opportunity to find out how much is produced by the manufacturers that their association is attacking all of the time, and that could be embarrassing.

Dr. APPLE. We have the same problem, frequently, with pharmacists in terms of convincing our own membership as to who is the actual manufacturer—a pharmacist may inquire as to a certain product, and we inform him that that product is actually being made by so-and-so for the well-known company that is distributing the product, and the first reaction of the pharmacist is total disbelief. But when we can cite some of the evidence to them, the pharmacist then says, "well, why should I not buy it directly from Mylan, or Strong-Cobb-Arner, or this firm, or that firm, instead of buying it under a brand name from the other manufacturer? And this is one of the issues that is involved in the so-called Crown Act.

Now, the Food and Drug Administration is requesting additional statutory authority from Congress now to improve its capacity and ability to function, and we have specifically suggested already to Dr. Edwards that the legislation the administration is currently seeking ought to be amended to include the requirement of the identity of the actual fabricator of the dosage form.

Senator NELSON. Thank you very much.

Gentlemen, we appreciate your very valuable testimony this morning.

Dr. APPLE. Thank you, Senator.

Senator NELSON. Our next witness is Dr. Daniel Banes, Director, Drug Standards Division, United States Pharmacopeia. Dr. Banes?

STATEMENT OF DR. DANIEL BANES, DIRECTOR, DRUG STANDARDS DIVISION, UNITED STATES PHARMACOPEIA, ACCOMPANIED BY DR. JOSEPH G. VALENTINO, EXECUTIVE ASSOCIATE, UNITED STATES PHARMACOPEIA

Dr. BANES. Thank you, Mr. Chairman.

I am Daniel Banes, Director of the Drug Standards Division of the United States Pharmacopeia, and I am accompanied today by an associate of the headquarters staff of the United States Pharmacopeia, Dr. Joseph G. Valentino on my right.

My professional history and qualifications are detailed on the

opening page of my prepared statement, and I will dispense with a recitation of them.[1]

Mr. Chairman, 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 35 years ago. Similarly, the potentialities of the Food and Drug Administration in monitoring the quality of our drug supply has 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 3 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 parts of Western Europe—and I should add Japan—approach or equal the levels of excellence that we have established. None of them surpass us to a significant degree.

Senator NELSON. Well, outside of Scandinavia, which countries in Western Europe?

Dr. BANES. Great Britain. The United Kingdom is at the stage where it is about equivalent to, or approaches, the standards set by the United States.

Senator NELSON. In addition to Canada and Scandinavia, does England have safety and efficacy requirements?

Dr. BANES. Yes, sir. They do. The British laws have been modified during the past few years, and they have approached the system now in effect in the United States.

Senator NELSON. How about the question of advertising?

Dr. BANES. In some respects advertising is even more restricted in some of these countries than in the United States. Furthermore,

[1] See page 10748.

most of these countries require registration and licensing of all drugs during definite periodic intervals, which in my opinion is a more stringent type of control than we have in the United States today.

A third dimension to be considered in evaluating the effectiveness of the present drug 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 ensure 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 advisers.

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 Admin-

istration, 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.

Senator NELSON. May I ask a question which we asked Dr. Apple also?

The Defense Department spokesmen have stated that they develop drug specifications that often exceed official or commercial standards.

What is your observation about that?

Dr. BANES. I have examined the responses sent to me by DPSC. When we circulate "Comment Proof' they respond as well as these other scientists I have mentioned. They sometimes say, we think certain standards ought to be adopted, see the specifications that we have put out. And they insert these specifications into our record for "Comment Proof."

My general impression is very similar to that narrated to you by Dr. Feldmann. For the most part, I would say they are trivial. In some instances, they are so exacting that you wonder why they were set up as they were.

For example, on the monograph for sulfasoxazole. (This is a sulfa drug. We have many such drugs in the U.S. Pharmacopeia with their standards, specifications and tests and assays.) I find in looking through the specifications sent by the Department of Defense that the tablets are to be examined by a method of analysis called X-ray diffraction. Now, this is an approach that requires a tremendous piece of apparatus costing in the neighborhood of $50,000 or $100,000. But when I examine the data to be obtained by this test, I see nothing that goes beyond what is already in the specifications. And here is a test to be applied which is superfluous, gives no more data than is already available from more readily procured equipment. And the question arises, what is the point of such a requirement? If I were to suggest to our committees of scientists that we add this specification, they would say,

> What on earth for? We have already pinned down the identity and quality and the purity of the material by means of our simpler tests. Why should we go to this one?

On top of it, we have a specification for the sulfisoxazole that goes into the tablet, requiring a chloride determination. Well, chloride determinations are worthwhile in some instances, and they are provided in many of the monographs, but not for these sulfa drugs.

But in addition to this trivial requirement, the method to be applied and so specified in the write-up given by the Department of

Defense is that it shall be done by X-ray fluorescence. Again, it is a question of shooting down a dragonfly with antiaircraft artillery. And at the end of it all, you ask what you wanted to bring down the dragonfly for in the first place. These are really superfluous.

This is not to say that all of their suggestions are of the same nature. When there are good suggestions that will improve the quality of the drug or the language of the standards, we do proceed to adopt these recommendations.

Senator NELSON. Have you adopted any of their recommendations?

Dr. BANES. Yes, indeed we have.

Senator NELSON. In what nature?

Dr. BANES. With respect to constituted solutions of injectables. In one of their comments, the Department of Defense said that they favored a specific statement in the Pharmacopeia that these materials, which are prepared for injections or dried powders to be dissolved, dissolve completely and be colorless and be free of significant particulate matter. Well, we have adopted that statement and it will be included in all of the pertinent monographs in the USP.

There was a statement with respect to ophthalmic ointments, that all of these be sterile. The Department of Defense stated that in 1966 and 1971—I am paraphrasing—they asked for sterile ophthalmic ointments, and in 1973 finally the USP and the NF and the FDA took action.

Well, the fact of the matter is that while I was with the Food and Drug Administration, the divisions under my supervision were doing the research on which that sterility test is based, that in 1970 when the 18th revision of the USP was published there was still doubt about the adequacy of the equipment available and the reagents, so that the USP did not contain the statement that ophthalmic ointments be sterile, but that as soon as a collaborative study in which FDA participated, and in which I think in fact FDA led, when these difficulties were resolved, a method of sterility was adopted. In 1971 the USP came out with a requirement that ophthalmic ointments shall be free of certain microorganisms, staphylococcus and pseudomonas, and in 1972 the interim revision said that hereafter all ophthalmic ointments in the USP will be sterile, because by now we had confidence that the method would work. As a matter of fact there are still criticisms of the method and we are still purifying the reagents.

But this is a mode of improving standards which is progressively pursued by the national compendia, by the USP and the National Formulary.

Now, the Department of Defense had the idea that these things should be sterile. FDA wanted them sterile and certainly tested all antibiotics to make sure that they were. As soon as the standards, as soon as the methods of analysis were available, the standards were promulgated. So here is an example of where DOD says we should have sterile ointments, everybody agrees we should, and as soon as scientifically we can support that position we adopt a standard, and there it is.

Senator NELSON. Thank you.

Dr. BANES. Continuing on page 5:

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 the 19th revision of the USP now in preparation will contain 38 percent 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 at USP 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 laws 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. Speciali-

zation 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, Mr. Chairman and staff, I should be pleased to respond. Thank you.

Senator NELSON. As I recall, yesterday—and the record will speak for itself—that the testimony of Dr. Schmidt was that there was about 800 inspectors in the FDA. I believe that he said about 800 or a few more. And that wherever problems arise they will have inspectors there as long as is necessary to solve the problem, that many of the companies producing a substantial percentage of the drugs in the country are inspected much more frequently than the statutory requirement of once every 2 years. But they have now a computerized system whereby any company that has not been inspected within the 2-year period, the computer kicks out the names and that they are all then inspected within the next 6 months. They go to the top of the list.

I have no notion of what may be required. I suppose if a company has a good quality control system, once every 2 years may be perfectly adequate. If it does not, once a month may not even be adequate. But the system they described rather impressed me as a pretty efficient, effective system, though I have no basis for making a judgment as to what the optimum or ideal frequency of inspection would be.

Do you?

Dr. BANES. No, sir. I do not. And I would leave that to the administrative judgment of those responsible for it. In the past I believe that these inspectors available to the Food and Drug Administration were assigned to all of the problems that come under its purview, and one of the difficulties there is that when you have a crisis hazard due to food problems there are no inspectors available for a steady continuous attention to drug problems.

The point of my discussion, Senator, was that in my opinion there ought to be a group of highly trained specialized drug inspectors who are continuously assigned to these drug problems, and when crises arise on the drug side the attention should be given. But this of course is the responsibility of the officials who are charged with that responsibility.

I note that the President in his health message has requested an augmented staff of inspectors for FDA, because I am sure they could use a far greater component of inspection force than they now have.

Mr. GORDON. Dr. Banes, with respect to the use of these large machines you mentioned to perform unnecessary assaying or testing,

would it be fair to say that if not the intent, at least the effect, is to eliminate competition?

Dr. BANES. Well, the effect is to limit the number of laboratories that are capable of doing that kind of an analysis. And if the specifications say that this chloride determination shall be done in the following manner, then that effectively limits the number of laboratories that can do that test.

Mr. GORDON. Now, how important and widespread is the problem of lack of bioavailability?

How many drugs do you know of that have this problem?

Is this problem manageable by the FDA?

Would you comment on that, please?

Dr. BANES. Well, there have been many, many references to problems in bioavailability. In my opinion, the number of authenticated episodes of lack of bioequivalence among chemically equivalent products for which there are compendial standards are a handful. The numbers have a habit of varying. I would say somewhere between half a dozen and a dozen authenticated cases of lack of bioavailability when the products actually meet the standards that are set up for them. And where we have recognized these problems, investigation has shown the reason for them, and we have taken regulatory measures to eliminate these problems.

Digoxin tablets have been mentioned here and it seems to be a very popular example of this kind of problem. And I think it should be, because it is the most significant one that we have encountered because of the high toxicity of digoxin. It is a very important drug. It is very important for heart patients. It is very widely used, and if the tablets do not deliver the active ingredient to the bloodstream in a predictable manner, then difficulties will result.

Dr. Feldmann spoke about the timeframe, that methods of analysis for digoxin in blood were developed only within the last 5 or 10 years, that in 1971 the paper by Lindenbaum of Columbia University and his associates first pinpointed the problem. Following his discovery there were many other studies that confirmed his results.

Some of these studies showed a very good correlation between bioavailability and rate of dissolution of the tablets. That is, if the digoxin tablets dissolved very quickly, then there was good, uniform bioavailability. If the tablets dissolved very slowly, then you can expect that the tablets will not deliver the active ingredient. As a consequence, USP was the first in the world to adopt a dissolution standard for digoxin tablets. Although the problem was widely recognized, USP was the first to set up a standard. FDA followed it up with a certification program, so-called, for digoxin tablets. And in my opinion, given these two quick reactions, with a strict dissolution standard and FDA's program, there should be no problem in the future with digoxin.

I should say that digitoxin tablets will, in my opinion, present a similar problem. But we are moving there to preclude it without waiting for further evidence from scientists throughout the world.

There are two further footnotes that I would like to make for the record with respect to digoxin tablets: First, the worst problem in bioavailability of digoxin tablets emerged in Great Britain with the original producer of this drug, the manufacturer who had had the lengthiest experience, the largest production in the United Kingdom. Serious problems were encountered with bioavailability that they did not know about, but which were discovered only later in practice, and they were serious because of the widespread use of that manufacturer's product.

Furthermore, the problems of bioavailability in Scandinavia were minimal, and in my opinion one of the reasons for that is that the Scandinavian Pharmacopeia sets standards not only for the finished tablets, but also gives a specified formulation, that is a fixed formula, for digoxin tablets. It says it must possess digoxin and only certain other inert ingredients which it enumerates, and then says it shall be punched in a certain manner.

One of the difficulties in this country was that manufacturers used their own imagination in incorporating inert ingredients and punching in any manner that they wished, and consequently some of these other ingredients interfered with the dissolution of digoxin from the tablet. That was one of the factors.

So in my opinion, this fixed formula, this requirement of the Scandinavian Pharmacopeia did eliminate some of the bioavailability problems.

Mr. GORDON. Why do we not have a fixed formula for all drugs?

Dr. BANES. That has been suggested, but that has never been a principle in the standardization of drugs for the most part in this country. I should say that there are fixed formulas for some types of products, and such formulas are in both the U.S. Pharmacopeia and the "National Formulary". Such articles as phenobarbital elixir have definite fixed formulas. Anything which purports to be phenobarbital elixir USP must be made in accordance with that formula. But that is true only of a small number of drugs in the United States.

Mr. GORDON. If you have a fixed formula, then, for most drugs, you would not have a problem of bioequivalency, is that correct?

Dr. BANES. Well, I think that would be too sweeping a statement. I would hesitate to predict. It is always risky to prophesy, and I am sure problems will emerge. But in my opinion, with certain drugs such as digoxin tablets, a fixed formula which is known to deliver the active ingredient in a predictable manner would be helpful. It might be helpful for some of the most important drugs, among which I would include digoxin tablets and digitoxin tablets.

Senator NELSON. Thank you very much.

Mr. Adams?

Mr. ADAMS. Just one question, Dr Banes.

As to the drugs that have a bioavailability problem, regardless of the number, are there any general statements you can make about them?

That is, are they all new drugs or new combinations?

Or are they critical in the treatment of common diseases. Are they generally the drug of first choice?

How common is their usage?

Do they fall into any of those kinds of groupings?

Dr. BANES. The drugs I have in mind are widely used and are of importance. As a general statement, the active ingredient is usually a substance which is difficultly soluble in aqueous fluids, so that when it goes into the stomach it does not readily dissolve and might pass through the whole gastrointestinal tract without being transferred to the bloodstream.

It is a question of transference from the inside of the gastrointestinal tract through the walls of that tract into the bloodstream, and if the material is very difficult to dissolve then it might not get into the bloodstream at the crucial points of the GI tract, and consequently will not be absorbed and go to the target organs.

Important drugs have been involved. I mentioned digoxin and digitoxin. Chloramphenicol was the subject of a bioavailability problem. Some of the Corticosteroids—all of these are important drugs. They all fell into that same category, somewhat difficultly soluble.

Now, for the most part the problems arise with such things as tablets and capsules which are swallowed and then require dissolution and the other steps in absorption. If you have a simple solution of a salt which is to be injected then there is no problem of bioavailability if it meets all of the standards. If it is pure and of high quality and the strength is proper, it is in solution and it is injected in the proper manner, then there is no question it will get into the bloodstream or the target organ in the correct manner and there are no problems.

It is most usually with tablets and capsules containing active ingredients that are difficult to dissolve that the problem does develop.

Mr. ADAMS. Thank you.

Mr. GORDON. I have one more question.

What about the other drugs mentioned by the DPSC, which, they claim, have turned out to be ineffective?

Do you recall that material?

Dr. BANES. Yes. There is a more extensive number of USP drugs and NF drugs, and I did not want to take the time to enumerate them. But in general my observations were like Dr. Feldmann's. For the most part, their specification as to color or colorless——

Mr. GORDON. They claim they are ineffective drugs. For example, diphenylhydantoin and nitrofurantoin. There are a few drugs that they claim they found to be ineffective and about which they had complaints.

Dr. BANES. Well, they had complaints that a particular batch did not do what it was supposed to. Let us take nitrofurantoin, which is a USP drug and has been for some time. In a certain proportion of users the drug is ineffective. In a certain proportion of users it leads to adverse effects.

Mr. GORDON. No matter who manufactures the drugs?

Dr. BANES. No matter who manufactures them.

There has been some talk about the rate of dissolution again, and the USP did adopt a dissolution test. We have been in contact with the Department of Defense on this particular drug, and I recall it specifically because there was a negotiation about the details about the dissolution test. And after a good deal of communication with them and with manufacturers and with the Food and Drug Administration and the Canadian Health Protection Branch—because they also use the U.S. Pharmacopeia and are involved—we decided on certain specifications, and then got a letter from Department of Defense saying, forget the whole thing. They decided that that specification was not necessary.

Well, we do think it is necessary, so we will continue with it. But that is typical of this kind of statement with respect to any drug. A doctor may administer it and not find the effect that he expects. And who knows whether it is the drug, that particular batch of drugs, or the patient not responding?

Senator NELSON. Thank you very much, Dr. Banes, for your very valuable testimony. We appreciate it.

Dr. BANES. Thank you.

Senator NELSON. Our next witness is Mr. Joseph Barrows, chairman of the board of directors, National Association of Pharmaceutical Manufacturers.

The committee is very pleased to have you here today.

Senator Javits was planning to be here. But because of other commitments he asked that I extend his regrets.

Mr. ADAMS. Senator Javits was unable to attend this morning's hearings due to a prior commitment, but he did want me to thank you for your taking the time and showing the interest in appearing and testifying before the committee. He has reviewed your written statement and was particularly interested in your comments and observations as to possible impact the drug procurement practices of certain agencies might have on small business. He asked me to extend his greetings to you and his apologies for not being here.

STATEMENT OF JOSEPH BARROWS, CHAIRMAN OF THE BOARD, NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS, ACCOMPANIED BY MRS. DOROTHY REICHELT

Mr. BARROWS. Thank you so much for conveying the sentiments of Senator Javits.

I am Joseph Barrows, chairman of the board of National Association of Pharmaceutical Manufacturers. I am accompanied today by my associate, Mrs. Dorothy Reichelt.

And, Senator Nelson, as chairman of the Senate subcommittee, I want to thank you for the opportunity for presenting the views of the National Association of Pharmaceutical Manufacturers to the Senate.

Gentlemen, the National Association of Pharmaceutical Manufacturers, also known as NAPM, is a nonprofit trade association representing over 80 manufacturers and distributors of generic drug products and drug specialties throughout the United States.

The purchasing actions of the U.S. Government reflect prejudices against small businesses. The philosophy of Federal purchasing agencies is that small businesses, because they are small, cannot produce quality drugs. By so doing the Government compounds the propaganda of the large companies who for their own selfish interests espouse the superiority of their comparable drug products.

In behalf of the National Association of Pharmaceutical Manufacturers, I appear here today to go on record to suggest means of eliminating unfair Government practices which require unreasonable duplication of inspections, absurd specifications designed to be discriminatory against the smaller drug manufacturers, and to prevent a practical solution to assure the equivalence of compendial drugs.

We want the opportunity to bid on Government business as we do manufacture quality drug products. In fact, many of the larger companies' labels are affixed to products manufactured for them by the smalled drug manufacturers.

Products such as, Nitrofurantoin, Propoxyphene Hydrochloride Capsules, Tetracycline Hydrochloride Capsules and Syrup, Ampicillin Capsules, Chloral Hydrate Soft Gelatin Capsules, a variety of controlled substances in tablet and capsule form, narcotics, parenterals—Lyophilized and solutions—ointments, lotions, suppositories, cough and cold preparations, sterile eyedrops, nasal decongestants, hormonal products, steroid products, chlorpromazine, et cetera.

Subsequent to the New Drug Amendment of 1962, particularly the Good Manufacturing Practices Regulations set forth by the FDA in 21, Code of Federal Regulations, part 133, and section 505(b) of the Federal Food, Drug and Cosmetic Act, no double standard of the quality of drugs can exist.

The tactics of Government purchasing agencies denying the right of HEW registered manufacturers to enter into competition for Federal health-care business, because of requirements and specifications which are arbitrarily contrived by the agencies, tend to undermine competition.

Smaller drug plants have been rejected by the Defense Personnel Support Center because the firms' windows, although permanently fixed and sealed, were not equipped with screens, and because the firm has a common door for both receiving and shipping, but diligently segregates quarantine drugs from release status drugs in conformity with good manufacturing practices.

FDA plant inspections in both large and small firms are conducted in like manner and with equal vigor to determine compliance with all requirements of the Federal Food, Drug and Cosmetic Act and all FDA regulations.

These GMP inspections are carried out on a routine basis, especially for holders of New Drug Applications. Dosage form samples are routinely collected by FDA inspectors for all classes of drugs and are subject to complete compendial assays for validation, often in two separate laboratories.

We, as representatives of the smaller drug manufacturers, can assure you that we subscribe to a single standard, the manufacture of high quality drug products in full conformity with the Federal Food, Drug and Cosmetic Act and all the regulations thereunder.

Therefore, competition should be encouraged to meet the drug needs of the Defense Personnel Support Center, the Veterans' Administration, and other Federal agencies.

It is reasonable to assume that if drug costs are considerably reduced by fair competition without sacrificing patient care, that more drugs will be available to treat more patients. It is unreasonable to assume that the reduction of drug costs necessarily means ineffective therapeutic response as some Government purchasing agents lead you to believe.

Mr. GORDON. Which ones?

Mr. BARROWS. Specifically, the spokesman for the DPSC, Mr. Max Feinberg.

The propaganda which has evolved from the larger firms that "Chemical equivalency is not clinical equivalency" emanates from the thirst and greed for the revenues of the medicare and medicaid programs, coupled with proposed national health insurance plans, and the drug requirements of Federal purchasing agencies.

It is indisputable that lack of therapeutic equivalence among comparable products conforming to official standards has been demonstrated in only a very limited number of cases.

We are told, in fact, that it has been demonstrated in only 20 drugs, out of literally thousands.

Products such as, Aminosalicylic Acid tablets, Nitrofurantoin tablets and oral suspension, Imipramine Hydrochloride tablets, Propoxphene Hydrochloride Capsules, Quinidine Sulfate tablets, Sulfasoxazole and Triple Sulfa tablets, Probenecid when used in conjunction with penicillin, primarily in gonorrhea. Chlorpromazine tablets, Thiazides, Glutethimide tablets, Digoxin tablets, Acetazolamide and diphenylhydantoin capsules. Primidone tablets. Procainamide Hydrochloride capsules, Isoproterenol, Amitriptyline, Hydrochloride tablets, Phenylbutazone and Aminophylline suppositories. As I mentioned before, many of these products are manufactured for the larger companies by the small drug manufacturers.

Mr. GORDON. Excuse me, what is the significance of this list of drugs?

Mr. BARROWS. These are products which the Food and Drug have indicated that there is a question with regard to the bioavailability equivalency of comparable products chemically the same.

In reviewing DPSC, defense medical purchase descriptions, for many drugs one notes that apparently the composers of the specifications are most often the recipient of the contract awards.

Federal Stock No. 6505–104–8672 for meprobamate tablets, 0.4 grams, U.S.P. The defense medical purchase description for this product states the following:

> The meprobamate powder used in the tablets shall be in accordance with the tests, standards and requirements of the USP, including any supplements or revisions thereto. In addition, the meprobamate powder shall comply with the infrared spectrum and the chloride limit as set forth in Volume 25, Number 3, pages 88 and 89 of "Drug Standards." The meprobamate powder shall comply with the following additional tests: The residue on ignition, sulfated ash, shall be more than 0.10 percent when determined by the USP method.

The Federal agency is requesting unnecessary additional tests as the U.S.P. XVIII under "Identification" requires, and I quote:

> The infrared absorption spectrum of a potassium bromide dispersion of it, about 1 mg. in 200 mg, previously dried at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of a similar preparation of USP meprobamate reference standard.

The USP XVIII does not set a "chloride limit," nor does it require a "residue of ignition test"; both of which have no significance as modern techniques assure that all impurities are eliminated.

Embodied in "S5.8" of the same description under "Pre-Award or Pre-Acceptance Samples" are the duplication of inspection and sampling requirements, as follows, and I quote:

> The approval of these samples will not constitute approval of the sample as meeting the other requirements of this purchase description.

Included in the same "S5.8," and I quote:

> Unless otherwise specified in the contract or purchase order, the supplier is responsible for the performance of all inspection requirements as specified herein.
>
> The government reserves the right to perform any of the inspections set forth in the specification where such inspections are deemed necessary to assure supplies and services conform to prescribed requirements.

This is a typical example of unnecessary duplication of good manufacturing practice surveillance by another Government agency as the FDA requires the following:

A New Drug Application from all firms manufacturing and distributing meprobamate tablets, USP.

Samples of the active ingredients and of the final dosage form have to be submitted to the FDA.

A commitment by each manufacturer to the FDA that they will perform, or will have performed in their behalf, all compendial tests both on the active ingredients and the final dosage form.

The producer has to certify that they will manufacture the product in conformity to the good manufacturing practice section, part 133.

Stability reporting, and updating data pursuant to the NDA is a definite requirement. And routine inspections by the FDA monitors the compliance.

Senator NELSON. Let me ask a question at this point.

On item 1, you say the FDA requires a New Drug Application from all firms manufacturing and distributing meprobamate tablets, USP.

Mr. BARROWS. That is correct.

Senator NELSON. Do you mean an abbreviated NDA?

Mr. BARROWS Well, Senator, this goes back originally to the recommendations of the Kefauver committee at a time when they released under the patent controls of the Carter Wallace Co. They had to release at a certain rate according to the index, the price index at that particular time, to other companies to manufacture. And originally, the firms that went into meprobamate at that particular time had to file a full NDA.

Just recently, the Food and Drug Administration has changed that policy; and they will accept now an abbreviated New Drug Application. But under an abbreviated New Drug Application, under paragraph 8, a company has to certify that they will conform and shall comply with chapter 133—with part 133 of the good manufacturing practice.

Senator NELSON. Which part is which?

Mr. BARROWS. That is under paragraph 8 of the abbreviated New Drug Application Form No. 356–H.

Senator NELSON. I do not have it before me. What is that requirement?

Mr. BARROWS. The requirement is that the company manufacturing or submitting the abbreviated New Drug Application must submit a certification statment to the effect that they will comply and conform to the good manufacturing practice section of part 133.

Senator NELSON. Is that objectionable?

Mr. BARROWS. Not at all.

Senator NELSON. Then as of now, that item 1, the FDA does not require a New Drug Application for firms manufacturing and distributing meprobamate. It is just abbreviated.

Mr. BARROWS. An abbreviated New Drug Application.

Senator NELSON. Now, is the abbreviated NDA a particularly burdensome discipline to go through?

Mr. BARROWS. No, Mr. Chairman, our Association was the first to suggest to the Food and Drug Administration the vehicle of abbreviated New Drug Application; that was under Commissioner Goddard. At that particular time there was a question with regard to the nitrates, the effectiveness of nitroglycerin.

Senator NELSON. All right. Please proceed.

Mr. BARROWS. Another example of DPSC specifications which is in variance with existing compendial monographs, and which curtails competition is as follows:

FSN 6505–290–0022 for Reserpine tablets, U.S.P. 0.25 mg, which apparently was composed by Ciba for their Serpasil tablets.

The DPSC's specifications state under specific rotation:

"Shall be between —115° and —121° when determined as follows:" The USP has no such requirement.

The British Pharmacopeia under specific rotation states: —113° to —123°.

Several years ago at one of our annual association meetings I criticized Mr. Max Feinberg, Directorate of Medical Material Defense Personnel Support Center, for the unscientific specification his Agency required for dextroamphetamine sulfate with and without amobarbital sustained release Capsules (FSN 6505–526–0393, 6505–526–0394, 6505–754–2486, 6505–754–2507) which stated that each capsule had to contain a specific number of pellets which had no significance to the safety, efficacy, potency or release rate of the medicament.

There is no doubt that this specification was written by Smith,

Kline & French, Inc. who was the sole recipient of the contract award.

Senator NELSON. Well, was it the only company that had capsules with that precise number of pellets?

Mr. BARROWS. Senator, when we tested this material, because at that particular time the Barrows Chemical Co. was a subcontractee of the S. F. Durst and Co. with regard to that specific contract award; and when we counted the pellets of Smith, Kline & French, we did not find it to conform specifically to that specification.

Senator NELSON. Well, then how do you conclude that there is no doubt that it was written—the specs were written by Smith, Kline & French?

Mr. BARROWS. Yes. Only because of the fact that the—at that particular time the people who were at the head of the S. F. Durst Co., particularly Admiral Knickerbocker was quite familiar with the practices of the DSA at that time and also with Smith, Kline & French, Inc., because he was affiliated with the DPSC. He at that particular time informed us that the specifications were then taken from Smith, Kline & French, and I have the——

Senator NELSON. You are suggesting that there is nobody at Smith, Kline & French who could count the number of pellets in their own capsules? You would think they could at least come out right on that one.

Mr. BARROWS. Senator, just of recent date I have examined some of the pellets with regard to the sustained release capsules of Smith, Kline & French, and I find there is quite a variance even with regard to content uniformity from one capsule to another.

And I would suggest that in the future, if they really want to have the capsules manufactured and manufactured with a better form of content uniformity, that perhaps they ought to have that farmed out.

Senator NELSON. Please proceed.

Mr. BARROWS. At that time I questioned Mr. Feinberg regarding the necessity of the Armed Services requiring a product whose main pharmacological use was as an anorexient, especially the one with Amobarbital—and if so required, why in a sustained release form. He did not reply.

It is my understanding that the product has since been deleted from the DPSC list of requirements.

We respectfully submit that discriminatory practices by Government agencies which lock out the smaller drug manufacturer should be immediately eliminated. The smaller manufacturer whose facilities, manufacturing and production practices comply with the law and FDA regulations should be able to bid and compete on an equal footing with the larger drug companies.

The economic powers of the larger companies permit them to absorb the costs of the unnecessary and duplicating tests, specifications and procedures, often authored by themselves, to exclude competition by the smaller company. The higher prices that Federal agencies are

expending for comparable drugs because of this scheme taxes all our citizens.

A responsible drug association must not only advance criticism but suggest means which will ameliorate that which is obviously wrong and in doing so assist their Government.

We have advocated the adoption of the fixed formula concept, whether it be incorporated into existing compendia or instituted by the FDA, which would negate much, if not all, of the duplication now necessary by all drug manufacturers pertaining to clinical studies and bioavailability comparisons.

The fixed formula concept when related to official drugs locks in the specifications, standards and methodology of analysis of not only the finished dosage form, but also of all of the components, the procedures and equipment to be employed in the compounding of the drug.

The fixed formula concept applied to an official drug will assure that the same drug manufactured by any registered firm will be the same in composition; was manufactured in the same manner; and will be the same in efficacy. The bioavailability will be assured as the drug will be equated with its bioavailability—then and only then will the formula be fixed, and the official drug of one company will be the same as the official drug of another. Without the implementation of the fixed formula concept, the problem of therapeutic equivalence will always be argued.

We are proposing a national drug formulary which will incorporate the fixed formula concept. This will resolve the criticisms that the official standards are too simple and not sufficiently advanced or sophisticated to be meaningful; and too, that the official standards are merely chemical or physical tests that have no relevance to therapeutic equivalence.

We have urged the USP and the NF organizations to consider the fixed formula concept from the standpoint of achieving uniformity in product equivalence and consistency of bioavailability—and were informed that our proposal has considerable merit.

It is exactly the procedure followed by the single producer of a drug product, who develops, tests, evaluates, and then freezes his product composition and method of manufacture, often on a world-wide basis in their plants all over the world.

The identification of like products of a given drug compound through the publication and acceptance of a common composition and procedure for manufacture would surely be in the public interest.

The concept of fixing compositions and manufacturing details for a number of established and important drug products is an extension of the standardization process and a way of assuring the equivalence of official drug products.

Before this very committee on May 20, 1969, Dr. John Adriani appeared and entered this statement into the record, and I quote:

A Code of Good Manufacturing Practices and other criteria with a licensing system and registration for all individual pharmaceutical products is essential. All drugs would then meet the same standards. This, of course, would be imposing the same requirements on all firms manufacturing drugs equally and would do much to solve the problem and obviate the objection which allegedly exists that some drugs are chemically equivalent but not biologically equivalent. This is not an impossible problem to resolve.

The fixed formula concept included in a National Drug Formulary would negate the licensing requirement and would accomplish the equivalency of official drug products.

Thank you. If there are any questions that you would like to ask, I would be perfectly willing to answer them.

In summary, we recommend that:

(1) HEW registered drug manufacturers in possession of approved New Drug Applications should be acceptable to all Federal agency drug bidders' lists for all products.

(2) Duplicative inspections, specifications, and requirements not having any medical or other significance should be eliminated so that competition may be encouraged.

(3) Inclusion of the fixed formula concept within a National Drug Formulary would assure that all official drugs are chemically as well as clinically equivalent.

(4) Resident drug plant inspectors now detailed by the Defense Personnel Support Center should be incorporated within the ranks of the Food and Drug Administration.

(5) The Food and Drug Administration should be adequately funded so that drug inspectors, trained as specialists, are not subject to diversion by food recalls.

(6) Payments for drugs delivered to Federal agencies should be made promptly to encourage the smaller drug manufacturers to submit their bids.

We appreciate this opportunity to submit our testimony before the Subcommittee on Monopoly of the Senate Small Business Committee, and trust that you will consider our recommendations.

Senator NELSON. How many small manufacturers does the National Association of Pharmaceutical Manufacturers represent?

How many manufacturers?

Mr. BARROWS. We have a membership of a little over 80 members, consisting of manufacturers and distributors. And at this time I would like to submit our roster of membership to the committee.

Senator NELSON. The committee will receive it.

[Testimony resumes at page 10253. The information referred to follows:]

NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS
342 Madison Avenue, New York, New York 10017

Membership List As of January 1974

Regular Members:

ALLIED LABORATORIES, INC.
975 Lake Road
Medina, Ohio 44256

ANTHONY PRODUCTS CO.
11634 McBean Drive
Elmonte, California

BARRE DRUG COMPANY, INC.
4128 Hayward Avenue
Baltimore, Maryland 21215

BARTH-SPENCER CORP.
270 W. Merrick Road
Valley Stream, New York 11580

BELL PHARMACAL CORP.
1-85 At Exit U.S. 276
P.O. Box 1968
Greenville, S.C. 29602

BIOCRAFT LABORATORIES, INC.
92 Route 46
East Paterson, N.J. 07407

BIOPHARMA, INC.
625 Broadway
New York, N.Y. 10012

BOLAR PHARMACEUTICAL CO., INC.
130 Lincoln Street
Copiague, New York 11726

CHROMALLOY AMERICAN CORP.
Route 7, P.O. Box 180-A
Evansville, Indiana 47712

COLUMBIA MEDICAL CO.
38 East 19 Street
New York, New York 10003

CONSOLIDATED MIDLAND CORP.
195 East Main Street
Brewster, New York 10509

CRAMER PRODUCTS, INC.
153 West Warren
Gardner, Kansas 66030

ROBERT DANIELS & CO., INC.
Div. of Generics Corp. of America
333 Sylvan Avenue
Englewood Cliffs, N.J. 07632

DAY-BALDWIN, INC.
1460 Chestnut Avenue
Hillside, N.J. 07205

DEL LABORATORIES, INC.
565 Broad Hollow Road
Farmingdale, N.Y. 11735

ENCAPSULATIONS, INC.
269 Chestnut Street
Newark, New Jersey 07105

FARADAY LABORATORIES
100 Hoffman Place
Hillside, New Jersey 07205

FOOD PLUS, INC.
77 Moonachie Avenue
Moonachie, New Jersey 07044

Regular Members Con't

G & W LABORATORIES, INC.
20 Markley Street
Port Reading, New Jersey 07064

HALSEY DRUG CO., INC.
1827 Pacific Avenue
Brooklyn, New York 11233

HUDSON PHARMACEUTICAL CORP.
89 Seventh Avenue
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HEATHER DRUG COMPANY
1 Fellowship Road
Cherry Hill, New Jersey

HUMPHREYS PHARMACAL, INC.
63 Meadow Road
Rutherford, New Jersey 07070

INWOOD PHARMACAL, INC.
303 Prospect Street
Inwood, New York 11696

KETCHUM LABORATORIES, INC.
26 Edison Street
Amityville, New York 11701

LIFE LABORATORIES, INC.
8111 Lankershim Blvd.
North Hollywood, Calif. 91605

LUNDBERG NUTRITION SERVICE
3945 Crenshaw Blvd.
Los Angeles, Calif. 90008

LUNDEN LABORATORIES, INC.
Div. of Chromalloy American Corp.
5353 Grosvernor Blvd.
Los Angeles, Calif. 90066

MERICON INDUSTRIES, INC.
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MIFFLIN McCAMBRIDGE CO.
6400 Rhode Island Avenue
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MURO PHARMACAL LABS., INC.
121 Liberty Street
Quincy, Mass. 02169

REXAR/OBETROL PHARMACEUTICAL CORP.
396 Rockaway Avenue
Valley Stream, New York 11581

O'CONNOR DRUG COMPANY
12115 Woodbine Avenue
Detroit, Michigan 48239

ORMONT DRUG & CHEMICAL CO., INC.
223 South Dean Street
Englewood, New Jersey 07631

PENNEX PRODUCTS CO., INC.
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Verona, Penn. 15147

PHARMACAPS, ICN.
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Elizabeth, New Jersey 07207

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Cantiague Rock Road, Box 730
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PHOENIX LABORATORIES
175 Lauman Lane
Hicksville, New York 11801

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Buffalo, New York 14207

SIMPAK CORPORATION
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Seattle, Washington 98119

STUR-DEE HEALTH PRODUCTS, INC.
Island Park
New York 11558

VITA-FORE PRODUCTS CO.
95-07 98 Street Inc.
Ozone Park, New York 11416

VITARINE COMPANY, INC.
227-15 North Conduit Avenue
Springfield Gardens, New York 11413

VITAMIN SPECIALTIES CO.
5521-25 Wayne Avenue
Philadelphia, Pa. 19144

WEST-WARD, INC.
765 Eagle Avenue
Bronx, New York 10456

XTRIUM LABORATORIES, INC.
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Chicago, Ill. 60609

ZENITH LABORATORIES
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Northvale, New Jersey

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N:w York, N.Y.

F:LLER PRODUCTS CO., INC.
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N:w York, N.Y. 10022

FOOD & DRUG RESEARCH LABS., INC.
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M:spеth, New York 11378

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G:MA LABORATORIES OF AMERICA, INC.
62-04 34th Avenue
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H:XAGON LABORATORIES, INC.
3536 Peartree Avenue
B:onx, New York 10469

HUNTINGTON LABS, INC.
P.O. Box 710
H:ntington, Indiana 46750

K:OLL FINE CHEMICAL, INC.
120 East 56 Street
N:w York, New York

LANCO CONTAINER CORP.
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Brooklyn, New York 11201

LEBERCO LABORATORIES
123 Hawthorne Street
Roselle Park, New Jersey 07204

P. LEINER & SONS, AMER., INC.
20101 Nine Mile Road
St. Clair, Michigan 48040

DR. MADIS LABORATORIES
375 Huyler Street
So. Hackensack, N.J. 07606

MAJESTIC DRUG CO., INC.
721 East 136th Street
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MALLINCRODT CHEMICAL WORKS
P.O. Box 384
223 West Side Avenue
Jersey City, N.J.

M:ER CORPORATION
9500 Railroad Avenue
North Bergen, New Jersey 07047

WILLAIM DOUGLAS MC'ADAMS, INC.
110 Est 39th Street
New York, New York 10011

NAPP-LEMIE CORPORATION
195 Main Street
Lodi, New Jersey 07644

NATIONAL MAGNESIA CO., INC.
83rd Street & Cooper Avenue
Brooklyn, New York 11227

S.B. PENICK & COMPANY
100 Church Street
New York, N.Y. 10008

Associate Members Con't.

PENN BOTTLE & SUPPLY CO.
7150 Lindbergh Blvd.
Philadelphia, Pa. 19153

J. RABINOWITZ & SONS, INC.
1300 Metropolitan Avenue
Brooklyn, New York 11237

S.S.T. CORPORATION
20 Vesey Street
New York, N.Y. 10007

SUPPOSITORIA LABS., INC.
135 Florida Street
Farmingdale, New York 11736

TRUESDALE CHEMICAL SALES CO., INC.
140 East 40th Street
New York, N.Y. 10016

GEORGE UHE COMPANY, INC.
76 Ninth Avenue
New York, New York 10011

STERWIN CHEMICALS, INC.
90 Park Avenue
New York, New York 10016

AMERICAN ROLAND CORP.
16 Hudson Street
New York, N.Y. 10013

SIERRA INTERNATIONAL
1144 Clifton Avenue
Clifton, New Jersey 07013

Senator NELSON. How many are manufacturers?

Mr. BARROWS. We have not broken it down. I could get that information for you, Mr. Chairman.

Senator NELSON. Do you know the dollar volume of the manufacturing done by your manufacturers?

Mr. BARROWS. I have no idea what the actual dollar volume is. I know it is considerable, and I know that many of our member firms do in fact manufacture many dosage forms for the larger firms.

Senator NELSON. Do you happen to know what percentage of the product manufactured by your members are marketed directly by them either into the wholesale or retail market, or by bid to hospitals, municipalities, State agencies, Federal agencies?

Do you know how much goes to other manufacturers?

Mr. BARROWS. I will make this information available to the committee, Senator.

Senator NELSON. If you would.

Now, you represent 80 some manufacturers and distributors.

Mr. BARROWS. That is correct.

Senator NELSON. Do any of them produce drugs under their own brand name?

Mr. BARROWS. Yes. They do.

Senator NELSON. And some of them produce drugs for other companies, is that correct?

Mr. BARROWS. That is right.

Mr. ADAMS. Mr. Barrows, on page 5 of your testimony, the third full paragraph, you state that:

> The USP XVIII does not set a chlolride limit nor does it require a residue of ignition test; both of which have no significance as modern techniques that all impurities are eliminated.

Mr. BARROWS. That is correct.

Mr. ADAMS. Would you tell me what the net effect of that particular requirement is on small manufacturers?

Mr. BARROWS. The net effect of that on small drug manufacturers is that it increases the overhead with regard to excessive testing which proves nothing; because if you are going to test for chlorides, for impurities which you know are not there, you might as well test for sulfates and phosphates, and where do you stop.

And it seems just a redundant thing to include into a procedure which just ups cost and reduces competition.

Mr. ADAMS. Thank you.

On page 7 you compare rotational requirements of certain specifications at the top of that page?

Mr. BARROWS. This is specific rotation requirement and specific rotation of —115° or —121°—the exactness of it is not that necessary, as the British Pharmacopeia gives you a wider range of —113° to —123° as versus —115° and —121° that the DPSC requires. The USP apparently does not require any because they probably feel it has no significance; that the existing compendial monograph requirements are sufficient to warrant not using the specific rotation test.

Mr. ADAMS. And the net effect of those requirements, you are suggesting, is to eliminate competition and cause the price of the drugs to be increased?

Mr. BARROWS. Exactly, exactly. I personally believe that the monograph was submitted to DPSC by Ciba.

Mr. ADAMS. Thank you, sir.

That is all I have, Mr. Chairman.

Senator NELSON. I want to thank you for your testimony. I think a number of your suggestions respecting bidding opportunities by small business is certainly valid. And I think the testimony we have accumulated over the years does indicate that artificial barriers for one reason or another have been erected by Government agencies, that end up barring small businesses from having an opportunity to bid on Government contracts.

And I would hope that we would be able to tackle that question and eliminate these barriers that are unnecessary and artificial.

Mr. BARROWS. Mr. Chairman, I want to thank you again for inviting us to present our views.

Senator NELSON. Thank you very much.

(Whereupon, the hearing in the above-titled matter was recessed at 12:40 p.m., to be resumed on March 5 in this same room.)

[Mr. Barrows submitted the following supplement to his testimony:]

NAPM

National Association of Pharmaceutical Manufacturers
342 Park Avenue, New York, New York 10017 • (212) 687-6565
Madison

February 26, 1974

Honorable Gaylord Nelson, Chairman
Subcommittee on Monopoly
Senate Small Business Committee
Russell Senate Building
Washington, D.C. 20510

Dear Senator Nelson:

As a supplement to my testimony of February 21, 1974 the following information is being submitted to substantiate our statements.

On page 1 of our submitted written testimony I stated:

"The purchasing actions of the U.S. Government reflect prejudices against small businesses. The philosophy of federal purchasing agencies is that small businesses, because they are small, cannot produce quality drugs. By so doing the government compounds the propaganda of the large companies who for their own selfish interests espouse the superiority of their comparable drug products."

Evidences of Prejudices:

(Exhibit A)

ABSTRACTS FROM PRESENTATION BY:
Mr. Max Feinberg
Directorate of Medical Material
Defense Personnel Support Center

PRESENTED TO:
1973 Symposium
"Assuring Quality in Health Care
Focusing on
Professional Standards Review Organizations"

ENTITLED: QUALITY PHARMACEUTICALS WITH THE PATIENT IN MIND.

Shoreham Hotel
Washington, D.C.
November 8, 1973

Exhibit A

Prejudices

Statements by Max Feinberg, Directorate DPSC : (1)

Pg. 8

"The Manufacture of Quality Merchandise doesn't ju: happen. For a company to regularly produce high quality me material, the firm must be effectively structured and organiz from the management to the lowest element. With fully qual: dedicated employees who have enthusiasm, craftsmanship, a ingenuity to build quality into the product with an objective (excellence. This requires the combined skills of experts in : disciplines, plus back-up personnel who are fully responsive the criticalities of the items and the needs of the users. Co that are adequately staffed, and employ scientifically sound methods and procedures, utilizing modern and sturdy equipme a high level of reproducibility, in appropriate facilities with quality control and housekeeping, do produce quality product: regular basis. This does not come cheaply."

Pg. 21-25

"In supporting our medical health care programs, the p of services and material is indeed of great significance. We fully acknowledge, however, that price is not more important quality insofar as the patient is concerned. Let's remember th all of the elaborate programs exist for one reason only, and th for the patient. And if we are ready to sacrifice quality for pri we are in turn creating a sacrificial platform for the patient. medical authorities do expect quality material in medical care ment. The PSRO's should remain mindful of this necessity, n standing the prominent objective for cost containment.

For the ultimate benefit of the patient, we must be ever ful that publicized information and data must be reviewed with analysis. For example, a comparison was recently publicly ma the wide discrepancy in price between the generic and brand na Meprobamate tablets. We examined the list of Meprobamate ta suppliers as taken from the blue book. Four other companies ic their products under trade names.

American Druggist Blue Book
Meprobamate tablets Listing

American Pharmaceutical	Barry Martin
American Quinine	Parke-Davis

SSC-1

Barr Labs.	Purepac
Bell Pharmaceutical	Richlyn
Bowman, Inc.	Sheraton Labs.
Carr Drug	Sherry Labs.
Columia Medical	Stanlabs
Consolidated Medical Corp.	Stayner
Fellows Medical	Towne
ICN	Ulmer
Kirkman	Wolins
	Zenith

DPSC had occasion to inspect the facilities of 11 of those firms. Six were disqualified in 1973, while four others were rejected prior to 1973 and we have not reinspected. The survey findings of several companies from that list are reviewed.

Plant Deficiencies

-One drug container with two labels "Ascorbic Acid and Starch"

-Container and lid had different lot numbers.

-Loss of lot number traceability.

-Failure to maintain building free of insects in production and other areas.

-Incomplete raw material testing

-Production equipment not cleaned before and after use.

-Live spider in drying oven.

-Inadequate quarantine of raw material

-No calibration program.

Pg. 26

"One cannot equate price without an adequate baseline for quality, and that applies to both plant and product.

The need to scrutinize public statements was vividly magnified when a prominent physician, in his testimony to a State legislative committee, advised the listeners that the basis for the Military's rejects of drug plants is for packaging reasons. The records are well established that a DPSC disqualifies a very substantial percentage of drug producers for serious quality control and housekeeping deficiencies."

Pg. 34

Plant Deficiencies

-President is both production and quality control director.

-No double-checking of weighing and measuring.

-Inadequate control over raw material.

-No master formula or batch production records.

-Single lot number for multiple batches.

-Theoretical yields and actual yields are not reconciled.

-No stability studies

-Inadequate laboratory facilities and testing."

Pg. 41

"We must not become over zealous in our aims for cost containment that we jeopardize the health and welfare of the patient by supplying the medical profession with substandard supplies and equipment or furnishing the patient with sub-standard or non-equivalent drug products. Let us not forsake the patient for the sake of the price."

Pg. 43

V.F.W. newly elected Commander-in-chief
Joseph L. Vicities - address - Dallas, 1971 (2)

"The Defense Department has been testing products from small drug companies that are not well-known. The Department of Defense is rejecting approximately 45% of the drugs and medicines it tests before making purchases."

Inspectors from the department have uncovered substandard sanitary conditions and a general absence of even rudimentary quality control in a number of small, back-alley drug manufacturing plants, some of which have been set up by fast buck operators.

The 45% rejection figure applies to drugs actually tested. The products of reputable research-oriented companies are not tested regularly because these companies have proven high standards."

(1) Presented to 1973 Symposium "Assuring Quality in Health Care Focusing on Professional Standards Review Organizations."
(2) Presented at the Veterans of Foreign Wars Convention - Statler Hilton Hotel, Dallas, 1971

DRUG TRADE NEWS, 9/6/71, P. 11

VFW Calls For U.S. Drug Testing; Warns Of 'Fast Buck Operators'

DALLAS—At its convention at the Statler Hilton here, the Veterans of Foreign Wars of the United States adopted a resolution calling on the government to institute a testing program "to assure that all Americans receive only medicines of the highest proven quality." The resolution also praised the Department of Defense program of testing drugs for quality and the work and products of research-oriented reputable manufacturers of drugs.

The Defense Department has been testing products from small drug companies that are not well-known and, said VFW's newly elected Commander-in-Chief, Joseph L. Vicites, "the Department of Defense is rejecting approximately 45% of the drugs and medicines it tests before making purchases."

Inspectors from the department have uncovered "substandard sanitary conditions and a general absence of even rudimentary quality control" in a number of "small, back-alley drug manufacturing plants, some of which have been set up by fast buck operators," Mr. Vicites said.

The 45% rejection figure, he explained, applies to drugs actually tested. "The products of reputable, research-oriented companies are not tested regularly because those companies have proven high standards," he added.

DUAL STANDARDS?

Supportive evidence:

The figure of 45% rejects which the DoD's Mr. Feinberg bandies about has been attributed over the years to drugs actually tested; and also to companies rejected upon inspection.

for example:

1. Mr. Joseph L. Vicities, the newly elected Commander-in-Chief of the Veterans of Foreign Wars as reported in the Drug Trade News dated, September 6, 1971, said the following:

"The Department of Defense is rejecting approximately 45% of the drugs and medicines it tests before making purchases. The 45% rejection figure applies to drugs actually tested. The products of reputable, research-oriented companies are not tested regularly because those companies have proven high standards" (see page 43 of Exhibit A)

2. The FDC Reports dated February 18, 1974 (p. B4) states:

"Forty-five percent of mfrs.' facilities inspected fail to meet DoD standards."

Exhibit B

[PMA's "alternate"] — BIOEQUIVALENCY/BIOAVAILABILITY BATTLE

Given the large number of mfrs. and products and FDA's limited resources, the agency is simply not in the position to assure the quality and eq uivalency of all products on the market. The number of annual inspections FDA can make is, by its own account, descreasing; indeed, FDA no longer reports publicly the number of plants it inspects. Similarly, the number of drug recalls for safety, potency and other quality problems is persistently high.

Another factor of importance is the experience under the Dept. of Defense (DoD) drug procurement program. It is reported that the Dept. rejects 42% of drug product samples submitted to it. Forty-five percent of mfrs.' facilities inspected fail to meet DoD standards. Furthermore, the scientific literature contains many reports showing a lack of therapeutic equivalency among Rx drugs.

The issue is not one of brandname versus generic drugs, as some would like to describe it. The issue is quality of drugs from different mfrs. Unless and until FDA is in a position to assure the therapeutic equivalence of all drugs on the market, the necessary underpinnings for limiting costs in the way the Secty. suggested simply do not exist.

Furthermore, the problem of quality of drugs cannot be solved simply by having FDA satisfy itself as to the quality of one particular mfr.'s product selected as being "generally available" at the lowest price because drugs from other sources available at similar prices but of unknown quality may be selected by the physician or the pharmacist.

> Most physicians and pharmacists, it should be added, do not agree with the premise that price *alone* should determine whether or not the drug prescribed and dispensed should be fully reimbursed. They reject the notion that there is no need for professional judgment in choosing a particular drug product and identifying a preferred source.

In the last analysis, only the prescribing physician is in a position to know which drug products have performed satisfactorily for his patient. Under the Dec. 19 proposal, in cases where the physician or the pharmacist determine that the patient will be better served by a product which costs more than the lowest priced product on the market, the patient would have to bear the additional cost.

This result is neither equitable nor consistent with the principles of the Medicare and Medicaid programs. Escape clauses, that would permit reimbursement of a higher priced product only if the doctor details his bases for selection and some govt. official or advisory cmte. accepts them, would only serve to discourage physicians from exercising their own professional judgment. Such procedures would also lead to expenditures that would dissipate the expected savings from the program.

Finally, the effect of the Dec. 19 proposal may well be to discourage competition in drug quality that has benefited patients by leading to improvements in product quality. It is exceptionally important to stress the relationship between quality pharmaceuticals and source identification, in our view, and to recognize that the need to preserve meaningful incentives toward excellence in all aspects of pharmaceutical manufacture, control and distribution is absolute.

The reputation of American medicines for excellence is unexcelled throughout the world, and is quite independent of the diverse regulatory environments in which these firms manufacture and market their products. Decades of effort to regulate quality into pharmaceutical manufacturing have not mitigated the significance, in the minds of the health professions, of the reputation of the maker of the product.

BIOEQUIVALENCY/BIOAVAILABILITY BATTLE

Or would in fact the patient receive drug B, contrary to the expressed declaration of the Secty. that his proposal would leave the physician free to prescribe the drug of his choice and that the govt. would not interfere in this decision.

As to Medicaid, outpatient drugs are available under some state programs. Here again the same questions can be raised. Since the ℞ would be filled at the local pharmacy, what is the "lowest price" at which the drug is available?

Surveys have shown that in the same community there can be a great variance with respect to cost for the same drug. If there are several drugs available in a class, it can be anticipated that at one pharmacy one drug of that class may be the lowest, while at another pharmacy a different drug will be the lowest.

There undoubtedly will arise many additional questions should this proposal materialize. It would be unfortunate if, in the interest of economy, patients under govt. programs would not have available to them the same spectrum of drugs which their physicians prescribe for other patients.

In his concluding remarks to your Subcmte., Secty. Weinberger stated: "Every physician must be free to prescribe whatever medication he believes is most appropriate for his patient. It is not the business of govt. to tell doctors what marketed drugs they may or may not prescribe. This is, and muse remain, solely a matter of the professional judgment of the prescribing physician."

We agree wholeheartedly with this statement and believe that professional judgment in the prescribing of drugs should extend to the choice of preparation of the same medication. We believe that such professional judgment will be seriously compromised if the physician is forced to administer only the least expensive drug.

TEXT OF PMA's "ALTERNATE APPROACH" TO OBJECTIVES OF HEW's "LOWEST COST" DRUG POLICY

EDITORS' NOTE: *"Alternate approach" -- result of extensive industry effort since Dec. 19 announcement of HEW's "lowest cost" drug policy -- became available following Pharmaceutical Mfrs. Assn. (PMA) Board meeting Feb. 12.*

The purpose of this memorandum is to urge reconsideration of this proposal, which we believe to be both unwise and impractical, and to suggest an alternate approach -- one that would achieve real economies in these govt. programs, one that would not interfere with the professional judgment of physicians and pharmacists, one that would assist rather than disadvantage program beneficiaries, and one that would encourage rather than discourage continued efforts by pharmaceutical companies to improve the quality of their products.

We are, of course, mindful of the Dept.'s interest in reducing the cost of drug purchases financed by federal funds, and agree that this is an important and legitimate goal. The proposal discussed in the Secty.'s Dec. 19 testimony for achieving this goal, however, is based on an erroneous premise -- that FDA is now able to assure the quality of all marketed drugs and that all drug products on the market, containing the same amount of the same active ingredients, are therapeutically equivalent.

If this premise were valid, then the Secty.'s proposal might have some merit. However, the plain facts are (1) that all such drugs are not of equal quality; and (2) that FDA is in no position to assure equivalency.

It is interesting to note that Vicities' statement discloses a "Double Standard" philosophy adopted by the DoD - that is :

> "The products of reputable, research-oriented companies are not tested regularly***

Mr. Vicities statement apparently was composed by Mr. Max Feinberg - as Mr. Vicities could not have been privy to this information.

Too, in Vicities' address, delivered almost 3 years ago, he employed similar rhetoric as does Mr. Feinberg today.

i.e. "Inspectors from the department have uncovered substandard sanitary conditions and a general absence of even rudimentary quality control in a number of small, back-alley drug manufacturing plants, some of which have been set up by fast buck operators."

Examples of -

"Government compounds the propaganda of the large companies who for their own selfish interests espouse the superiority of their comparable products."

Bristol Laboratories, Ciba Pharmaceutical Company, Eaton Laboratories, Lederle Laboratories, Eli Lilly & Co. and Stuart Pharmaceuticals are so assured of their contract awards from the DoD that they have paid advertisements lising the respective Federal Stock Numbers for their products in the Physicians' Desk Reference." The listing had to be submitted 1/2 year (6 months) prior to publication.

i.e. PDR-1972 page 598
Bristol Labs.
"Polycillin" (Ampicillin trihydrate)
FSN 6505-770-8343
FSN 6505-935-1148
FSN 6505-181-7635
FSN 6505-926-8924
FSN 6505-827-5710
FSN 6505-935-6535

PDR-1974 page 697
Ciba Pharmaceutical Company
Serpasil tablets (Resperine)
FSN 6505-957-9531

PDR-1974 page 742
Eaton Laboaratories

a) "Furadantin Oral Suspension"
(Nitrofurantoin)
FSN 6505-082-2658

b) "Furacin Vaginal Suppositories"
(Nitrofurazone) page 742
FSN 6505-823-7924

c) "Macrodantin Capsules" page 744
(Nitrofuradantoin)
FSN 6505-119-9321

PDR-1974 page 850
Lederle Laboratories

"Ferro-Sequels"
(Sustained Release Iron Capsules)
FSN 6505-074-2981

PDR-1974 page 898
Eli Lilly & Co.

a) Darvon Pulvules
(Propoxyphene Hydrochloride)
FSN 6505-660-1720
FSN 6505-725-6992
FSN 6505-958-2364

b) Darvon Compound Pulvules
(Propoxyphene Hydrochloride, Aspirin, Phenacetin, and Caffeine)
FSN 6505-967-8735
FSN 6505-784-4926

PDR-1974 page 1448
Stuart Pharmaceuticals

a) Mylanta Liquid
FSN 6505-890-2218

b) Mylanta tablets
FSN 6505-890-1373

These are just a few examples of evidence which connote pre-arranged assurances by DoD to a select group of companies that they will receive the contract awards for products.

The impact of these listings in the PDR has a devastating effect on competitive generic equivalent drugs as the 'detailmen' of the select group of companies state the following to physicians they call on:

> "Doctor - the U.S. Government only accepts our drug as the quality of the smaller drug firms' so called equivalent is no good; the FSN is the Federal Stock Number for our product."

32-814 (Pt. 24) O - 74 - 23

Exhibit C

Lists examples of specifications apparently composed by the recipient of the contract awards.

EXAMPLES OF SPECIFICATIONS APPARENTLY COMPOSED BY THE RECIPIENT OF THE CONTRACT AWARDS

FSN No.	PRODUCT	COMPANY	TRADE MARK PRODUCT
6505-550-8464	Meprobamate tablets, U.S.P. 0.4 Gram	Wallace	Miltown
6505-290-0022	Reserpine tablets, U.S.P. 0.25mg.	Ciba	Serpasil
6505-890-2218	Aluminum Hydroxide Gel, Magnesium Hydroxide & Simethicone Susp.	Stuart	Mylanta
6505-890-2012 6505-926-8926	Chlorpheniramine Maleate, Chloroform, Codeine Phosphate, Glyceryl Guaiacolate, Menthol, & Phenylephrine HCL Syrup	Dow	Novahistine
6505-116-9325	Sodium Diphenylhydantoin Capsules, U.S.P. 100mg.	Parke, Davis & Co.	Dilantin Kapseals
6505-753-4766	Theophylline, Ephedrine Hydrochloride & Phenobarbital Tablets N.F.	Warner-Chilcott	Tedral
6505-116-7750	Digoxin Tablets, U.S.P. 0.25mg.	Burroughs Wellcome	Lanoxin
6505-106-8700	Dextroamphetamine Sulfate tablets, U.S.P. 5mg.	Smith, Kline & French	Dexedrine
6505-132-6904	Isoniazid tablets, U.S.P. 0.3 Gram	Squibb & Sons.	Nydrazid
6505-851-6589	Meperidine Hydrochloride Tablets, U.S.P. 50mg.	Winthrop	Demerol
6505-527-6885	Probenecid Tablets, U.S.P. 0.5 Gram	Merck, Sharp & Dohme	Benemid
6505-299-9678	Kaolin Mixture with Pectin, N.F.	Upjohn	Kaopectate
6505-926-9055	Acetaminophen Elixir, N.F.	Smith, Kline & French	SK-APAP
6505-890-2010 6505-926-9026	Promethazine Hydrochloride, Chloroform, Ipecac Fluid Extract, and Potassium Guaiacolsulfonate Syrup	Wyeth	Phenergan Syrup

Exhibit D

Illustrates the effect of generic drugs in the market place on the price of the brand name products.

EFFECT OF GENERIC DRUGS IN THE MARKET PLACE ON THE PRICE OF THE BRAND NAME PRODUCTS:

1) METICORTEN TABLETS 5 mg. (SCHERING)
reduced from $17.50 per 100 tablets to $2.25 per 100
Generic name is PREDNISONE

2) METICORTELONE TABLETS 5 mg. (SCHERING)
reduced from $17.50 per 100 to $10.80 per 100.
Generic name is Prednisolone

3) BRISTOL POLYCILLIN CAPSULES 500 mg.
reduced from $48.00 per 100 to 30.00 per 100
Generic name is AMPICILLIN.

4) ERYTHROCIN TABLETS 250 mg. (ABBOTT)
reduced from $22.00 per 100 to 12.00 per 100
Generic name is ERYTHROMICIN

5)ACHROMYCIN CAPSULES (LEDERLE)
reduced from $30.00 per 100 to $3.75 per 100.

6) THORAZINE TABLETS 100 mg. (SMITH, KLINE & FRENCH)
reduced from $9.00 per 100 to 5.40 per 100
Generic name is CHLORPROMAZINE.

7) THERAGRAN-M TABLETS (SQUIBBS)
reduced from $7.95 per 100 to 4.90 per 100
Generic name is THERAPEUTIC VITAMINS & MINERALS

Exhibit E

Comparative prices between faster selling brand name drugs compared with the generic counterpart.

COMPARATIVE PRICES BETWEEN FASTER SELLING BRAND NAME DRUGS COMPARED WITH THE GENERIC COUNTERPART:

BRAND NAME	PRICE	GENERIC NAME & PRICE
CHLORTRIMETON TABLETS 4 mg. (C Schering)	21.00/m	CHLORPHENIRAMINE MALEATE TABLETS 4 mg. $1.05/M
DARVON COMPOUND CAPSULES (Eli Lilly)	32.50/500's	PROPOXYPHENE & APC CAPSULES 7.75/500's
DEXEDRINE TABLETS 5 mg. (SKF)	22.85/M	DEXTROAMPHETAMINE SULFATE 5 mg. 5.50/M
HYDRODIURIL TABLETS 50 mg. (MSD)	52.50/M	HYDROCHLORTHIAZIDE TABLETS 50 mg. 8.50/M
PAVABID CAPSULES 150 mg. (Marion)	98.50/M	TIMED RELEASE PAPAVERINE 150 mg. CAPS. 13.90/M
PENTIDS (Squibb)	9.30/100's	BUFFERED PENICILLIN TABS 400,000 Units 1.30 per 100's
PLEGINE TABLETS 35 mg. (Ayerst)	47.50/M	PHENDIMETRAZINE tabs 35 mg. 6.95/M
PRE SATE TABLETS 65 mg. (W-C)	112.80/M	CHLORPHENTERMINE TABS 65 mg. 13.95/M
TERRAMYCIN CAPSULES 250 mg. (Pfizer)	19.95/100's	OXYTETRACYCLINE CAPS. 1.90 / 100's

Exhibit F

Copies of Defense Medical Purchase Descriptions - indicating by underscoring the absurd specifications and the duplication of inspection requirements by the DPSC; and examples of where only one company's product is acceptable.

i.e.

1) Sodium Diphenylhydantoin Capsules, U.S.P., 100mg.

'Shall be Parke, Davis and Company's "Dilantin Capsules 100mg."

(Exhibit F - page 90)

2) Tetracycline Hydrochloride Capsules, U.S.P. 0.25 Gram, 100s

'Shall be tetracycline Hydrochloride Capsules, U.S.P., as produced by Lederle Laboratories as "Achromycin V Capsules"

(Exhibit F - page 87)

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 1	DATE 30 January 1973

FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-104-8672	MEPROBAMATE TABLETS, USP, 0.4 Gram, 25s	Box

Shall be Meprobamate Tablets, U.S.P., and shall be in accordance with all applicable requirements of Federal Standard Fed. Std. No. 1h0a, dated 30 October 1966, and Amendment-1, dated 25 March 1970, and as specified herein:

S2. Classification. Shall be type I, class 1.

S5.2 The following additional requirements and tests are added to this paragraph:

Shall be tablets containing 0.4 gram of Meprobamate per tablet, within the applicable assay limits for the tablets.

Note: See U.S.P. XVIII, 1st Supplement, dated 1 October 1971, for change in "Dissolution."

The Meprobamate powder used in the tablets shall be in accordance with the tests, standards, and requirements of the U.S.P., including any supplements or revisions thereto. In addition, the Meprobamate powder shall comply with the infrared absorption spectrum and the chloride limit as set forth in Volume 25, Number 3, pages 88 and 89 of "Drug Standards."

The Meprobamate powder shall comply with the following additional test:

The residue on ignition (sulfated ash) shall be not more than 0.10 percent when determined by the U.S.P. method.

All other ingredients shall comply with S5.1.

Add the following new paragraph:

"S5.8 Pre-Award or pre-acceptance samples. Upon a separate request of the contracting officer, the offeror or bidder shall submit three (3) individually packaged samples (each containing 25 tablets) of the Meprobamate Tablets, representative of the product which the bidder or offeror proposes to furnish, to the contracting officer. Samples will be tested to the extent necessary to determine compliance with S6.4.8, as well as any other specified requirements. One (1) box (sample) will be used to perform the above testing; another box will be used by the cognizant quality assurance representative as a standard reference sample for determining compliance of deliveries with S6.4.8 requirements; and the third box will be held by the Defense Personnel Support Center for whatever use is deemed necessary. The approval of these samples will not constitute approval of the sample as meeting the other requirements of this purchase description.

S6.4.2 Color. Uncoated tablets shall be uniformly white.

6505-104-8672 (P. D. No. 1)

S6.4.7 Scoring. Tablets shall be scored.

S6.4.8 Odor. Delete the first sentence and substitute: "Tablets shall be odorless or shall have not more than a slight odor, characteristic of meprobamate."

S6.4.9.1 Disintegration. The uncoated tablets shall disintegrate in not more than 30 minutes when tested by the U.S.P. method for "Uncoated Tablets."

PREPARATION FOR DELIVERY

Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-00186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, and as specified herein:

Immediate containers (strip pockets). Shall comply with the following: Twenty-five (25) tablets shall be packaged in a commercially available, continuous roll strip package. Each tablet shall be sealed in its own pocket and so designed that the end pocket can be removed and the seal on the adjoining pocket shall not be disturbed. The individual pockets shall be consecutively numbered from one (1) to twenty-five (25). One roll of twenty-five tablets shall be contained in a carton (box) as specified. The numbers on the strip package roll shall be in reverse order so that the first pocket removed shall be number twenty-five (25) and the second number shall be twenty-four (24), etc.

Labeling. Labeling shall be in accordance with the requirements of the Federal Food, Drug, and Cosmetic Act, and shall include the information required below:

Immediate containers. Each immediate container (pocket) shall be permanently and legibly marked with the following information. The labeling shall appear in the center of the pocket and shall not extend into the heat-sealed area:

Labeling information in accordance with commercial practice. In addition, the numbering shall be in reverse order as specified under "Immediate containers (strip pockets)" see above. The date of manufacture shall not be required.

6505-104-8672 (P. D. No. 1)

Unit packages. Each unit package (box) label shall bear the following information. However, the information is not required to appear in the sequence indicated:

(a) the item name designated as "MEPROBAMATE TABLETS, U.S.P."

(b) the quantity of active ingredient designated as "0.4 Gram" or "400 mg"

Note: The official abbreviation "g." may be used in lieu of the word "gram."

(c) the Federal Stock No.

(d) the lot or control number

(e) the date of manufacture

(f) the name and address of the manufacturer. When the manufacturer is not the contractor, the name and address of the contractor shall also appear.

When both names are placed on the label, the following designations shall precede the names:

"MFR" for the manufacturer and
"CONTR" for the contractor.

(g) the statement "Caution: Federal law prohibits dispensing without prescription."

(h) the following statements or similar statements:

1. Multiple dispensing package.
2. This package not for household use.

(i) the usual dosage

(j) all labeling information and the controlled substance schedule symbol as required by the Bureau of Narcotics and Dangerous Drugs regulations

(k) the unit of issue designated as

"1 BOX
(1 roll of 25 tablets)"

The parenthetical phrase shall appear in smaller characters than the unit of issue designation.

6505-104-8672 (P.D. No. 1)

Packaging.

Unit of issue. One box containing 25 tablets, as specified, constitutes one unit of issue.

Packaging quantities. The number of units of issue indicated in the following tablet shall be packaged in each unit, intermediate, and exterior container, as applicable for the required level of protection specified in the procurement document.

Packaging quantities

Unit package	Intermediate package	Exterior container
1 unit	10 units	120 units

Packing variation permitted. If the required number of units in the entire shipment is less than the number of units specified to be over-packed in an exterior container, such units may be packed in an exterior container of suitable size and design, acceptable to a common carrier, which shall insure safe delivery to destination.

Level A.

Unit package. One roll of twenty-five tablets shall be packaged in a dispensing, tamperproof type box of appropriate size and design. The numbers on the strip package roll shall be in reverse order so that the first pocket removed s hall be number 25 and the second number shall be 24, etc. The box shall have one transparent plastic window on the side opposite that of the label.

Intermediate package. Intermediate package shall be a box of appropriate size and design constructed in accordance with PPP-B-566 or PPP-B-676, except commercial colors will be acceptable, or PPP-B-636, type CF, class domestic. Closure shall be adequate to prevent accidental opening under normal handling.

Level C. Units shall be packaged in standard commercial containers of the size and kind commonly used, which will afford the degree of protection required for shipment and use of the product for its intended purpose.

6505-104-8672 (P. D. No. 1)

Packing.

Level A.

Exterior container. Exterior container shall be designed for a type 2 load and constructed in accordance with PPP-B-585, class 3, style 3; PPP-B-601, overseas type; PPP-B-621, class 2; or PPP-B-636, class weather-resistant. Closure and strapping shall be as specified in the appendix of the applicable box specification. Fiberboard boxes shall conform to the special requirements specified in PPP-B-636.

Case liner. Each level A wood box shall be lined with a waterproof case liner conforming to Specification MIL-L-10547. Closure and sealing shall conform to applicable paragraphs of appendix thereto. Case liner shall not be required for fiberboard boxes. Each fiberboard box shall be waterproofed in accordance with 30.4 of PPP-B-636.

NOTE: Strapping shall not be required for shipments forwarded to a receiving activity within the continental limits of the United States for storage and redistribution.

Level B.

Exterior container. Exterior container shall be designed for a type 2 load and constructed in accordance with PPP-B-585, class 1, style 3; PPP-B-601, domestic type; PPP-B-621, class 1; or PPP-B-636, class domestic. Closure of wood boxes shall be as specified in the appendix of the applicable box specification. Closure of fiberboard boxes shall conform to method II of PPP-B-636. In addition, fiberboard boxes shall conform to the special requirements specified in PPP-B-636.

Level C. The subject commodity shall be packed in substantial commercial containers of the type, size, and kind commonly used for the purpose, so constructed as to insure acceptance and safe delivery by common or other carriers, at the lowest rate, to point of delivery called for in the contract or purchase order.

Marking.

Intermediate packages. Each intermediate package shall be marked in accordance with MIL-STD-129. When labels are utilized, waterproofing shall be required only when applicable carton is fabricated of water-resistant material. Lot (control) number, contract or purchase order number, and name of contractor shall be shown. The date of manufacture shall be shown in lieu of date packed.

Exterior container. Exterior container shall be marked as specified in MIL-STD-129. Lot (control) number shall be shown. The date of manufacture shall be shown in lieu of date packed. The Item Identification shall not appear on the exterior container.

6505-104-8672 (P. D. No. 1)

SUPPLIER RESPONSIBILITY FOR INSPECTION

Unless otherwise specified in the contract or purchase order, the supplier is responsible for the performance of all inspection requirements as specified herein. Except as otherwise specified in the contract or order, the supplier may use his own or any other facilities suitable for the performance of the inspection requirements specified herein, unless disapproved by the Government. The Government reserves the right to perform any of the inspections set forth in the specification where such inspections are deemed necessary to assure supplies and services conform to prescribed requirements.

Records of examinations and tests performed by or for the contractor shall be maintained by the contractor and made available to the Government, upon the Government's request, at any time, or from time to time, during the performance of the contract and for a period of 3 years after delivery of the supplies to which such records relate.

No company supplying any ingredient(s) to the contractor will be considered an acceptable facility for the performance of any inspection requirements specified herein.

DATE: 30 January 1973

APPROVED NEW DRUG APPLICATION REQUIRED

The supplier of any item(s) listed below must possess, at time of award of contract for such item(s), a New Drug Application which has been approved by the Food and Drug Administration.

FSN	Item Identification
6505-104-8672	MEPROBAMATE TABLETS, USP, 0.4 Gram, 25s

SSC-1

MODIFICATION NO. 2
DATE: 3 November 1972

MODIFICATION TO DEFENSE MEDICAL PURCHASE DESCRIPTION

This modification forms a part of Defense Medical Purchase Description No. 7, dated 24 August 1970, and covers the following item to the extent specified herein:

Federal Stock No.	Item Identification
6505-550-8464	MEPROBAMATE TABLETS, USP, 0.4 Gram, 500s

Page 1:

Line 2, after "1966," insert "and Amendment-1, dated 25 March 1970,".

Under "S2. Classification" - insert new paragraph:

"Shall be suitable for use as a daytime sedative and hypnotic and also as a skeletal muscle relaxant."

Under "S5.2" insert the following:

"See U.S.P. XVIII, 1st Supplement, dated October 1, 1971, for change in 'Dissolution.' "

Page 3:

Under "Labeling" - "Immediate containers" - Add the following new subparagraph:

"(j) all labeling information and the controlled substance schedule symbol as required by the Bureau of Narcotics and Dangerous Drugs regulations."

DATE: 3 November 1972

APPROVED NEW DRUG APPLICATION REQUIRED

The supplier of any item(s) listed below must possess, at time of award of contract for such item(s), a New Drug Application which has been approved by the Food and Drug Administration.

FSN	Item Identification
6505-550-8464	MEPROBAMATE TABLETS, USP, 0.4 Gram, 500s

515

SSC-1 M

MODIFICATION NO. 1
DATE: 25 May 1971

MODIFICATION TO DEFENSE MEDICAL PURCHASE DESCRIPTION

This modification forms a part of Defense Medical Purchase Description No. 7, dated 24 August 1970, and covers the following item to the extent specified herein:

Federal Stock No.	Item Identification
6505-550-8464	MEPROBAMATE TABLETS, USP, 0.4 Gram, 500s

Page 1:

Line 2, after "1966," insert "and Amendment-1, dated 25 March 1970,".

Under "S2. Classification" - insert new paragraph:

"Shall be suitable for use as a daytime sedative and hypnotic and also as a skeletal muscle relaxant."

Under "S5.2" - preceding line reading "All other ingredients. . . . " insert the following new paragraphs:

"In addition to the U.S.P., the following shall apply:

'Determination of Meprobamate in dissolution medium:

'Internal standard solution. Transfer about 25 mg of U.S.P. Phenacetin Reference Standard, accurately weighed to a 50-ml volumetric flask. Add methylene chloride to volume and mix.

'Standard preparation. Transfer about 50 mg of U.S.P. Meprobamate Reference Standard, accurately weighed to a 50-ml volumetric flask. Add methylene chloride to volume and mix.

'Sample preparation. Withdraw a 10 ml aliquot of the filtered dissolution medium after 30 minutes of rotation and transfer it to a 60 ml separatory funnel containing 15 ml of methylene chloride. Add two drops of sulfuric acid, shake vigorously, allow the layers to separate, and filter the organic layer through about 4 grams of anhydrous sodium sulfate suitably supported in a funnel. Repeat the extraction two additional times collecting the combined extracts in a suitable beaker. Evaporate to small volume with the aid of a stream of nitrogen and gentle warming and transfer to a small conical centrifuge tube or other suitable vessel, with the aid of additional small portions of methylene chloride and evaporate to dryness. Add, by pipet, 2.0 ml of the internal standard solution to the residue and mix.

330-1

M

6505-550-8464 (Mod. No. 1)

"Standard curve. Pipet into separate conical centrifuge tubes or suitable vessels, duplicate 1-, 3-, and 5-ml portions, respectively of Standard preparation, and evaporate to dryness. Add, by pipet, 2.0 ml of the Internal standard solution to each of the tubes and dissolve the residue. Inject 2.0 ul from each solution, successively, into a suitable gas chromatograph (see page 793, U.S.P.), equipped with a flame ionization detector. Under typical conditions, the instrument contains a 1:2 meter by 4-mm glass column packed with 3 percent (w/w) methylphenyl-silicone oil (OV-17) on 80 to 100-mesh silanized, acid-washed, flux-calcined siliceous earth suitably cured (see page 794, U.S.P.). Maintain the column at 160°, and maintain the injection port and detector at 170°. Use helium as the carrier gas, at a flow of 70 ml per minute. Measure the heights, Hp and Hm, of the phenacetin and meprobamate peaks, respectively, in each chromatogram, and calculate the ratio Rs, by the formula Hm/Hp. Plot the standard curve of the values of Rs against the amount, in mg of U.S.P. Meprobamate Reference Standard contained in each portion of Standard preparation taken.

"Procedure. Inject 2.0 ul of Sample preparation into the chromatograph, and obtain a chromatogram as directed under Standard curve. Measure the height of the meprobamate and phenacetin peaks, and calculate the ratio, Ru, of the height of the meprobamate peak to that of phenacetin. Read from the Standard curve the quantity, in mg of $C_9H_{18}N_2O_4$ in the volume of the dissolution medium taken." "

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 7	DATE 24 August 1970

FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-550-8464	MEPROBAMATE TABLETS, USP, 0.4 Gram, 500s	Bottle

Shall be Meprobamate Tablets, U.S.P., and shall be in accordance with all applicable requirements of Federal Standard Fed. Std. No. 1l0a, dated 30 October 1966, together with the options, additions, and deletions stated herein:

S2. Classification. Shall be type I, class 1.

S5.2 The following additional requirements and tests are added to this paragraph:

Shall contain 0.4 gram of Meprobamate per tablet, within the applicable assay limits for the tablets.

The Meprobamate powder used in the tablets shall be in accordance with the tests, standards, and requirements of the U.S.P., including any supplements or revisions thereto. In addition, the Meprobamate powder shall comply with the infrared absorption spectrum and the chloride limit as set forth in Volume 25, Number 3, pages 88 and 89 of "Drug Standards."

The Meprobamate powder shall comply with the following additional test:

> The residue on ignition (sulfated ash) shall be not more than 0.10 percent when determined by the U.S.P. method.

All other ingredients shall comply with S5.1.

Add the following new paragraphs:

"S5.8 Pre-award or pre-acceptance samples. Upon a separate request of the contracting officer, the offeror or bidder shall submit three (3) individually packaged samples (each containing 500 tablets) of the Meprobamate Tablets, representative of the product which the bidder or offeror proposes to furnish, to the contracting officer. Samples will be tested to the extent necessary to determine compliance with S6.4.8, as well as any other specified requirements. One (1) bottle (sample) will be used to perform the above testing; another bottle will be used by the cognizant quality assurance representative as a standard reference sample for determining compliance of deliveries with S6.4.8 requirements; and the third bottle will be held by the Defense Personnel Support Center for whatever use is deemed necessary. The approval of these samples will not constitute approval of the sample as meeting the other requirements of this purchase description.

6505-550-8464 (P. D. No. 7)

"S5.9 Aging test. 100 tablets of each lot shall be placed in an amber glass bottle, tightly sealed with Closure B. Place the bottle in an oven at 55° C. (between 53° and 56° C.) and maintain at that temperature for 10 consecutive days. At the end of that period, remove the bottle and allow to stand at room temperature overnight. Select a total of 18 tablets from the top, middle, and bottom of the bottle. Test the tablets for disintegration by the U.S.P. Tablet Disintegration Test for Meprobamate Tablets. Not less than 16 of the 18 tablets tested shall completely disintegrate within 30 minutes. In addition, the aged tablets shall comply with the dissolution test of the U.S.P."

S6.4.2 Color. Uncoated tablets shall be uniformly white.

S6.4.7 Scoring. Tablets shall be scored.

S6.4.8 Odor. Delete the first sentence and substitute the following: "Tablets shall be odorless or shall have not more than a slight odor, characteristic of meprobamate."

S6.4.9.1 Disintegration. The uncoated tablets shall disintegrate in not more than 30 minutes when tested by the U.S.P. method for "Uncoated Tablets."

PREPARATION FOR DELIVERY

Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-001186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, together with deletions or additions as indicated herein:

Immediate containers. Shall comply with the following classification:

GROUP A	CLASS 1	TYPE e	STYLE 2	GRADE 1
CLOSURE B				SEAL A or B

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6505-550-8464 (P. D. No. 7)

Labeling. Labeling shall be in accordance with the requirements of the Federal Food, Drug, and Cosmetic Act, and shall include the information required below:

Immediate containers. Each immediate container label shall bear the following information. However, the information is not required to appear in the sequence indicated:

(a) the item name designated as "MEPROBAMATE TABLETS, U.S.P."

(b) the quantity of active ingredient designated as "0.4 Gram"

Note: The official abbreviation "g." may be used in lieu of "gram."

(c) the phrase "500 tablets" or a similar phrase

(d) the Federal Stock No.

(e) the lot or control number

(f) the name and address of the manufacturer. When the manufacturer is not the contractor, the name and address of the contractor shall also appear.

When both names are placed on the label, the following designations shall precede the names:

"MFR" for the manufacturer and
"CONTR" for the contractor.

(g) the date of manufacture

(h) the recommended dosage

(i) the statement "Caution: Federal law prohibits dispensing without prescription."

Unit packages. Each unit package label shall bear the same information as required for the label of the immediate container.

A circular, brochure, or other printed matter shall be packaged within each unit package setting forth as a minimum: Indications; Recommended dosage; Contraindications; Side Reactions, and Toxicity.

6505-550-8464 (P. D. No. 7)

Packaging and Packing.

Unit of issue. One bottle (500 tablets), as specified, constitutes one unit of issue.

Unit package. Each unit shall be packaged as specified in 5.2.5 of PPP-C-00186a.

Procedure code. Procedure code No. 6 applies.

Marking.

Intermediate package. In paragraph 5.5.3 of PPP-C-00186a, at end of paragraph, add: "Date of manufacture shall be shown in lieu of date packed."

Exterior container. In paragraph 5.5.4 of PPP-C-00186a, at end of paragraph, add: "Date of manufacture shall be shown in lieu of date packed."

SUPPLIER RESPONSIBILITIES FOR INSPECTION

Unless otherwise specified in the contract or purchase order, the supplier is responsible for the performance of all inspection requirements as specified herein. Except as otherwise specified in the contract or order, the supplier may use his own or any other facilities suitable for the performance of the inspection requirements specified herein, unless disapproved by the Government. The Government reserves the right to perform any of the inspections set forth in the specification where such inspections are deemed necessary to assure supplies and services conform to prescribed requirements.

Records of examinations and tests performed by or for the contractor shall be maintained by the contractor and made available to the Government, upon the Government's request, at any time, or from time to time, during the performance of the contract and for a period of 3 years after delivery of the supplies to which such records relate.

No company supplying any ingredient(s) to the contractor will be considered an acceptable facility for the performance of any inspection requirements specified herein.

STANDARD FORM 33, JULY 1966 GENERAL SERVICES ADMINISTRATION FED. PROC. REG. (41 CFR) 1-16.101	CONTINUATION SHEET	REF. NO. OF DOC. BEING CONTD. DSA 120-71-R-2364	PAGE	OF

NAME OF OFFEROR OR CONTRACTOR

1 March 1971

ITEM NO.	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT

The following addition to the U.S.P. dissolution test is applicable.

Determination of meprobamate in dissolution medium.

Internal standard solution. Transfer about 25 mg. of U.S.P. Phenacetin Reference Standard, accurately weighed to a 50-ml. volumetric flask. Add methylene chloride to volume and mix.

Standard preparation - Transfer about 50 mg. of U.S.P. Meprobamate Reference Standard, accurately weighed, to a 50-ml. volumetric flask. Add methylene chloride to volume, and mix.

Sample preparation - Withdraw a 10 ml. aliquot of the filtered dissolution medium after 30 minutes of rotation and transfer it to a 60 ml. separatory funnel containing 15 ml. of methylene chloride. Add two drops of sulfuric acid, shake vigorously, allow the layers to separate, and filter the organic layer through about 4 grams of anhydrous sodium sulfate suitably supported in a funnel. Repeat the extraction two additional times collecting the combined extracts in a suitable beaker. Evaporate to small volume with the aid of a stream of nitrogen and gentle warming and transfer to a small conical centrifuge tube or other suitable vessel, with the aid of additional small portions of methylene chloride and evaporate to dryness. Add, by pipette, 2.0 ml. of the internal standard solution, dissolve the residue and mix.

Standard Curve - Pipet into separate conical centrifuge tubes or suitable vessels, duplicate 1 -, 3-, and 5- ml. portions, respectively of Standard preparation, and evaporate to dryness. Add, by pipette, 2.0 ml. of the Internal standard solution to each of the tubes and dissolve the residue. Inject 2.0 ml. from each solution, successively, into a suitable gas chromatograph (see page 793) equipped with a flame ionization detector. Under typical conditions, the instrument contains a 1.2 meter x 4- mm glass column packed with 3 percent (w/w) methylphenyl-silicone oil (OV-17) on 80 to 100-mesh silanized, acid-washed, flux-calcined siliceous earth suitably cured (see page 794). Maintain the column at 105° and maintain the injection port and detector at 170°. Use helium as the carrier gas, at a flow of 70 ml. per minute. Measure the heights, Hp and Hm, of the phenacetin and meprobamate peaks, respectively, in each chromatogram, and calculate the ratio Rs, by the formula Hm/Hp. Plot the standard curve of the values of Rs against the amount, in mg. of U.S.P. Meprobamate Reference Standard contained in each portion of Standard preparation taken.

Procedure - Inject 2.0 ml of Analysis preparation into the chromatograph, and obtain a chromatogram as directed under Standard curve. Measure the height of the meprobamate and phenacetin peaks, and calculate the ratio, Ru, of the height of the meprobamate peak to that of phenacetin. Read from the Standard curve the quantity, in mg, of $C_9H_{18}N_2O_4$ in the volume of the dissolution medium taken.

Serpasil

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 7	DATE 10 June 1971

FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-290-0022	RESERPINE TABLETS, USP, 0.25 mg, 1000s	Bottle

Shall be Reserpine Tablets, U.S.P., and shall be in accordance with all applicable requirements of Federal Standard Fed. Std. No. 1l0a, dated 30 October 1966, and Amendment-1, dated 25 March 1970, and as specified herein:

S2. Classification. Shall be type I, class 1.

S5.2 The following additional requirements and tests are added to this paragraph:

Shall be tablets containing 0.25 mg of Reserpine per tablet, within the applicable assay limits for the tablets.

The Reserpine powder used in the manufacture of the tablets shall be in accordance with the tests, standards, and requirements of the U.S.P., including any supplements or revisions thereto, and, in addition, shall comply with the following:

Description. Shall be white or pale buff to slightly yellowish, odorless, crystalline powder.

Identification. The infrared absorption spectrum (graph) of the powder in a Nujol dispersion shall compare qualitatively with the spectrum (graph) of the U.S.P. Reserpine Reference Standard.

Specific rotation. Shall be between -115° and -121° when determined as follows:

Accurately weigh about 100 mg of powder previously dried at 60° C. for 3 hours, into a 10-ml volumetric flask. Dissolve in, and dilute to volume with chloroform. Determine the optical rotation of the solution in accordance with the U.S.P. procedure, at 25° C., using a 1-decimeter tube and the D line of the sodium spectrum. Calculate the specific rotation.

Paper chromatography. The reserpine sample shall show a homogeneous spot comparable in size, and having the same Rf value as the reference standard, except that a trace impurity may remain at the origin and another trace impurity at approximately Rf 0.04. The procedure to be employed shall be as follows:

BRITISH PHARM. SAYS -113° → -123° determined at 20°C — NOT DRIED. —

USP HAS NO SUCH REQUIREMENT. —

WHAT IS THIS SUPPOSED TO DO FOR THEM? — DID THIS COME FROM THEIR FAVORED SUPPLIER?

SSC-1

DPSC FORM 2087 OCT 68 REPLACES DMSC FORM T-4120/11, MAR 64, WHICH WILL BE USED UNTIL EXHAUSTED

60

6505-290-0022 (P. D. No. 7)

Reagents and Solutions.

Standard Solution. Prepare a solution of U.S.P. Reserpine Reference Standard containing a known final concentration of 1.0 mg per ml in chloroform. Prepare this solution prior to use.

Sample Solution. Prepare a sample Reserpine solution containing a known final concentration of 1.0 mg per ml in chloroform. Prepare this solution prior to use.

Solvent System.

Immobile Phase. Dilute 70 ml of formamide (99%) to 100 ml with methanol.

Mobile Phase. One part by volume of benzene and one part by volume of cyclohexane equilibrated with formamide.

Procedure:

Line standard chromatography jars which have been set up for descending chromatography with 12-1/4 by 22-1/2 inch Whatman No. 1 chromatography paper. Fill the solvent troughs with mobile phase solvent, and place sufficient amount of the same solvent in the chamber to allow the liner to dip into the solvent. Allow the chamber to equilibrate 12 hours.

Cut Whatman No. 1 chromatography paper into strips 5 inches by 18 inches and make a line 2-1/2 inches from one end. Mark application points at one inch intervals along this line. Immerse the paper in the immobile phase solvent and remove the excess solvent by pressing between two dry chromatography sheets and passing through a hand wringer. Spot 20.0 ul of standard and sample solutions, respectively, at separate application points, using a micropipet. Place the chromatogram in the chamber and allow it to develop for approximately 5 hours, or until the solvent front is one inch from the bottom of the paper. Remove the chromatograms, mark the solvent front, and air dry for a few minutes to remove the excess solvent. Observe, while still wet, under ultraviolet light at 360 mu. Note the spots, then completely dry in a 90° C. oven for 10 to 15 minutes. Again observe under the ultraviolet light. The chromatogram may be sprayed lightly with glacial acetic acid to intensify the fluorescence. The Rf value for Reserpine shall be 0.34 ± 10 percent.

All other ingredients shall comply with S5.1.

S6.4.2 Color. Uncoated tablets shall be white.

S6.4.7 Scoring. Tablets shall be scored.

If samples of the tablets are submitted to Defense Personnel Support Center, a quantity of not less than 5 grams of each lot of Reserpine Powder, U.S.P., shall also be submitted with the finished product, to the Technical Operations Division, Directorate of Medical Materiel, Defense Personnel Support Center, 2800 South 20th Street, Philadelphia, Pa. 19101, Attention: Quality Assurance Branch.

PREPARATION FOR DELIVERY

Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-00186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, and as specified herein:

Immediate containers. Shall comply with the following classification:

GROUP A	CLASS 1	TYPE e	STYLE 2	GRADE 1
CLOSURE A, B, or F			SEAL A or B for Closures A and B only.	

Labeling. Labeling shall be in accordance with the requirements of the Federal Food, Drug, and Cosmetic Act, and shall include the information required below:

Immediate containers. Each immediate container label shall bear the following information. However, the information is not required to appear in the sequence indicated:

(a) the item name designated as "RESERPINE TABLETS, U.S.P."

(b) the quantity of active ingredient per tablet designated as "0.25 mg"

(c) the phrase "1000 tablets" or a similar phrase

(d) the Federal Stock No.

(e) the lot or control number

(See additional label information on page 4)

(f) the date of manufacture

(g) the name and address of the manufacturer. When the manufacturer is not the contractor, the name and address of the contractor shall also appear.

When both names are placed on the label, the following designations shall precede the names:

"MFR" for the manufacturer and
"CONTR" for the contractor.

(h) the statement "Caution: Federal law prohibits dispensing without prescription."

Packaging and Packing.

Unit of issue. One bottle containing 1000 tablets, as specified, constitutes one unit of issue.

Unit package. At the option of the contractor, each unit shall be packaged as specified in 5.2.5 of PPP-C-00186a.

Procedure code. Procedure code No. 5 as specified in Table I of PPP-C-00186a shall apply.

Marking.

Unit package. When furnished, each unit package shall bear the same information as required for the immediate container.

Intermediate package. Each intermediate package shall be marked as specified in 5.5.3 of PPP-C-00186a, except that the date of manufacture shall be shown in lieu of the date packed.

Exterior container. Exterior container shall be marked in accordance with 5.5.4 of PPP-C-00186a, except that the date of manufacture shall be shown in lieu of the date packed.

6505-290-0022 (P. D. No. 7)

SUPPLIER RESPONSIBILITY FOR INSPECTION

Unless otherwise specified in the contract or purchase order, the supplier is responsible for the performance of all inspection requirements as specified herein. Except as otherwise specified in the contract or order, the supplier may use his own or any other facilities suitable for the performance of the inspection requirements specified herein, unless disapproved by the Government. The Government reserves the right to perform any of the inspections set forth in the specification where such inspections are deemed necessary to assure supplies and services conform to prescribed requirements.

Records of examinations and tests performed by or for the contractor shall be maintained by the contractor and made available to the Government, upon the Government's request, at any time, or from time to time, during the performance of the contract and for a period of 3 years after delivery of the supplies to which such records relate.

No company supplying any ingredient(s) to the contractor will be considered an acceptable facility for the performance of any inspection requirements specified herein.

MYLANTA

MODIFICATION NO. 1
DATE: 21 May 1971

MODIFICATION TO DEFENSE MEDICAL PURCHASE DESCRIPTION

This modification forms a part of Defense Medical Purchase Description No. 2, dated 10 April 1970, and covers the following item to the extent specified herein:

Federal Stock No.	Item Identification
6505-890-2218	ALUMINUM HYDROXIDE GEL, MAGNESIUM HYDROXIDE, AND SIMETHICONE SUSPENSION, 5 fl oz (148 cc)

Page 1:

3.3.1 Aluminum content. Delete in its entirety and substitute:

"3.3.1 Aluminum content. The aluminum content in each 5 cc of finished suspension shall be not less than 47.6 mg and not more than 60.0 mg, when determined as specified in 4.3.1."

Page 10:

Following the label information, insert:

"NOTE: As an alternate, the label information on the immediate containers may be embossed."

"MYLANTA" (STUARTS) Stuart's spec. - Viscosity & palatability tests are medicine-like!

SSC-1

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 2	DATE 10 April 1970

FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-890-2218	ALUMINUM HYDROXIDE GEL, MAGNESIUM HYDROXIDE, AND SIMETHICONE SUSPENSION, 5 fl oz (148 cc)	Bottle

1. SCOPE

1.1 This specification covers Aluminum Hydroxide Gel, Magnesium Hydroxide, and Simethicone Suspension.

2. APPLICABLE DOCUMENTS

2.1 Specifications and standards. Unless otherwise indicated, the issue in effect on date of invitation for bids or request for proposals of the specifications and standards referenced in the body of this specification shall apply to the extent specified herein. These documents may be obtained as directed by the contracting officer.

3. REQUIREMENTS

3.1 Material. Shall contain the following ingredients in each 5 cc, in addition to suitable flavoring and preservative agents:

Aluminum Hydroxide Gel - - approximately 200 mg
Magnesium Hydroxide - - approximately 200 mg
Simethicone- - - - - - - approximately 20 mg

The actual amounts of the above ingredients may vary, depending upon the aluminum, magnesium, and silicon assays (see 3.3) in the respective ingredient. The aluminum hydroxide gel and the magnesium hydroxide are not the official U.S.P. or N.F. preparations.

3.2 Description. The finished suspension shall be a white, homogeneous, oral suspension with a pleasant odor and a pleasant and palatable taste.

3.3 Assay.

3.3.1 Aluminum content. The aluminum content in each 5 cc of finished suspension shall be not less than 50.3 mg and not more than 60.0 mg, when determined as specified in 4.3.1.

3.3.2 Magnesium content. The magnesium content in each 5 cc of finished suspension shall be not less than 77.6 mg and not more than 97.6 mg, when determined as specified in 4.3.2.

3.3.3 Silicon content. The silicon content in each 5 cc of finished suspension shall be not less than 5.82 mg and not more than 8.72 mg, when determined by a suitable, accurate, and reproducible method.

DPSC FORM 2007 OCT 63

REPLACES DMTC FORM 7-4120/11, MAR 64, WHICH WILL BE USED UNTIL DEPLETED

6505-890-2218 (P. D. No. 2)

3.4 pH. The pH of the finished suspension shall be not less than 7.50 and not more than 8.00 when determined potentiometrically at 25° C., using the U.S.P. method.

3.5 Viscosity. The finished suspension shall have a viscosity of not less than 492 centipoises (cps) and not more than 1002 cps, when determined at 25° C., using a Brookfield Viscometer, Model LVF, with a No. 2 spindle, and a speed of 12 revolutions per minute (r.p.m.). The use of another suitable instrument giving comparable results is permitted.

3.6 Specific gravity. The finished suspension shall have a specific gravity of not less than 1.060 and not more than 1.120 when determined as at 25° C., using a pycnometer.

3.7 Acid-consuming capacity. The finished suspension shall have an acid-consuming capacity of not less than 115 ml of 0.1N hydrochloric acid per 5 cc, when determined as specified in 4.3.3.

3.8 Bacteria and mold content. The finished suspension shall comply with the following:

3.8.1 Total bacteria count. The total bacteria count in 1 ml of finished suspension shall not exceed 50 colonies at the end of the incubation period, when tested as specified in 4.3.4.

3.8.2 Mold content. No molds shall be present at the end of the incubation period when tested for mold content as specified in 4.3.5.

3.9 Defoaming action. The collapse time for the foam shall not exceed 45 seconds when determined as specified in 4.3.6.

3.10 Palatability and flavor. The suspension shall be lemon-mint flavored, and shall be palatable and pleasant to the taste with no unpleasant aftertaste. Not later than the time specified for opening of bids or receipt of proposals, the offeror shall submit to the contracting officer six (6) individually packaged samples (each containing 5 fl oz) of finished suspension, representative of the product which the offeror proposes to furnish. Two (2) samples will be subjected to panel testing for a determination of palatability (see 4.3.7 Palatability Test). The remaining samples will be used by cognizant Government inspection and quality assurance activities for determining compliance of supplies furnished hereunder with the palatability requirement. Approval as to palatability of any sample submitted by the offeror will not constitute approval of the sample as to any other requirement of this specification. The requirement for submission of samples for use in determining compliance with the palatability requirement may be waived, provided the offeror states, in his bid or proposal, that the product he proposes to furnish is the same product he has offered to the purchasing activity on a previous procurement and the contracting officer determines that such product was previously procured and/or tested by the purchasing activity and found to comply with the palatability requirement.

tive ingredients.

Magnesium hydroxide. The magnesium hydroxide used in the of the finished suspension shall be of the highest pharmaceutical use in this suspension.

1.2 Aluminum hydroxide gel. The aluminum hydroxide gel used in the cure of the finished suspension shall comply with the following:

Shall be a smooth white paste.

Shall comply with the U.S.P. Identification test for Aluminum Hydroxide Gel.

Shall contain not less than 9.3 percent and not more than 10.5 percent aluminum oxide when tested by the U.S.P. assay method for Aluminum Hydroxide Gel.

Shall consume not less than 50 ml and not more than 60 ml of 0.1 N hydrochloric acid per gram (g.) when tested by the U.S.P. acid-consuming capacity test for Aluminum Hydroxide Gel.

3.11.3 Simethicone emulsion. The simethicone emulsion used in the manufacture of the finished suspension shall comply with the following:

Shall be a white, creamy liquid having a slight characteristic odor and taste.

Shall be miscible with water.

The collapse time for the foam shall not exceed 15 seconds when determined as specified in 4.3.8.

3.12 Added substances. Added substances may be included to assure a suitable, stable product. Such substances shall be nontoxic and harmless in the amounts administered and shall not interfere with the therapeutic efficacy of the finished suspension or with the tests and assays specified herein. In addition, when such added ingredients are used in the manufacture of the finished suspension, they shall be of U.S.P. or N.F. quality or, if not included in either of these compendia, they shall be suitable for use in this suspension.

3.13 Delivery. Not more than 6 months shall have elapsed from the date of manufacture of the product, to the date of delivery to the Government.

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4. QUALITY ASSURANCE PROVISIONS

4.1 Supplier responsibilities for inspection. Such examinations and tests as are set forth in this specification, or as shall otherwise be appropriate or necessary to insure that supplies conform to specification requirements, shall be performed by and at the expense of the supplier. Suppliers who do not have facilities adequate for such tests shall arrange for the use of test facilities acceptable to the Government. Records of examinations~~tions~~ and tests performed by the supplier shall be maintained by the supplier and made available to the Government, upon the Government's request at any time, or from time to time, for a period of 3 years after delivery of the supplies to which such records relate.

4.1.1 Lot. For purpose of this specification, a lot, batch, or control is that single, uniform, and homogeneous quantity of elixir produced from one formulation, subjected to the same compounding and manufacturing operations, and filled into final containers.

4.2 Sampling. Sampling shall be conducted in accordance with the procedures set forth in Military Standard MIL-STD-105, with an acceptable quality level (AQL) of 1.0 percent defective for major defects and 2.5 percent defective for minor defects.

4.3 Tests.

4.3.1 Aluminum content. The aluminum content in the finished suspension shall be determined as follows:

Reagents.

1. 0.1N EDTA solution.
2. 4M Ammonium acetate solution.
3. Hematoxylin indicator. Dissolve 1 gram of Hematoxylin in 40 ml of 0.05N hydrochloric acid. Neutralize with 1N sodium hydroxide. Dilute to 200 ml with SDA-3A alcohol.
4. Hydrochloric acid. Concentrated, and 1N strengths.

Sample preparation. Pipet 10.0 ml of finished suspension into a clean, 250-ml beaker. Cautiously add 5 ml of concentrated hydrochloric acid and 50 ml of purified water. Boil until sample dissolves. Filter the solution, while hot, through Whatman No. 541 filter paper and collect into a 100-ml volumetric flask. Cool to room temperature and dilute to mark with purified water. Transfer the solution to a 50-ml buret and drain excess to zero.

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Procedure. To a 250-ml beaker, add 10 ml of 0.1N EDTA, 40 ml of 1M ammonium acetate, and 5 drops of hematoxylin indicator. Heat to 70° C. with constant stirring. The sample shall be yellow-orange after adding the indicator; if not, add sufficient 1N hydrochloric acid to attain the yellow-orange color (pH 5.5 to 6.0). Titrate the hot solution with the sample preparation until a rose-purple endpoint is reached. Calculate the amount of aluminum present in 5 cc of finished suspension, as follows:

$$\frac{N \times V_1 \times 1.349 \times 500}{V_2 \times S} = \text{mg Aluminum per 5 ml}$$

Where:

N = actual normality of EDTA solution
V1 = volume of EDTA solution, in ml
V2 = volume of sample preparation used for titration, in ml
S = sample size, in ml
1.349 = equivalent weight of aluminum, in mg per ml.

4.3.2 Magnesium content. The magnesium content in the finished suspension shall be determined as follows:

Reagents.

1. Triethanolamine solutions. Dilute triethanolamine, reagent grade, with purified water in a 1:1 ratio.
2. 0.1N EDTA solution.
3. Hydrochloric acid, concentrated.
4. Ammonia-Ammonium Chloride Buffer T.S.
5. Eriochrome Black T indicator. Dissolve 500 mg of Eriochrome Black T and 4.5 g. of hydroxylamine hydrochloride in sufficient methanol to make 100 ml.

Sample preparation. Pipet 10 ml of finished suspension into a clean 250-ml beaker. Add 5 ml of concentrated hydrochloric acid and 50 ml of purified water. Heat on a hot plate for 15 minutes, filter the solution, while hot, through Whatman No. 541 filter paper and collect in a 100-ml volumetric flask. Wash the filter paper with several small portions of hot purified water and add these washings to the filtrate. Cool to room temperature and dilute to mark with purified water. Mix thoroughly.

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Procedure. Pipet 10 ml of the sample preparation into a 125-ml Erlenmeyer flask and add the following reagents in the order specified: 50 ml of purified water, 5 ml of triethanolamine solution, 5 ml of 0.1N EDTA solution, 4 drops of Eriochrome Black T indicator, and 5 ml of ammonia-ammonium chloride buffer T.S. Titrate with 0.1N EDTA solution to a blue endpoint (titrating slowly as endpoint color change occurs). Record the total volume of EDTA used (including the original 5 ml added previous to titration), and calculate the amount of magnesium present in 5 cc of finished suspension, as follows:

$$\frac{N \times V_1 \times 1.216 \times 500}{S} = \text{mg Magnesium per 5 ml}$$

Where:

N = actual normality of EDTA solution
V = total volume of EDTA solution, in ml
S = sample size, in ml
1.216 = equivalent weight of magnesium, in mg per ml.

4.3.3 Acid-consuming capacity. The acid-consuming capacity shall be determined as follows:

Reagents.

1. 0.1N hydrochloric acid (accurately standardized).
2. Bromophenol blue indicator - Dissolve 100 mg bromophenol blue in sufficient 50 percent SDA 3-A alcohol to make 100 ml of solution.
3. 0.1N sodium hydroxide (accurately standardized).

Procedure. Pipet 1.0 ml of finished suspension into a 125-ml Erlenmeyer flask containing exactly 50 ml of the accurately standardized 0.1N hydrochloric acid. Rinse the pipet thoroughly into the flask using the dilute acid. Place the flask in a suitable shaker and shake for one hour at 37° C. Filter the samples immediately after shaking and titrate a 10 ml aliquot of the filtrate with the accurately standardized 0.1N sodium hydroxide, using four drops of bromophenol indicator. Titrate 10 ml of the 0.1N hydrochloric acid with the 0.1N sodium hydroxide to the same endpoint using the same amount of indicator. Record the titers of base used for both the sample and the acid. Calculate the acid-consuming capacity of the sample.

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4.3.4 Total bacteria count. The bacteria content shall be determined as follows:

Reagent.

1. Plate Count Agar. Prepare according to label directions (Trypton Glucose Extract Agar may also be used).

Procedure. Place 4 ml of purified water in a 18 by 140 mm test tube and sterilize by autoclaving for 1 hour at 15 pounds pressure. Incubate the sample of the finished suspension for three (3) days at 37° C. before plating. Remove sample from oven, shake thoroughly and aseptically transfer a 1.0 ml aliquot to 18 by 140 mm test tube containing 4 ml of sterile purified water, using standard serological procedure for rinsing the pipet and mixing the sample. Aseptically pipet 1.0 ml of the diluted sample into a sterile Petri dish and pour about 10 ml of plate count agar (48° - 50° C.) into the plate. Cover and mix the sample by swirling. Allow the agar to gel and then incubate at 37° C. for 40 to 48 hours. Remove the plates and count the number of organisms on each plate.

4.3.5 Mold content. The mold content shall be determined as follows:

Proceed as for the bacteria count (4.3.4), except use Sabouraud's dextrose or maltose agar and incubate at 25° - 30° C. for 5 days.

4.3.6 Defoaming action. The defoaming action shall be determined as follows:

Reagents.

1. Triton X-100
2. F.D. & C. Blue #1 dye.

Procedure. Prepare a 1 percent (w/v) solution of Triton X-100 in purified water. To each liter of this solution add 5 mg of F.D. & C. Blue #1. Clamp a new, clean eight ounce, flint glass jar in a vertical position on a wrist action shaker so that the distance between the center of the shaft and the center of the jar is 5-1/4 inches. Add 100 ml of the Triton X-100 solution to the jar. Shake a sample of the finished suspension thoroughly and withdraw 1.0 cc using a 1.0 cc syringe. Add the 1.0 cc sample directly to the jar, cap the jar, and using the position for maximum stroke, shake the jar for 10 seconds. Determine the collapse time of the foam in seconds. The collapse time is taken when the first portion of foam-free liquid surface can be observed. The presence of the blue dye aids in the detection of the foam-free liquid surface. Repeat the test with a fresh sample and a new clean jar. Average the results to report the defoaming activity.

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4.3.7 Palatability test. A taste panel consisting of 10 members will be used to determine acceptability of samples. Samples will be prepared for testing (samples will be tested undiluted), coded, and served to panel members under controlled serving conditions, e.g., all samples will be of the same amount, and served at the same temperature; each panel member will receive an equal number of samples; the order of serving will varied among panel members; an interval of at least five (5) minutes will elapse between successive samples and panel members will rinse their mouths with water (room temperature) after each sample; panel members will test without interference either from each other or from outsiders. The product offered shall be rated equal to or better than the FSN 6505-890-2218 Palatability Standard* when determined by the taste panel, using the 9-point hedonic rating scale. The average rating of the sample shall be equal to or greater than the average rating of the standard, similarly prepared and tested.

1	2	3	4	5	6	7	8	9
Dislike extremely	Dislike very much	Dislike moderately	Dislike slightly	Neither like nor dislike	Like slightly	Like moderately	Like very much	Like extremely

*The FSN 6505-890-2218 Palatability Standard is available, upon separate request to the contracting officer, Defense Personnel Support Center.

4.3.8 Foam collapse time. The collapse time for the simethicone emulsion shall be determined as follows:

Reagents.

1. Triton X-100.
2. F.D. & C. Blue #1 dye.

Procedure. Prepare a 1 percent (w/v) solution of Triton X-100 in purified water. To each liter of this solution add 5 mg of F.D. & C. Blue #1. Clamp a new, clean, eight-ounce flint glass jar in a vertical position on a wrist action shaker so that the distance between the center of the shaft and the center of the jar is 5-1/4 inches. Add 100 ml of the Triton X-100 solution to the jar. Weigh 1.0 gram of the simethicone emulsion into a 50-ml bottle. Add 30 ml of purified water and shake thoroughly. Using a serological 1.0 ml pipet, withdraw three 1.0 ml samples and discard. Draw an additional 1.0 ml sample and slowly transfer (dropwise) 0.5 ml to the center of the jar. Discard the remainder. (Note: DO NOT BLOW OUT THE PIPET OR TOUCH PIPET TO THE SIDES OF THE JAR.) Cap the jar and using the position for maximum stroke, shake the jar for 10 seconds. Determine the collapse time of the foam in seconds. The collapse time is taken when the first portion of foam-free liquid surface. Repeat the test with a fresh sample and a new clean jar. Average the results to report the defoaming activity.

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5. PREPARATION FOR DELIVERY

5.1 Shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-00186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, together with deletions or additions as indicated herein:

5.1.1 Immediate containers. Shall comply with the following classification:

GROUP A	CLASS 1	TYPE e	STYLE 2	GRADE 1
CLOSURE B				SEAL A

As an alternate, the immediate containers shall comply with the following classification:

GROUP A	CLASS 2* - suitable plastic	STYLE 2	GRADE 1 or 3 (light resistant)
CLOSURE B			SEAL A

*The plastic shall be linear polyethylene having a density of 0.960 ± 0.003.

5.1.2 Labeling. Labeling shall be in accordance with the requirements of the Federal Food, Drug, and Cosmetic Act, and shall include the information required below:

5.1.2.1 Immediate containers. Each immediate container label shall bear the following information. However, the information is not required to appear in the sequence indicated:

(a) the item identification designated as "ALUMINUM HYDROXIDE GEL, MAGNESIUM HYDROXIDE, AND SIMETHICONE SUSPENSION"

(b) the quantity of contents designated as "5 fl oz (148 cc)".

(c) the stock number

(d) the lot or control number

(See additional label information on page 10)

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(e) the name and address of the manufacturer. When the manufacturer is not the contractor, the name and and address of the contractor shall also appear.

When both names are placed on the label, the following designations shall precede the names:

"MFR" for the manufacturer and
"CONTR" for the contractor.

(f) the date of manufacture

(g) a statement indicating the quantity of aluminum hydroxide, magnesium hydroxide, and simethicone in each 5 cc (teaspoonful) of suspension

(h) the following statements or similar statements:

1. Shake well before using.
2. Keep tightly closed.
3. DO NOT FREEZE.

5.2 Packaging and packing.

5.2.1 Unit of issue. One bottle, containing 5 fl oz, as specified, constitutes one unit of issue.

5.2.2 Unit package. At the option of the contractor, each unit shall be packaged as specified in 5.2.5.

5.2.3 Procedure code. Procedure code No. 5 applies.

5.3 Marking.

5.3.1 Unit package. When furnished, each unit package shall bear the same information as required for the immediate container.

5.3.2 Intermediate package. In paragraph 5.5.3, at end of paragraph, add: Date of manufacture shall be shown in lieu of date packed. Marking shall include the legend:

"DO NOT FREEZE."

5.5.3 Exterior container. In paragraph 5.5.4, at end of paragraph, add: "Date of manufacture shall be shown in lieu of date packed. Marking shall include the legend:

"DO NOT FREEZE."

SPECIFICATION ANALYSIS SHEET

Form Approved
Budget Bureau No. 22-R255

TRUCTIONS: This sheet is to be filled out by personnel, either Government or contractor, involved in the use of the specifica-n in procurement of products for ultimate use by the Department of Defense. This sheet is provided for obtaining information on use of this specification which will insure that suitable products can be procured with a minimum amount of delay and at the st cost. Comments and the return of this form will be appreciated. Fold on lines on reverse side, staple in corner, and send to paring activity. Comments and suggestions submitted on this form do not constitute or imply authorization to waive any portion the referenced document (s) or serve to amend contractual requirements.

ECIFICATION FSN: 6505-890-2218

GANIZATION

Y AND STATE | CONTRACT NUMBER

TERIAL PROCURED UNDER A

☐ DIRECT GOVERNMENT CONTRACT ☐ SUBCONTRACT

HAS ANY PART OF THE SPECIFICATION CREATED PROBLEMS OR REQUIRED INTERPRETATION IN PROCUREMENT USE?

A. GIVE PARAGRAPH NUMBER AND WORDING.

B. RECOMMENDATIONS FOR CORRECTING THE DEFICIENCIES

2. COMMENTS ON ANY SPECIFICATION REQUIREMENT CONSIDERED TOO RIGID

3. IS THE SPECIFICATION RESTRICTIVE?

☐ YES ☐ NO *(If "yes", in what way?)*

REMARKS *(Attach any pertinent data which may be of use in improving this specification. If there are additional papers, attach to form and place both in an envelope addressed to preparing activity)*

SUBMITTED BY *(Printed or typed name and activity - Optional)* | DATE

DD FORM 1426 REPLACES EDITION OF 1 OCT 54, WHICH MAY BE USED.

CAUTION

NOTICE TO BIDDERS/OFFERORS

DO NOT CONDITION OR BASE YOUR BID/OFFER ON ANY CURRENT PROCUREMENT ON THE INFORMATION SUBMITTED ON THIS FORM SINCE ANY CHANGES OR DELETIONS IN THE SPECIFICATIONS MAY RENDER YOUR BID/OFFER NON-RESPONSIVE IN WHICH CASE IT CANNOT BE CONSIDERED FOR AWARD.

Fold

DEFENSE PERSONNEL SUPPORT CENTER
2800 SOUTH 20TH STREET
PHILADELPHIA, PA. 19101

DEFENSE SUPPLY AGENCY
OFFICIAL BUSINESS

POSTAGE AND FEES PA
DEFENSE SUPPLY AGEN

HEADQUARTERS, DEFENSE PERSONNEL SUPPORT CENTER
ATTN: DIRECTORATE OF MEDICAL MATERIEL, CODE ATS
2800 SOUTH 20TH STREET
PHILADELPHIA, PA. 19101

Fold

DPSC FORM 2418
MAR 68

EDITION AUG 66, WILL BE USED UNTIL EXHAUSTED

-- NOVAHISTINE EXPECTORANT --

DEFENSE MEDICAL PURCHASE DESCRIPTION	NUMBER 3	DATE 28 April 1971

FEDERAL STOCK NO.	ITEM IDENTIFICATION	UNIT
6505-890-2012 and 6505-926-8926	CHLORPHENIRAMINE MALEATE, CHLOROFORM, CODEINE PHOSPHATE, GLYCERYL GUAIACOLATE, MENTHOL, AND PHENYLEPHRINE HYDROCHLORIDE SYRUP	Bottle

1. SCOPE

1.1 This specification covers the following items in the quantity per bottle as indicated for the appropriate Federal Stock No. (FSN) and Item Identification, as follows:

Federal Stock No. (FSN)	Item Identification
6505-890-2012	CHLORPHENIRAMINE MALEATE, CHLOROFORM, CODEINE PHOSPHATE, GLYCERYL GUAIACOLATE, MENTHOL, AND PHENYLEPHRINE HYDROCHLORIDE SYRUP, 1 gal (3.78 liters)
6505-926-8926	CHLORPHENIRAMINE MALEATE, CHLOROFORM, CODEINE PHOSPHATE, GLYCERYL GUAIACOLATE, MENTHOL, AND PHENYLEPHRINE HYDROCHLORIDE SYRUP, 4 fl oz (118 cc)

2. APPLICABLE DOCUMENTS

2.1 Specifications and standards. Unless otherwise indicated, the issue in effect on date of invitation for bids or request for proposals of the specifications and standards referenced in the body of this specification shall apply to the extent specified herein. These documents may be obtained as directed by the contracting officer.

2.2 Other publications. The following documents form a part of this specification to the extent specified herein. Unless otherwise indicated, the issue in effect on date of invitation for bids or request for proposals shall apply.

AMERICAN PHARMACEUTICAL ASSOCIATION

National Formulary.

(Application for copies should be addressed to the Mack Publishing Company, Easton, Pa. 18042.)

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, FOOD AND DRUG ADMINISTRATION

Federal Food, Drug, and Cosmetic Act and Applicable Regulations thereto.

(Application for copies should be addressed to the Food and Drug Administration, Washington, D. C. 20204.)

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U. S. PHARMACOPEIAL CONVENTION, INC.

Pharmacopeia of the United States.

(Application for copies should be addressed to the Mack Publishing Company, Easton, Pa. 18042.)

3. REQUIREMENTS

Federal Stock No. 6505-890-2012 and FSN 6505-926-8926 shall meet the following requirements:

3.1 Material. Each 5 ml of syrup shall contain the following:

Phenylephrine Hydrochloride	10.0 mg
Chlorpheniramine Maleate	2.0 mg
Codeine Phosphate	10.0 mg
Glyceryl Guaiacolate	100.0 mg
Chloroform (approximately)*	13.5 mg
Levorotatory Menthol	1.0 mg

in a suitable base containing 5% alcohol.

*NOTE: Sufficient quantity of chloroform shall be added to assure the above chloroform content (approximately 13.5 mg) at the time of delivery.

Shall be suitable for use in the treatment of bronchitis and coughs of allergic origin.

3.2 Description. The finished syrup shall be a clear, red-brown, fruit flavored preparation having a pleasant and palatable taste, and shall comply with the stability requirements specified herein.

3.3 Additives. The coloring, flavoring, and sweetening agents used in the syrup shall be in the amounts approved by the Federal Food and Drug Administration.

3.4 Finished syrup.

3.4.1 Assay. The syrup shall assay to contain not less than 93.0 percent and not more than 107.0 percent of the required amounts of phenylephrine hydrochloride, chlorpheniramine maleate, and codeine phosphate, when determined as specified in 4.4.1. The syrup shall assay to contain not less than 93.0 percent and not more than 107.0 percent of the required amount of glyceryl guaiacolate, when determined as specified in 4.4.2.

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3.4.2 Alcohol (ethanol). The syrup shall assay to contain not less than 4.50 percent and not more than 5.50 percent alcohol v/v (90.0 to 110.0 percent of the required amount), when determined as specified in 4.4.3.

3.4.3 Chloroform and levorotatory menthol. Chloroform and levorotatory menthol content in the syrup shall be determined from the batch formulation sheet kept on file by the manufacturer. The contents of the two ingredients shall be in conformance with the formulation specified in 3.1.

3.4.4 pH. The pH of the syrup shall be not less than 4.00 and not more than 6.50, at 25° C., when determined potentiometrically using the U.S.P. method.

3.4.5 Specific gravity. Specific gravity of the syrup shall be not less than 1.225 and not more than 1.279 when determined, at 25° C., using a suitable pycnometer.

3.4.6 Refractive index. Refractive index of the syrup shall be not less than 1.431 and not more than 1.449 when determined, at 25° C., using a Bausch and Lomb Refractometer, Abbe-56, or equivalent instrument giving comparable results.

3.4.7 Absorption spectrum. Absorption spectrum of 10 ml of syrup diluted to 100 ml with purified water, when measured on a Beckman DK-2A spectrophotometer, or equivalent instrument, shall show maxima at 630 millimicrons (mu), 525 mu, and 430 mu (broad), and minima at 670 mu, 605 mu, 505 mu, and 350 mu (broad).

3.4.8 Optical rotation. Optical rotation of the syrup shall be not less than +26.5° and not more than +32.5°, when determined as specified in 4.6.

3.4.9 Stability. The finished syrup shall comply with the following:

(a) Any sedimentation formed on standing or during storage shall be readily resuspendible after moderate shaking.

(b) During storage, shall not thicken to point where contents cannot be poured readily from the immediate container (bottle).

(c) Any crystals which develop in storage shall redissolve upon warming the syrup to room temperature.

(d) Shall remain palatable and shall meet all specification requirements during storage.

3.4.10 Flavor and palatability. The finished syrup shall be fruit flavored, and shall be palatable and pleasant to the taste with no unpleasant after-taste. Not later than the time specified for opening of bids or receipt of proposals, the offeror shall submit to the contracting officer six (6) individually packaged samples (each containing 4 fl oz) of the finished syrup, representative of the product which the offeror proposes to furnish. Two (2) samples will be subjected to panel testing for a determination of palatability (see 4.7 - Palatability test). The remaining samples will be used by cognizant Government inspection and quality assurance activities for determining compliance of supplies furnished hereunder with the palatability requirement. Approval as to palatability of any sample submitted by the offeror will not constitute approval of the sample as to any other requirement of this specification. The requirement for submission of samples for use in determining compliance with the palatability requirement may be waived, provided the offeror states, in his bid or proposal, that the product he proposes to furnish is the same product he has offered to the purchasing activity on a previous procurement and the contracting officer determined that such product was previously procured and/or tested by the purchasing activity and found to comply with the palatability requirement.

3.5 Ingredients.

3.5.1 Chlorpheniramine maleate, phenylephrine hydrochloride, codeine phosphate, alcohol, and levorotatory menthol. The chlorpheniramine maleate, phenylephrine hydrochloride, codeine phosphate, alcohol, and levorotatory menthol, used in the manufacture of the syrup, shall be in accordance with the tests, standards, and requirements of the applicable compendium, as shown below:

Ingredient	Compendium
Chlorpheniramine maleate	U.S.P.
Phenylephrine hydrochloride	U.S.P.
Codeine phosphate	U.S.P.
Alcohol	U.S.P.
Levorotatory Menthol	U.S.P.
Chloroform	N.F.
Glyceryl guaiacolate	N.F.

3.5.2 Glyceryl guaiacolate. The glyceryl guaiacolate used in the manufacture of the syrup shall be in accordance with the tests, standards, and requirements of the N.F., including any supplements or revisions thereto, and, in addition, shall comply with the following:

* Residue on ignition. Residue on ignition shall be not more than 0.1 percent when determined according to the N.F. method.

3.6 Other ingredients. All other ingredients entering into the finished syrup shall be of U.S.P. or N.F. quality or, if not included in either of these compendia, the ingredients shall be suitable for use in this preparation.

3.7 Quantity of contents. Each immediate container (bottle) shall contain one (1) gallon (3.78 liters) for FSN 6505-890-2012, and four (4) fl oz (118 cc) for FSN 6505-926-8926, when tested in accordance with 3.12 of Interim Federal Specification PPP-C-00186a, and Amendment-1, thereto.

3.8 Workmanship. The material and its containers shall be free from defects which detract from their appearance or may impair their serviceability.

3.9 Delivery. Not more than 6 months shall have elapsed from the date of manufacture of the syrup, to the date of delivery to the Government.

4. QUALITY ASSURANCE PROVISIONS

4.1 Supplier responsibility for inspection. Unless otherwise specified in the contract or purchase order, the supplier is responsible for the performance of all inspection requirements as specified herein. Except as otherwise specified in the contract or order, the supplier may use his own or any other facilities suitable for the performance of the inspection requirements specified herein, unless disapproved by the Government. The Government reserves the right to perform any of the inspections set forth in the specification where such inspections are deemed necessary to assure supplies and services conform to prescribed requirements.

4.1.1 Records of examinations and tests performed by or for the contractor shall be maintained by the contractor and made available to the Government, upon the Government's request, at any time, or from time to time, during the performance of the contract and for a period of 3 years after delivery of the supplies to which such records relate.

4.1.2 No company supplying any ingredient(s) to the contractor will be considered an acceptable facility for the performance of any inspection requirements specified herein.

4.2 Lot. For purposes of this specification, a lot, batch, or control is that single, uniform, and homogeneous quantity of syrup produced from one formulation, subjected to the same compounding and manufacturing operation, and filled into final containers.

4.3 Sampling. Sampling shall be conducted in accordance with the procedures set forth in Military Standard MIL-STD-105, with an acceptable quality level (AQL) of 1.0 percent defective for major defects and 2.5 percent defective for minor defects.

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4.4 Tests.

4.4.1 Assays for phenylephrine hydrochloride, chlorpheniramine maleate, and codeine phosphate in the finished syrup shall be conducted in accordance with the method specified in the article titled "Analysis of Combinations Containing Phenylephrine in Liquid Dasage Forms," by K. O. Montgomery, P. V. Jennings, and M. Y. Weinswig, which appears in the Journal of Pharmaceutical Sciences, Vol. 56, No. 3, page 393, March 1967.

As an alternate, the method may be modified to provide for the elution of phenylephrine with 0.5N hydrochloric acid in purified water, the codeine with 1N hydrochloric acid in (1:1) methanol:purified water, and the chlorpheniramine with 5N hydrochloric acid in (1:1) methanol:purified water. Absorbances shall be determined using the base line technique.

In addition, the method may be further modified by the use of an anion column between the reservoir and the cation column.

4.4.2 Assay for glyceryl guaiacolate in the finished syrup.

Standard.

Accurately weigh approximately 40 mg of Glyceryl Guaiacolate N.F. Reference Standard into a 250-ml volumetric flask and dilute to volume with chloroform. Pipet 20 ml of this solution into a 100-ml volumetric flask and dilute to volume with chloroform.

Procedure.

Pipet 2 ml, using a "to contain" pipet, of syrup (sample) into a 125-ml separator. Rinse the pipet with purified water. Add purified water to the separator until the volume is approximately 45 ml. Add 10 grams of anhydrous sodium sulfate and shake vigorously to dissolve the salt. Add 5 ml of 10 percent sodium hydroxide solution and mix well. Wash the aqueous layer thoroughly with 50 ml isooctane (A.R.). Transfer the aqueous layer to a second 125-ml separator. Wash the isooctane with 2 ml of purified water. Add this wash to the second separator. Discard the isooctane. Extract the aqueous layer with five 40-ml portions of chloroform (A.R.). Filter the chloroform through Whatman No. 1 paper into a 250-ml volumetric flask. Rinse the paper and funnel with chloroform, dilute to volume, and mix. Pipet 20 ml of this solution into a 100-ml volumetric flask, q.s. with chloroform, and mix well.

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Measure the absorbances of the final sample and standard solutions at 276 millimicrons on a ratio-recording double beam spectrophotometer. Employ base line technique in measurement of the absorbance.

Calculation:

$$\frac{Au}{As}\left(\frac{\text{mg standard}}{250} \times \frac{20}{100}\right)\left(\frac{250}{\text{ml of sample}} \times \frac{100}{20}\right) \times 5 = \text{mg of glyceryl guaiacolate per 5 ml.}$$

4.4.3 Assay for alcohol in the finished syrup. Shall be determined by either the U.S.P. distillation method or the U.S.P. gas-liquid chromatographic method.

4.5 Identification. Methods of identification for each of the active ingredients in the finished syrup shall be submitted with the bid or proposal and shall be subject to approval and acceptance by the Government. If the methods are approved and accepted by the Government, such methods shall be used to identify the active ingredients. No further submission of methods is required, provided the contractor states that the product and identification tests have not been modified in any way.

4.6 Optical rotation of the finished syrup. Add 5 grams activated charcoal to 40 ml of syrup (sample) and mix well. Allow to stand 5 minutes and filter through a medium porosity filter paper (Whatman No. 40, or equivalent). Transfer the colorless filtrate to a 100 mm sample tube and determine the optical rotation on a Kern full circle polarimeter (or similar instrument which provides comparable results), using a sodium lamp light source, and air as the blank.

4.7 Palatability test. A taste panel consisting of 10 members will be used to determine acceptability of samples. Samples will be prepared for testing (samples will be tested undiluted), coded, and served to panel members under controlled serving conditions, e.g., all samples will be of the same amount, and served at the same temperature; each panel member will receive an equal number of samples; the order of serving will be varied among panel members; an interval of at least five (5) minutes will elapse between successive samples and panel members will rinse their mouths with water (room temperature) after each sample; panel members will test without interference either from each other or from outsiders. The product offered shall be rated equal to or better than the FSN 6505-890-2012 and FSN 6505-926-8926 Palatability Standard,* when determined by the taste panel, using the following 9-point hedonic rating scale. The average rating of the sample shall be equal to or greater than the average rating of the standard, similarly prepared and tested.

*For FSN 6505-890-2012 and FSN 6505-926-8926. Palatability Standard is available, upon separate request to the contracting officer, Defense Personnel Support Center.

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1	2	3	4	5	6	7	8	9
Dislike extremely	Dislike very much	Dislike moderately	Dislike slightly	Neither like nor dislike	Like slightly	Like moderately	Like very much	Like extremely

5. PREPARATION FOR DELIVERY

5.1 Preparation for delivery shall be in accordance with all applicable requirements of Interim Federal Specification PPP-C-00186a, dated 15 May 1969, and Amendment-1, dated 27 October 1969, and as specified herein:

5.1.1 Immediate containers. Immediate containers shall comply with the following classification:

GROUP A	CLASS 1	TYPE c	STYLE 1	GRADE 1
CLOSURE A				SEAL A

5.2 Labeling. Labeling shall be in accordance with the requirements of the Federal Food, Drug, and Cosmetic Act, and shall include the information required for the appropriate FSN, as indicated.

5.2.1 Immediate containers.

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For FSN 6505-926-8926 - See page 10.

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5.2.1.1 FSN 6505-890-2012. Each immediate container label for FSN 6505-890-2012 shall bear the following information. However, the information is not required to appear in the sequence indicated:

(a) the item name designated as "CHLORPHENIRAMINE MALEATE, CHLOROFORM, CODEINE PHOSPHATE, GLYCERYL GUAIACOLATE, MENTHOL, AND PHENYLEPHRINE HYDROCHLORIDE SYRUP"

(b) the quantity of contents designated as "1 gal (3.78 liters)"

(c) a statement of the quantity of active ingredients expressed in milligrams per 5 cc (teaspoonful) of syrup

(d) the Federal Stock No. designated as "FSN 6505-890-2012" or "Stock No. 6505-890-2012"

(e) the lot or control number

(f) the name and address of the manufacturer. When the manufacturer is not the contractor, the name and address of the contractor shall also appear.

When both names are placed on the label, the following designations shall precede the names:

"MFR" for the manufacturer and
"CONTR" for the contractor.

(g) the date of manufacture

(h) the following or similar statements:

1. NOTE: Crystals of Glyceryl Guaiacolate may form if product is subjected to cold temperatures. On warming to room temperature, crystals will slowly redissolve.

2. the statement "Do Not Freeze."

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5.2.1.2 FSN 6505-926-8926. Each immediate container label for FSN 6505-926-8926 shall bear the following information. However, the information is not required to appear in the sequence indicated:

(a) the item name designated as "CHLORPHENIRAMINE MALEATE, CHLOROFORM, CODEINE PHOSPHATE, GLYCERYL GUAIACOLATE, MENTHOL, AND PHENYLEPHRINE HYDROCHLORIDE SYRUP"

(b) the quantity of contents designated as "4 fl oz (118 cc)"

(c) a statement of the quantity of active ingredients expressed in milligrams per 5 cc (teaspoonful) of syrup

(d) the Federal Stock No. designated as "FSN 6505-926-8926" or "Stock No. 6505-926-8926"

(e) the lot or control number

(f) the name and address of the manufacturer. When the manufacturer is not the contractor, the name and address of the contractor shall also appear.

When both names are placed on the label, the following designations shall precede the names:

"MFR" for the manufacturer and
"CONTR" for the contractor.

(g) the date of manufacture

(h) the following or similar statements:

1. NOTE: Crystals of Glyceryl Guaiacolate may form if product is subjected to cold temperatures. On warming to room temperature, crystals will slowly redissolve.

2. the statement "Do Not Freeze."