NAME OF DRUG	COMPANY	DATE
Aristomin Capsules	Lederle Laboratories	8/29/70
Atropine and Phenobarbital Tablets	Cole Pharmacal Co., Inc.	3/27/70
Aureomycin Pharyngets	Lederle Laboratories	9/19/70
Aureomycin Triple Sulfas Tablets	Lederle Laboratories	4/2/69
Aureomycin Troches	Lederle Laboratories	9/19/70
Azotrex Capsules	Bristol Laboratories	4/2/69
Azotrex Syrup	Bristol Laboratories	4/2/69
Bacimycin Tabs.	Walker Laboratories	7/2/70
Betadine Mouthwash/Gargle	The Purdue Frederick Co.	8/4/70
Bicillimycin All Purpose Injection	Wyeth Laboratories, Inc.	4/2/69
Bicillin-Sulfa Susp.	Wyeth Laboratories, Inc.	4/2/69
Bicillin-Sulfas Tablets (oral)	Wyeth Laboratories, Inc.	4/2/69
Bilcain Tablets	Cole Pharmacal Co.	9/12/69
Biomydrin Antibiotic Nasal Spray, Solution, Drops	Warner-Chilcott Laboratories	8/21/70
Biomydrin-F Nasal Spray	Warner-Chilcott Laboratories	8/21/70
Biosulfa 125M Tablets	The Upjohn Company	4/2/69
Biosulfa 250M Tablets	The Upjohn Company	4/2/69
Bistrimate Tabs.	Smith, Miller, & Patch, Inc.	8/25/70
Blutene (Tolonium Chloride)	Abbott Laboratories	7/11/68
Bradosol Lozenges	Ciba Pharmaceutical Co.	3/28/70
Brisk Activated Toothpaste	Colgate-Palmolive Co.	7/21/70
Pabirin AC Buffered Tablets	Dorsey Laboratories	3/28/70

NAME OF DRUG	COMPANY	DATE
Cepacol Mouthwash/Gargle	Wm. S. Merrell Co.	8/4/70
Cepacol Throat Lozenges	Wm. S. Merrell Company	9/12/69
Cer-O-Strep-One	The Upjohn Company	4/2/69
Cer-O-Strep-One-Half	The Upjohn Company	4/2/69
Chlortetracylline Hydrochloride Dental Cones	Lederle Laboratories	9/16/69
Chlortetracycline Hydrochloride Dental Paste	Lederle Laboratories	9/16/69
Chymar Aqueous Injection	Armour Pharmaceutical Co.	6/25/70
Chymar Injection in Oil	Armour Pharmaceutical Co.	6/25/70
Chymar-L Powder	Armour Pharmaceutical Co.	6/25/70
Chymotrypsin Injection	Chicago Pharmacal Div.	6/25/70
Chymotrypsin Injection	Wilson Laboratories	6/25/70
Coco-Sulfonamides Triplex Suspension	Eli Lilly & Company	9/11/69
Colgate Chlorophyll Toothpaste w/Gardol	Colgate-Palmolive Co.	7/21/70
Colgate Dental Cream w/Gardol	Colgate-Palmolive Co.	7/21/70
Compocillin VK w/Sulfas Filmtab Tablets	Abbott Laboratories	4/2/69
Compocillin VK w/Sulfas Granules for Oral Suspension	Abbott Laboratories	4/2/69
Comycin Capsules	The Upjohn Company	4/2/69
Comycin Half-Strength Capsules	The Upjohn Company	4/2/6
Curad Medicated Adhesive Bandage	The Kendall Company	11/6/68
C.V.P. w/Vitamin K.	USV Pharmaceutical Corp.	7/10/68

NAME OF DRUG	COMPANY	DATE
Cyclex Tablets	Merck Sharp & Dohme	2/6/70
Cytran Tablets	Upjohn Company	10/15/70
Dactil-OB	Lakeside Laboratories	7/10/68 7/11/68
Decadron Phosphate w/Xylocaine Injection	Merck, Sharp & Dohme	9/23/70
Decadron Phosphate w/Xylocaine Injection, Dilute	Merck, Sharp & Dohme	9/23/70
Declostatin Capsules	Lederle Laboratories	4/2/69
Declostatin for Oral Suspension	Lederle Laboratories	4/2/69
Declostatin 300 Tablets	Lederle Laboratories	4/2/69
Delfeta-sed Plus T. Stedytabs (S.R. Tablets)	Eastern Research Laboratories, Inc.	9/17/68
Dexa-Pyramine Injection	Vitamix Pharmaceutical Inc.	10/15/70
Di-Ademil-K Tablets	E. R. Squibb & Sons	9/5/69
Diapec Oral Suspension	Charles Pfizer & Co. (International)	4/2/60
Dihydrostreptomycin-chlortetracycline-chloramphenicol-bacitracin Dental Cement	Oskar Schaefer, Inc.	6/25/70
Dihydrostreptomycin with streptomycin Sulfate Powder	Merck & Co., Inc.	2/6/70
Dihydrostreptomycin Sulfate Powder (1 gm/vial)	Chas. Pfizer & Co., Inc.	2/6/70
Dihydrostreptomycin Sulfate Powder (1 gm. & 5 gm/vial)	Pure Laboratories, Inc.	2/6/70
Dihydrostreptomycin Sulfate Powder (5 gm/vial)	E. R. Squibb & Sons, Inc.	2/6/70
Dihydrostreptomycin Sulfate Powder (1 gm/vial)	E. R. Squibb & Sons, Inc.	2/6/70

NAME OF PRODUCT	COMPANY	DATE
Dihydrostreptomycin with Streptomycin Sulfate Powder	E. R. Squibb & Sons, Inc.	2/6/70
Dihydrostreptomycin Sulfate Powder & Solution	Merck & Co., Inc.	2/6/70
Dihydrostreptomycin Sulfate Powder & Solution (500 mg./cc.)	Philadelphia Labs., Inc.	2/6/70
Dihydrostreptomycin Sulfate Solution (0.5 gm/cc)	Pure Laboratories, Inc.	2/6/70
Donnagel w/Neomycin Liquid	A. H. Robins Co.	7/2/70
Drilitol Solution & Drilitol Spraypak	Smith, Kline & French Labs.	8/21/70
Duo C.V.P. w/Vitamin K	U.S. Vitamin Corp.	7/10/68
Duografin Injection	E. R. Squibb & Sons, Inc.	2/6/70
Durycin A.S. (Aqueous Suspension)	Eli Lilly & Co.	4/2/69
Durycin F.A. for Aqueous Injection	Eli Lilly & Co.	4/2/69
Emivan Tablets	U.S. Vitamin Pharmaceuticals	4/10/70
Equalysen Tablets	Wyeth Laboratories	10/15/70
Erythrocin Sterate Sulfas Film Tabs	Abbott Laboratories	9/27/69
Erythrocin Ethyl Succinate Sulfas Chewable Tablets	Abbott Laboratories	9/27/69
Erythrocin Ethyl Succinate Sulfas Granules	Abbott Laboratories	9/27/69
Erythromycin Sulfate-polymyxin B Sulfate-pramoxine-Hydrochloride Otic Solution	Abbotories	9/26/69
Erythrosulfa Tablets	The Upjohn Company	4/2/69
Eskay's Theranates	Smith, Kline & French	9/25/70

NAME OF DRUG	COMPANY	DATE
Esidrix-K Tablets	Ciba Pharmaceutical Co.	9/5/69
Estrosed Tablets	Conal Pharmaceuticals, Inc.	2/6/70
Flanithin Capsules (glutamic acid hydrochloride)	Table Rock Labs., Inc.	9/12/69
Flavocillin-CS Powder	Philadelphia Laboratories	4/2/69
Flavoserp Tablets	The Blue Line Chemical Co.	7/10/68
Frenquel I.V. Injection	The Wm. S. Merrell Co.	4/2/69
Frenquel Tablets 20 mg.	The Wm. S. Merrell Co.	4/2/69
Frenquel Tablets 100 mg.	The Wm. S. Merrell Co.	4/2/69
Gantricillin Tablets, 100, 200, 300	Hoffman-La Roche, Inc.	4/2/69
Gantrisin Nasal Solution	Roche Laboratories	9/9/69
Germicidal Detergent, Liquid	Parke, Davis & Company	9/12/69
Geroniazol Injection	Philips Roxane Laboratories	8/26/69
Gluco-Fedrin w/Sulfathiazole Suspension (Nasal)	Parke, Davis & Company	9/9/69
Guanidine Hydrochloride Tablets	Rose-Hoyt Pharmaceutical	3/27/70
Hormatone "T" Tablets	G.W. Carnrick Co.	8/29/70
Hydrodiuril-Ka Tablets	Merck Sharp & Dohme	9/5/69
Hydropres-Ka Tablets	Merck Sharp & Dohme	9/5/69
Ilosone Sulfa for Oral Suspension	Eli Lilly & Company	4/2/69
Ilosone Sulfa Tablets	Eli Lilly & Company	4/2/69
Ilotycin Gluceotate Dental Cones	Eli Lilly & Company	2/21/69
Ilotycin Ethyl Carbonate-Sulfa Pediatric for Oral Suspension	Eli Lilly & Company	4/2/69
Ilotycin Gluceptate Otic w/Polymyxin B & Benzocaine	Eli Lilly & Company	12/18/68

NAME OF DRUG	COMPANY	DATE
Ilotycin Sulfa (79) Tablets	Eli Lilly & Company	4/2/69
Intromycin Powder	Pitman-Moore	5/16/70
Isodine Gargle & Mouthwash	Isodine Pharmacal	8/4/70
Kaomycin Suspension	The Upjohn Company	7/2/70
Kasdenol Mouthwash & Gargle	Kasdenol Corp.	8/4/70
K-Cillin Sulfa Powder for Syrup	Biocraft Laboratories, Inc.	4/2/69
Kectil Suspension	Bristol Laboratories	7/2/70
Koagamin Parenteral Hemostat	Chatham Pharmaceuticals, Inc.	3/29/69
Kolynos Fluoride Toothpaste	Whitehall Laboratories, Inc.	7/21/70
Ledercillin Troches	Lederle Laboratories	9/19/70
Lutrexin Tablets (lututrin 3,000 units)	Hynson, Westcott & Dunning, Incorporated	5/24/68
Mannitrau Tablets	Richlyn Laboratories, Inc.	7/3/70
Maxitate w/Rauwolfia Compound Tablets	Strasenburgh Laboratories	7/10/68
Medrol w/Orthoxine Tabs.	The Upjohn Company	8/29/70
Menacyl Tablets	Lakeside Laboratories, Inc.	2/11/70
Mephosal w/Hydrocortisone Tablets	Crookes-Barnes Laboratories, Incorporated	3/28/70
Mesulfin Tablets	Ayerst Laboratories, Inc.	9/27/69
Metreton Tabs.	Schering Corporation	8/29/70
Micrin Oral Antiseptic	Johnson & Johnson	8/4/70
Milprem-200 and Milprem-400	Wallace Laboratories	8/26/70
Mulsopaque Injection	Lafayette Pharmacal, Inc.	2/11/70
Mycifradin N. Tab.	The Upjohn Company	7/2/70

NAME OF DRUG	COMPANY	DATE
Mycillin Suspension	Maurry Biological Co., Inc.	4/2/69
Myospaz Tablets	North American Pharmacal, Inc.	9/27/69
Mysteclin F Capsules	E. R. Squibb & Sons, Inc.	12/24/68
Mysteclin F 125 Capsules	E. R. Squibb & Sons, Inc.	12/24/68
Mysteclin F Pediatric Drops	E. R. Squibb & Sons, Inc.	12/24/68
Mysteclin F Syrup	E. R. Squibb & Sons, Inc.	12/24/68
Mysteclin V Capsules	E. R. Squibb & Sons, Inc.	4/2/69
Nasal Spray Neo-Hydeltrasol	Merck Sharp & Dohme	8/21/70
Nasal Suspension Hydrospray	Merck Sharp & Dohme	8/21/70
Naturetin c/K Tablets	E. R. Squibb & Sons, Inc.	9/5/69
Neo-Cortef 1.5% Nasal Spray	The Upjohn Company	8/21/70
Neo-Cortef 0.5% Nasal Spray	The Upjohn Company	8/21/70
Neo-Cortef Sterile Inj. Susp.	The Upjohn Company	8/28/70
Neocyclone Tablets	The Central Pharmacal Co.	3/28/70
Neo-Delta Cortef 0.1% Nasal Spray	The Upjohn Company	8/21/70
Neomycin Sulfate-Kaolin-Pectin Oral Suspension	E. W. Heun Company	7/2/70
Neomycin Sulfate, Kaolin Pectin Suspension	Vitamin Pharmaceuticals Inc.	7/2/70
Neoparbel Tablets	Central Pharmacal Co.	10/24/70
Neopenzine Suspension	Eli Lilly & Company	4/2/69
Neopenzine (150) Tablets	Eli Lilly & Company	4/2/69
Neopenzine (300) Tablets	Eli Lilly & Company	4/2/69
Neo-Semhyten Capsules	The S.E. Massengill Co.	7/10/68
Neo-Synephrine-Sulfathiazolate Nose Drops	Winthrop Laboratories	7/9/68

NAME OF DRUG	COMPANY	DATE
Neuro-Centrine Tab	Bristol Laboratories	9/27/69
Nicozol w/Reserpine Tablets	Nysco Laboratories	8/26/69
Nisulfazone Suspension	Breon Laboratories, Inc.	8/28/70
Novahistine w/Penicillin Capsules	Pitman-Moore	9/12/69
Onixol Solution (topical)	Scholl Manufacturing Co. Inc.	6/7/69
Orabiotic Chewing Gum Troches	White Laboratories, Inc.	9/19/70
Pabalate-HC Tablets	A. H. Robins Co., Inc.	3/28/70
Pabicortal Tablets	Nysco Laboratories	3/28/70
Pabirin AC Tablets	Dorsey Laboratories	3/28/70
Pacatal Injection 25 mg/cc	Warner-Chilcott Labs.	5/28/70
Pacatal 25, 50, 100 mg. Tabs.	Warner-Chilcott Labs.	11/29/69
Panalba Capsules	The Upjohn Company	12/24/68
Panalba Half-Strength Capsules	The Upjohn Company	12/24/68
Panalba KM Drops	The Upjohn Company	12/24/68
Panalba KM Granules	The Upjohn Company	12/24/68
Paredrine-Sulfathiazole Susp.	Smith, Kline & French Labs.	9/9/69
Parenzyme Aqueous for Injection	National Drug Company	6/25/70
Parenzyme Ointment	National Drug Company	6/25/70
Piptal w/Phenobarbital Pediatric Drops	Lakeside Laboratories	9/27/69
Pell-Biotic 250 Tablets	Richlyn Laboratories	4/2/69
Penicillin-dihydrostreptomycin-bacitracin Dental Paste	Biotic Drug Co., Inc.	6/25/70
Penicillin-dihydrostreptomycin Dental Cones	Strong Cobb Arner, Inc.	6/25/70

NAME OF DRUG	COMPANY	DATE
Penicillin G Potassium w/Three Sulfas Buffered Powder for Syrup	Nysco Laboratories	4/2/69
Penicillin G w/Triple Sulfonamides, Flavored	Vitamix Pharmaceuticals,Inc.	4/2/69
Penicillin Streptomycin Readimixed Sterile Aqueous Suspension	Upjohn Co.	4/2/69
Penicillin-Streptomycin Bacitracin Dental Paste	Procol-Sol Chemical Co.	6/25/70
Penicillin w/Sulfonamides Powder for Solution	Biocraft Laboratories, Inc.	4/2/69
Penicillin Three Sulfonamide Tablets "100"	Nysco Laboratories, Inc.	4/2/69
Penicillin Three Sulfonamide Tablets "300"	Nysco Laboratorienc.	4/2/69
Penicillin w/Triple Sulfas Tabs.	Biocraft Laboratories, Inc.	4/2/69
Penicillin w/Triple Sulfas No. 1, No. 2 and No. 3 Tablets	Richlyn Laboratories, Inc.	4/2/69
Penicillin w/Triple Sulfas Tabs.	Supreme Pharmaceutical Co.	4/2/69
Penicillin G w/Triple Sulfas Tabs.	Vitamix Pharmaceuticals,Inc.	4/2/69
Penicillin w/Triple Sulfonamides (100,000 units) Tablets	Zenith Laboratories, Inc.	4/2/69
Penicillin w/Triple Sulfonamides (200,000 units) Tablets	Zenith Laboratories, Inc.	4/2/69
Penicillin w/Triple Sulfonamides (250,000 units) Tablets	Zenith Laboratories, Inc.	4/2/69
Penicillin w/Triple Sulfonamides (300,000 units) Tablets	Zenith Laboratories, Inc.	4/2/69
Pen Strep Powder for Injection (4:1; 4:1/2)	Merck & Company, Inc.	4/2/69
Pentid Sulfas for Syrup	E. R. Squibb & Sons	4/2/69

NAME OF DRUG	COMPANY	DATE
Pentid Sulfas "400" for Syrup	E. R. Squibb & Sons	4/2/69
Pentids-Sulfas Tablets	E. R. Squibb & Sons	4/2/69
Pentocin	Pure Laboratories, Inc.	4/2/69
Pen-Vee Cidin Capsules	Wyeth Laboratories, Inc.	9/12/69
Pen-Vee Sulfas Suspension	Wyeth Laboratories, Inc.	4/2/69
Pen-Vee Sulfas Tablets	Wyeth Laboratories, Inc.	4/2/69
Pepsodent Antiseptic Mouthwash	Lever Brothers	8/4/70
Perithiazide SA Tablets	Warner-Chilcott Laboratories	8/29/70
Pharycidin Concentrate	Purdue Frederick	10/7/70
Phemerol Solution (benzethonium chlordie) 1:750	Parke, Davis & Company	9/12/69
Phemerol Tincture (benzethonium chloride) 1:500	Parke, Davis & Company	9/12/69
Phemerol Topical	Parke, Davis & Company	9/12/69
Plimasin Tablets	Ciab Pharmaceutical	10/15/70
PMB-200 & PMB-400 Tabs	Ayerst Laboratories	8/26/70
Polanil Tabs	Schering Corporation	8/29/70
Polycycline Suspension w/Triple Sulfonamides	Bristol Laboratories, Inc.	4/2/69
Polymagma Oral Suspension	Wyeth Laboratories, Inc.	7/2/70
Polymagma Tablets	Wyeth Laboratories, Inc.	7/2/70
Potassium Penicillin G. w/Triple Sulfonamides Tablets	Philadelphia Laboratories, Incorporated	4/2/69
Powdalator ES	Abbott Laboratories	12/9/69
Prednaman Tabs	Dome Laboratories	8/29/70
Presniscord Tablets	Nysco Laboratories, Inc.	3/28/70

NAME OF DRUG	COMPANY	DATE
Pree MT Tablets	Wallace Pharmaceuticals	2/6/70
Procaine Penicillin in Streptomycin Sulfate Solution	Roehr Products Co., Inc.	4/2/69
Protamide Injection	Sherman Laboratories	7/17/70
Quercetin Tablets	Abbott Laboratories	7/10/68
Quintess-N Suspension	Eli Lilly & Co	7/2/70
Raumannite-50 Tablets	Nysco Laboratories, Inc.	7/10/68
Rautrax Improved Tablets	E. R. Squibb & Sons, Inc.	9/5/69
Rautrax N Modified Tablets	E. R. Squibb & Sons, Inc.	9/5/69
Rautrax N Tablets	E. R. Squibb & Sons, Inc.	9/5/69
Rautrax Tablets	E. R. Squibb & Sons, Inc.	9/5/69
Rauwiloid and Hexamethonium Tablets	Riker Laboratories	10/15/70
Rauwolfia Serpentina-Mannitol Hexanitrate-Rutin Tablets	Best Pharmaceuticals	7/10/68
Rauwolfia Serpentina-Mannitol Hexanitrate-Rutin-Veratrum Viride Tablets	Robin Pharmacal Co.	7/10/68
Remanden-250	Merck Sharp & Dohme	7/1/70
Reserthonium Tablets	Nysco Laboratories	10/15/70
Retrografin Solution	E. R. Squibb & Sons, Inc.	1/14/70
Retropaque Solution	Winthrop Laboratories	1/14/70
Rhinazine (nasal solution)	Lederle Laboratories	9/9/69
Ritonic Capsules	Ciba Pharmaceutical Co.	9/12/69
Robaxisal	A. H. Robins Co., Inc.	2/11/70
Robaxisal-PH Tablets	A. H. Robins Co., Inc.	2/11/70
Roniacol w/Aminophylline Tablets	Roche Laboratories	9/17/70

NAME OF DRUG	COMPANY	DATE
Ruhexatal w/Reserpine	Lemmon Pharmacal Co.	7/10/68
Rusyntal	Central Pharmacal Co.	10/7/70
Rutin Tablets	Abbott Laboratories	7/10/68
Rutin Tablets	The Maltine Company	7/10/68
Rutin Tablets	Parke, Davis & Co.	1/23/68
Rutorbin Tablets	E. R. Squibb & Sons, Inc.	1/23/68
Salcort-Delta Tablets	The S. E. Massengill Co.	3/28/70
Sergynol Tablets	B. F. Ascher & Co., Inc.	2/6/70
Seromycin w/Isoniazid	Eli Lilly & Co.	9/18/69
Signemycin Capsules "250"	J. B. Roerig & Co.	4/2/69
Signamycin Capsules "250"	Chas. Pfizer & Co.	4/2/69
Signemycin Capsules "375"	J. B. Roerig & Co.	4/2/69
Signamycin Capsules "375"	Chas. Pfizer & Co.	4/2/69
Signemycin Pediatric Drops	J. B. Roerig & Co.	4/2/69
Signemycin Pediatric Drops	Chas. Pfizer & Co.	4/2/69
Signemycin Syrup	J. B. Roerig & Co.	4/2/69
Signemycin Syrup	Chas. Pfizer & Co.	4/2/69
Siltrobarb Tablet	Cole Pharmacal Co., Inc.	3/27/70
Sinaxar Tablets	Armour Pharmaceutical Co.	9/27/69
Skelaxin Tablets	A. H. Robins Co., Inc.	2/6/70
Somacort	Wallace Pharm.	5/7/70
Sorboquel w/Neomycin Tabs.	White Laboratories, Inc.	7/2/70
Spectrocin Nasal Spray	E. R. Squibb & Sons, Inc.	8/21/70

NAME OF DRUG	COMPANY	DATE
Spectrocin-T Troches	E. R. Squibb & Sons, Inc.	9/19/70
Stenediol Sublinqual Tabs.	Organon, Inc.	2/11/70
Sterisol	Warner-Lambert Pharm. Co.	8/4/70
Strep-Combiotic Aqueous Suspension (multidose)	Chas. Pfizer & Co. Inc.	4/2/69
Strep-Combiotic for Aqueous Suspension (single dose)	Chas. Pfizer & Co. Inc.	4/2/69
Strep-Combiotic Isoject Aqueous Suspension	Chas. Pfizer & Co., Inc.	4/2/69
Strep-Dicrysticin	E. R. Squibb & Sons, Inc.	4/2/69
Strep-Dicrysticin-800	E. R. Squibb & Sons, Inc.	4/2/69
Strep-Dicrysticin Fortis	E. R. Squibb & Sons, Inc.	4/2/69
Strep-Dicrysticin Fortis-800	E. R. Squibb & Sons, Inc.	4/2/69
Strep-Distrycillin-A.S. Sterile Suspension	E. R. Squibb & Sons, Inc.	4/2/69
Streptomagma Liquid	Wyeth Laboratories, Inc.	7/2/70
Streptomagma Tab.	Wyeth Laboratories, Inc.	7/2/70
Streptomycin-Bipenicillin Injection	Pure Laboratories, Inc.	4/2/69
Strexate Tablets	Armour Pharmaceutical Co.	9/27/69
Strycin Syrup	E. R. Squibb & Sons, Inc.	7/2/70
Sulfaguanidine Tablets (0.5 gram)	Lederle Laboratories	6/7/69
Sulfa-Sugracillin 125M Granules	The Upjohn Company	4/2/69
Sulfa-Sugracillin 250M Fortified Granules	The Upjohn Company	4/2/69
Sulfathiazole Gum Tablet	White Laboratories, Inc.	11/6/68
Sulfathiazole Tablet (0.5 gram)	Bowman, Mell & Co.	9/11/69

NAME OF DRUG	COMPANY	DATE
Sulfathiazole Tablet (0.5 gram)	Vale Chemical Co. Inc.	9/11/69
Sulfathiazole Tablet (0.5 gram)	Eli Lilly & Co.	9/11/69
Sulfathiazole w/Tuamine Sulfate Suspension	Eli Lilly & Co.	9/9/69
Sulfedex Nasal Solution	Abbott Laboratories	9/9/69
Sulfel Tablet	The Vale Chemical Co., Inc.	11/6/68
Sulfonamets w/Topicaine Lozenges	National Drug Co.	9/6/68
Super Amm-I-Dent	Block Drug Co., Inc.	7/21/70
Super Anapac Cough Syrup	Rexall Drug & Chemical Co.	7/10/68
Syndecon for Oral Solution	Bristol Laboratories	9/12/69
Syndecon Tablets	Bristol Laboratories	9/12/69
ce with Ergonovine Capsules	William S. Merrell Co.	10/24/70
Tain Oral Suspension	Dorsey Laboratories	9/12/69
Tain Tablets	Dorsey Laboratories	9/12/69
Tao-AC Capsules	J. B. Roerig & Co.	9/12/69
Taomid Oral Suspension	J. B. Roerig & Co.	9/5/69
Taomid Tablets	J. B. Roerig & Co.	9/5/69
Tenserine Tablets	Abbott Laboratories	7/10/68
Tergemist (Inhalant)	Abbott Laboratories	7/17/68
Terramycin Dental Cones	Chas. Pfizer & Co., Inc.	2/21/69
Terramycin Dental Paste	Chas. Pfizer & Co., Inc.	2/21/69
Terramycin S.F. Capsules	Chas. Pfizer & Co., Inc.	4/2/69
Terrastatin Capsules	Chas. Pfizer & Co., Inc.	4/2/69
Terrastatin for Oral Suspension	Chas. Pfizer & Co., Inc.	4/2/69

NAME OF DRUG	COMPANY	DATE
Tetracydin Capsules	J. B. Roerig & Co.	9/12/69
Tetrastatin Capsules	Chas. Pfizer & Co., Inc.	4/2/69
Tetrastatin for Oral Suspension	Chas. Pfizer & Co., Inc.	4/2/69
Tetrex-AP Syrup	Bristol Laboratories, Inc.	9/12/69
Tetrex APC w/Bristamin Capsules	Bristol Laboratories, Inc.	9/12/69
Tetrex Syrup w/Triple Sulfonamides	Bristol Laboratories, Inc.	4/2/69
Theoglycinate w/Rutin & Phenobarbital Tablets	Brayton Pharmaceutical Co.	7/10/68
Thizodrin Solution (nasal)	Eli Lilly & Co.	9/9/69
Toldex Tabs.	Pitman-Moore	8/29/70
Trexinest Tablets	Hynsen, Westcott & Dunning	5/24/68
Triaminic HC Tabs	Dorsey Laboratories	8/29/70
Triple Hormone Suspension	Taylor Pharmaceutical Co.	8/29/70
Trisem-Pen Powder	The S. E. Massengill Co.	4/2/69
Trisem-Pen Tablets	The S. E. Massengill Co.	4/2/69
Trisocort Spraypak	Smith, Kline & French Labs.	8/21/70
Trypsin Injection	Wilson Laboratories	6/25/70
Tyrolaris Mouthwash	Merck & Co.	8/4/70
Urethane Tablets	Eli Lilly & Co.	8/21/70
Urobiotic Capsules, 100, 250	Pfizer & Co.	6/30/70
V-Cillin K Sulfa Pediatric for Oral Suspension	Eli Lilly & Company	4/2/69
V-Cillin K Sulfa Tablets	Eli Lilly & Company	4/2/69
V-Cillin Sulfa Pediatric for Oral Suspension	Eli Lilly & Company	4/2/69
V-Cillin Sulfa Tablets	Eli Lilly & Company	4/2/69
V-Kor	Eli Lilly & Company	9/12/69
Visciodol	E. Fougera	2/11/70
Wybiotic	Wyeth Laboratories, Inc.	9/19/70
Wycillin SM Injection 400	Wyeth Laboratories, Inc.	4/2/69
Wycillin SM Injection 600	Wyeth Laboratories, Inc.	4/2/69

UNITED STATES GENERAL ACCOUNTING OFFICE
WASHINGTON, D.C. 20548

HUMAN RESOURCES AND WELFARE
DIVISION

May 9, 1972

Dear Mr. Twiname:

At the request of the Chairman, Subcommittee on Long-Term Care, Senate Special Committee on Aging, we obtained information on prescribed drugs provided to recipients of old-age assistance in nursing homes under the Medicaid program in Illinois, New Jersey, and Ohio. In response, we issued a report to the Chairman on information obtained on the Medicaid drug program in Illinois (B-164031(3), dated September 10, 1971) and a consolidated report on all three States entitled "Drugs provided to elderly persons in nursing homes under the Medicaid program" (B-164031(3), dated January 5, 1972). These reports have been made public by the Chairman and copies have been furnished to officials of the Social and Rehabilitation Service (SRS) and to officials of the Department of Health, Education, and Welfare (HEW).

This letter report presents our views concerning the need for SRS to issue instructions to States which would implement the Department's policy relating to the payment for purchases of ineffective and possibly effective drugs under the Medicaid program.

INTRODUCTION

On December 11, 1970, the Surgeon General directed HEW agencies to establish the necessary procedures within 45 days to implement departmental policy prohibiting the use of Federal funds for the purchase of drug products classified as ineffective and possibly effective by the Food and Drug Administration (FDA). This policy was applicable to HEW's direct care programs, contract-care programs under its direct care programs, grant programs, and the Medicaid and Medicare programs.

In January 1971, the Medical Services Administration (MSA) of SRS notified all Associate Regional Commissioners for Medical Services of the departmental policy relating to purchases of ineffective and possibly effective drugs. MSA stated that program regulations were being amended to implement this policy for Medicaid. The Commissioners were instructed to notify Medicaid State agencies as soon as possible of the change in Federal policy so that they in turn could notify hospitals, nursing homes, pharmacies, physicians,

dentists, and any other providers of drugs, and begin making the necessary changes in drug formularies, drug purchasing guides and drug claims payment processes.

As of May 1, 1972, regulations have not been issued to implement the revised Federal drug policy for Medicaid.

SUBSTANTIAL FUNDS BEING EXPENDED UNDER MEDICAID FOR INEFFECTIVE AND POSSIBLY EFFECTIVE DRUGS

Officials who administer the Medicaid drug programs in Illinois, New Jersey, and Ohio, furnished us with computer printouts listing purchases by drug name, number of prescriptions, and amount paid during the first month of each quarter of calendar year 1970. We compared this information to FDA's November 1970 listing[1/] of drugs classified as ineffective and found the following.

--In Ohio about $196,000 was expended in January, April, July, and October for about 38,000 prescriptions for 106 drugs classified as ineffective.

--In Illinois and New Jersey about $99,000 was expended in July and October for about 21,000 prescriptions for 16 drugs classified as ineffective.

Although our identification of purchases of ineffective drugs was limited to these three States, similar conditions probably exist in other States. For example, the Mississippi Medicaid Commission--the single State agency administering the program--reported that in a study of drug usage from July 1, 1970, to February 19, 1971, about $89,000 was expended for about 22,000 prescriptions for three drugs classified as either ineffective (two drugs) and possibly effective (one drug).

State officials in Illinois, New Jersey, and Ohio informed us that they would continue to pay for such drugs until HEW notifies them that such drugs are no longer eligible under Medicaid. These officials further informed us that their States were not in a position to determine drug efficacy and if they were to declare such drugs not eligible for Medicaid they would be subject to strong criticism from pharmaceutical manufacturers.

1/ We did not compare this information to FDA's October 1970 listing of drugs classified as possibly effective; however, as discussed above, expenditures were made under Mississippi's Medicaid program for the purchase of drugs classified as possibly effective.

For calendar year 1970, Illinois, New Jersey, and Ohio reported drug expenditures under their Medicaid programs of about $50 million, of which about $25 million, or 50 percent, represented the Federal share. These expenditures accounted for about 12 percent of the total $425 million expended nationwide for drugs under Medicaid for calendar year 1970.

As discussed above, Ohio expended about $196,000 for ineffective drugs during January, April, July, and October 1970--an average of $49,000 a month. If these monthly expenditures for ineffective drugs were representative of the entire calendar year, then as much as $588,000 could have been expended in Ohio for these drugs during 1970. Considering the large amount of expenditures for Medicaid drugs during 1970--$425 million--and the probability that other States are purchasing ineffective and possibly effective drugs under their Medicaid programs, then nationwide expenditures for such drugs purchased under Medicaid could be substantial.

RECOMMENDATION TO THE ADMINISTRATOR, SOCIAL AND REHABILITATION SERVICE

Because of the substantial amounts expended for drugs under the Medicaid program--and the probability that a significant portion of these expenditures are being made for ineffective and possibly effective drugs--we recommend that SRS issue, without further delay, regulations to preclude the purchase of ineffective and possibly effective drugs under Medicaid.

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We shall appreciate receiving your comments and advice as to any actions taken or planned with respect to our recommendation.

Sincerely yours,

John D. Heller
Associate Director

Mr. John D. Twiname, Administrator
Social and Rehabilitation Service
Department of Health, Education,
and Welfare

Senator NELSON. In the letter dated May 9, 1972, Mr. Heller, the Associate Director of the GAO states: "As of May 1, 1972, regulations have not been issued to implement the revised Federal drug policy for medicaid."

Do you have any comment to make on that?

Mr. SEGGEL. Yes, sir. As I mentioned, for medicare we have issued a notice of rulemaking, and are evaluating comments on that notice. With regard to medicaid, SRS has actually developed a similar notice of rulemaking. But we have, at the Department level, been studying this with particular reference to how we would administer it, how we would actually get enforcement of that through the reimbursement mechanism.

It is a very complicated thing. We have no way, obviously, of controlling what the doctor prescribes except by means of our regulatory process of taking things off the market, or by our educational process of informing him of the classification. And we have no way through the fiscal mechanism of determining exactly what drugs are prescribed to what patients. We don't know quite how we would deal with that kind of thing, except with some kind of post audit that we might make on a sample basis. And that would be somewhat less than effective enforcement, doing it by post audit.

And also we are concerned about the question of whether, if the doctor prescribed a drug that we wouldn't pay for, the burden would fall on the patient rather than on the Federal Government.

We are emphasizing the twin strategies, I would say, of our regulatory process of vigorous enforcement through regulation and our regulatory process of vigorous enforcement through regulation and our education process.

In the meantime, we are trying to study ways and means by which we could actually get some enforcement of this if we decide to go forward with it.

We have comments, as I have mentioned, on the SSA proposal.

Mr. GORDON. Comments from whom?

Mr. SEGGEL. From manufacturers and others.

Mr. GORDON. They don't want you to do this at all, do they?

Mr. SEGGEL. That is right in many cases. As I understand it, some of them point out the inconsistency of, on the one hand, being given the opportunity to provide further evidence on the efficacy of their products, yet, on the other hand, Federal funds to purchase those drugs are turned off before that evidence is provided. I think that is one of the main concerns. However, we are committed to this policy of trying to cut out the national support for these drugs. Certainly, as Dr. Finkel has indicated, as we get them off the market. The question of reimbursement becomes moot in any event.

The "possibly effectives" are a little bit tougher problem. There, how we would audit, for example, the question of a doctor prescribing a drug which he says is the appropriate therapy for that patient I don't know. At any rate, I want to say that we have this under study trying to determine how we could enforce it through the reimbursement machinery.

Mr. GORDON. This "possibly effective" business disturbs me. I have read the Food, Drug and Cosmetic Act, and I don't see any reference to "possibly effective" at all. Any drug that is on the market is

supposed to be effective. In fact, there is supposed to be substantial evidence of efficacy in addition to safety. How do we get to this "possibly effective" and "probably effective" business anyhow at this point?

Dr. FINKEL. Well, we feel, and the National Academy of Sciences felt, that there was some evidence of efficacy, and that is why they have used that classification of "possibly" and "probably". And we want to give the patients the benefit of the doubt and see whether efficacy can in fact be established. When those drugs came on the market the methods for studying them were unsophisticated. And some of them may indeed be effective. In fact, we have raised some, "possibly effectives" to "effective." And we feel that the drug should be studied according to present day methods before we make the final decision.

Mr. GORDON. How long are you going to study them? You gave the "possibly effectives" 6 months. It is many years for some of them and they are still on the market.

Dr. FINKEL. We recognize that 6 months—or even a year, for the "probably" effectives—is insufficient to develop and perform clinical trials and analyze them. So that we have allowed extensions for a good number of drugs where the firms have been interested in doing the studies. For many of the "possibly effectives" drugs—a number of firms have simply decided that there was no commercial interest, and have removed the drugs from the market.

Senator NELSON. Let me ask some questions just to refresh my memory.

We have had some testimony on this in the past, and it is vague in my mind.

The Kefauver amendment, which was passed in 1962, provided that, in addition to safety, substantial proof of efficacy had to be presented to maintain the drug in the marketplace. Was it, then, in 1966 when the implementation began under Dr. Goddard?

Dr. FINKEL. Yes.

Senator NELSON. And when did the drug companies get notice that the National Academy of Sciences was following the procedure of classifying drugs as effective, ineffective, possibly effective, and probably effective? How long had they had notice that these classifications were going to be used, and that they would have a certain amount of time to produce adequately controlled studies to qualify their drug as an effective drug to remain in the marketplace, do you recall?

Dr. FINKEL. I don't recall exactly when those, actually five, different classifications were announced. But the first publications of the Federal Register began to appear about 1969.

Senator NELSON. The first classifications by the NAS/NRC?

Dr. FINKEL. Right.

And it was then that it was announced in public, in print, anyway, that the firms would be given that amount of time to perform studies.

Senator NELSON. Let me see. If the drug is described as ineffective, it must be removed from the marketplace in what period?

Dr. FINKEL. Well, the firms are given 30 days to respond to the announcement of inefficiency and produce some evidence.

Now, some of them have, and it had to be reviewed. There were a few, though, that were given some extensions of time to perform clinical trials while the drug remained on the market.

Senator NELSON. Give me the time span allowed by the FDA for each one of these classifications, I have forgotten what they were. The ineffectives were given 30 days, as I recall.

And possibly effective is the next category.

Dr. FINKEL. Possibly effective was given 6 months, and probably effective was given 1 year.

Senator NELSON. And what was the description of the standards they had to meet to satisfy the requirements for adequately and scientifically controlled studies to support the claim of efficacy? What was the language used?

Dr. FINKEL. In May of 1970 we published a policy statement which defined adequately and well controlled studies. And those were the principles that the firms were to follow.

Senator NELSON. You don't recall when the NAS/NRC first proposed the categories of ineffective, possibly effective and probably effective?

Dr. FINKEL. I believe it was the FDA that devised that, the then Commissioner at that time.

Senator NELSON. Was it the FDA that suggested these classifications to be followed by the NAS/NRC?

Dr. FINKEL. Yes, sir.

Senator NELSON. When was that, do you know?

Dr. FINKEL. I am afraid I don't know.

Senator NELSON. What I am trying to get at is, how many years, how much time, have the drug companies had notice that adequate and well-controlled studies would have to be submitted to support claims of efficacy? Is it 3, 4, or 5 years since they knew?

Dr. FINKEL. Well, they knew in 1962 that all drugs on the market would have to be shown to be effective. However, they didn't know the ratings for their particular drugs until the publications, or shortly before each publication appeared in the Federal Register.

Senator NELSON. Did they know they would have to prove by some standard that the drug was efficacious?

Dr. FINKEL. Yes.

Senator NELSON. And now it has been 10 years since the drug companies have had notice that they were going to have to come forward with adequate and well-controlled scientific studies to prove the efficacy of their drug, isn't that correct?

Dr. FINKEL. Yes.

Mr. BRANDS. May I add a statement, Mr. Chairman.

Senator NELSON. Yes.

Mr. BRANDS. In the publication "Drug Efficacy Study," on July 9, 1966, the Commissioner of Food and Drug published an order in the Federal Register requiring each holder of an NDA approved between 1938 and 1962 to submit to FDA specified information on each drug that the manufacturer wished to retain on the market. So, you might say that in July 1966 was the first official notice they had that the study was going to take place.

Senator NELSON. I am looking at a publication, "Federal Food, Drug and Cosmetic Act as Amended May 1966," in which it says: "As used in this subsection and subsection (e), the term 'substantial evidence' means evidence consisting of adequate and well-controlled investiga-

tions, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug would have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof."

So, that definition of the standard was published in 1962. Counsel advises me that this was part of the Kefauver Act of 1962. So it has been 10 years since they knew what the standard would be. And it seems peculiar to me that they are still fussing around about producing evidence of effectiveness of the drug when they have had 10 years notice that that is what they had to do.

Dr. FINKEL. Well, the definition of "substantial evidence" really was not defined until May of 1970. What I meant was that there is a difference of opinion as to the definition of what constitutes substantial evidence and how it is to be obtained.

Senator NELSON. And how clear a notice can you have that you have to produce scientific evidence of effectiveness? The law says it in considerably more detail. The point is that the drug companies know what that means, and they know that they have got a drug in the marketplace, and they have to prove that it does what it claims it does, and if they can't prove that this does what they claim it does, then it is not to be permitted to be marketed under the Kefauver amendment.

Do you think there is any misunderstanding by the drug company that they had to prove that the drug effectively attacks the target organism that they claim it attacks, or the physical situation that they claim that it relieves? There isn't any doubt about that, is there?

Dr. FINKEL. I don't think so. But I think in some cases there has been a difference of opinion as to what constitutes substantial evidence.

Senator NELSON. I can only conclude that they have filibustered for 10 years, and the Government has been far too lenient in permitting them to continue to maintain less than effective drugs in the marketplace.

Ten years is an awfully long time. And the drug should not have been on the market in the first place if they couldn't prove that they do what they claim they do. And if 10 years later you are still arguing about "possibly effective" and "ineffective" and "probably effective" drugs, it is disgraceful, I think.

Mr. SEGGEL. Mr. Chairman, may I make a comment on that?

Senator NELSON. Yes.

Mr. SEGGEL. I am not familiar with all the past history you mentioned, but I will say this, that the Department is moving in aggressively now. The Food and Drug Administration is being greatly strengthened to carry out its regulatory function and has received a large increase in its budget. For a long time FDA didn't have the resources to do all that was necessary. What we are now doing is moving into the specific processes by which the requirement of that act can be carried forward effectively.

Mr. GORDON. The chairman previously referred to the memo that was sent out by the Surgeon General on December 11, 1970, to all agencies of the Department of Health, Education, and Welfare.

Now, are you saying that nothing has been done to carry out those policies?

Mr. SEGGEL. I am saying that the two agencies involved, SRS and SSA, have come forward with notices of rulemaking. In one case it was published last fall and we have received comments on that. The other one was recently submitted by the agency and is being reviewed in the Department. We want to be sure, before we go forward with the regulations, that they can be effectively administered and not just express another pious statement of policy. At this point there are complex questions of how we can do it with the resources available, how we can possibly get into the prescription of individual drugs through the mechanisms of these huge programs. And, particularly, we want to avoid anything which would put the burden back on the patient, if indeed the doctor goes ahead and prescribes a drug for which we have said the Federal Government would not provide reimbursement.

Senator NELSON. Perhaps you are familiar with a study made of the use of the drugs under the Mississippi medicaid program, done by Alton B. Cobb, M.D., and others. Dr. Alton B. Cobb is director of the Mississippi Medicaid Commission. They found, among other things, that the top ranking drug by amount spent was Indocin in 25 milligram capsules. The top ranking drug by number of prescriptions was Darvon Compound 65, which is described as irrational by the Drug Evaluations of the AMA's Council on Drugs. On page 5 of the study we find:

> It is interesting to note that among the ten leading drugs ranged by total amount paid, five drugs are specified as "not recommended" or as "irrational mixtures" by the AMA Drug Evaluations 1971. Also, one drug among the ten has been classified as "possibly ineffective" by the Food and Drug Administration. This indicates an overall negative relationship between popular usage of drugs and the evaluation of their efficiency and safety by the AMA Council on Drugs and the FDA. It is suggested that this represents a fertile area for professional education.

That study indicates that top-selling drugs were irrational combinations or only "possibly effective." I wonder how widespread that is in Medicaid programs throughout the country!

Mr. SEGGEL. It is a largely decentralized program. It undoubtedly varies from State to State.

I would like to reiterate the point that I have made, however, that the way we are trying to attack this problem basically is through the process of education and information, as well as through the process of taking drugs off the market through the Food and Drug Administration's regulatory machinery.

I would point out that earlier I mentioned that the Food and Drug Administration now requires package inserts and advertisements to reflect efficacy evaluations, while clinical evidence is being sought to establish whether the drug is or is not effective for each indication.

In other words, the physicians should know what the story is in this process.

Senator NELSON. But I would suppose that for most prescriptions written, the physician doesn't see the package insert, which is in the hands of the pharmacist.

Mr. SEGGEL. I don't know about that. But I know that we have additional means of getting information to the physician. FDA—I think Dr. Edwards, the Commissioner of Food and Drug, mentioned it in his testimony—has launched a broad set of endeavors to get the message to the physicians as well as to the patients. I mentioned some of these later on in my prepared statement.

Senator NELSON. You know perhaps much better than I the difficulty of getting the educational information out when you have to compete with the "educational information," in quotes, coming from the drug companies.

But here is a paper entitled "Market Research Summary of Physicians' Attitudes Toward Antibiotics," a study that was done in behalf of the Lilly Co., and which I shall insert in the record. I will just read part of it to you to give you some idea of what your competition is in the field of education. This was sent to detail men to advise them how to deal with some of these problems. This particular drug under section IV says, "Determinants affecting choice of Ilosone." That is what they are sending to their detail men.

The physicians' study reveals that Ilosone is not differentiated from other erythromycins by most physicians. It shares the dominant image characteristic of all erythromycins in regard to main uses, safety, efficacy, and spectrum. There is only a minority awareness and belief in Ilosone's advantages of absorption, blood levels, and acid stability. In terms of market impact, however, this lack of brand differentiation is counterbalanced by an even smaller minority awareness and concern about Ilosone's associations with liver toxicity. Among the relatively small group of physicians with awareness of Ilosone's liver toxicity side effects, there are two basic reactions:

Users rationalize Ilosone's side effects in various ways, and generally attach little significance to it.

For a small but potentially influential group of nonusers, past users, or cautious occasional users, this concern is a serious deterrent. Even more detrimental, this group may be spreading negative word-of-month far beyond its numerical size.

Ilosone is favored by regular users mainly because of their loyalty to Lilly and their perception of absorption advantages (patient-proof, reliable, etc.). About one in ten physicians in the groups saw Ilosone as superior because of faster, higher, or longer-lasting blood levels and better absorption. Among those who use it, fear of side effects reinforced expectations of therapeutic potency.

Physician attitudes regarding Ilosone, as outlined, suggest certain marketing implications which are summarized below:

(A) Ilosone is not substantially differentiated from other erythromycins. Thus, Lilly can promote Ilosone as an erythromycin which conveys safety. However, there exists a responsibility to adequately inform those physicians who are unaware of the infrequent side effects. A delicate balance is required so as not to raise unnecessary concern among those physicians who are not generally concerned about the jaundice problem.

(B) The relatively low overt concern regarding Ilosone's side effects may be taken as evidence for a positive attitude regarding the detailing of this product by the sales force.

(C) Selective detailing may be required to avoid the discussion of Ilosone with any physician who is aware of and concerned about liver toxicity side effects. Where there is any awareness of Ilosone's liver toxicity associations, the known availability of a "safe alternative like Erythrocin" is competitively decisive.

(D) By not attempting to further differentiate Ilosone from other erythromycins, Lilly may capitalize on its strong reputation in the antibiotic field to increase Ilosone use as total erythromycin use increases.

I will ask that the whole memorandum be printed in the record.

(The memorandum referred to follows:)

MARKET RESEARCH SUMMARY OF PHYSICIANS' ATTITUDES TOWARD ANTIBIOTICS

The objectives of this study were to explore physicians' attitudes toward antibiotic drugs and the determinants which influence selection among antibiotic brands with special attention to V-cillin K and Ilosone. At our request, National Analysts of Philadelphia conducted 24 group-depth interviews in eight cities throughout the United States. In each city, separate groups of GP's, internists, and pediatricians were interviewed. Average group size ranged between 10 and 12 physicians. While a qualitative study of this sort may not be statistically projectable, the major findings are confirmed by market data and our current general understanding of the market.

From the study, it is possible to make a logical ordering of the decision-making processes experienced by physicians in choosing and using antibiotic drugs. Such a model of the physician "decision tree" permits the study to be organized in five major areas as follows: 1) determinants of treatment (Should an antibiotic be used?), 2) determinants of therapeutic route (Should it be IM or oral?), 3) determinants of antibiotic choice (Which generic group of antibiotics is indicated?), 4) determinants affecting choice of V-cillin K, and 5) determinants affecting choice of Ilosone.

Since physicians' thinking and behavior may not always be logical, many of the determinants may interact simultaneously or there may be a "short circuiting" in which physicians may move directly to a brand choice without pausing first to consider which group is appropriate. Such action reflects the formation of individual ideas about antibiotic therapy over a long time period or at some point in the past. As a result antibiotic use decisions may be largely automatic and unconscious for many physicians.

I. DETERMINANTS OF TREATMENT

(A) The study indicates that physicians feel pressured to treat with antibiotics even when they are not convinced that the illness is bacterial in nature and they frequently do prescribe antibiotics in illnesses that they suspect are viral in origin.

(B) Factors influencing the initial decision to treat or not to treat with an antibiotic generally fall into characteristics related to the nature of the illness, those related to the patients, and those related to the physician. Characteristics related to illness include severity of illness, degree of pain, magnitude of visible signs of tissue change, viral or bacterial diagnosis and the duration of illness.

(C) Characteristics related to the patient which determine antibiotic use include such factors as predisposition to serious infections, presumed vulnerability to the illness, patient expectations or demands for antibiotic therapy and the socio-economic class or degree of "medical sophistication" of the patient.

(D) Characteristics related to the doctor which may determine antibiotic treatment are personality type and professional focus. Here the study identified two different personality types with regard to their professional approach in coping with an infection—these may be called "problem solvers" and the humanist or healer." The relatively small group of physicians is "problem solving" in that they see themselves as practicing scientists depending upon cultures, tests, rigorous evaluation of objective data. Of the three groups considered in this study, the "problem solving" type of doctor was found more often among internists, secondly among pediatricians, and least among GP's. The other and larger group of physicians may be classified as more humanistic than scientific, more concerned with the well-being of the total patient than the specific form and locus of infection alone. They use antibiotics to assure patients of the doctor's active role in genuine concern, to maintain confidence in morale, and bolster patient cooperation.

Other characteristics related to the physicians which determine antibiotic use are classified as professional sophistication and security, nature of the doctor-patient relationship (degree of authoritarianism), the satisfactions of giving medication (using antibiotics rather than palliatives), fear or risks of treatment (side-effects, malpractice, and censure by colleagues), apprehension about the consequences of no treatment, time and place of examination and initial treatment, and fear of developing resistant organisms if antibiotics are given (expressed by only a few physicians).

II. DETERMINANTS OF THERAPEUTIC ROUTE—INTRAMUSCULAR VERSUS ORAL

(A) Once the physician concludes that antibiotic therapy is indicated, he must next decide what therapeutic route is desirable for this particular case before he can move on to the choice of a particular antibiotic drug. The main factors influencing preference for the IM or oral route are shown below:

Intramuscular.—Rapidity of action; potency; higher therapeutic blood levels; avoids oral or gastric intolerance; duration of action and independence from patient cooperation in taking medication; better control over patient; and more efficient for very high dosage.

Oral.—Safety; multiple convenience advantages; portability, self-administration, versatility, time; net cost—saving fees for office visits reduces therapy costs; and avoids pain of injection.

III. DETERMINANTS OF ANTIBIOTIC CHOICE

The study revealed seventeen major determinants of antibiotic choice. Summary discussion will focus upon the three determinants which appear to be probably the most important in selecting the antibiotic of choice.

(A) Perceived efficacy is the prime consideration when dealing with severe ills or when the most potent drugs available are relatively safe. Efficacy includes anticipated effectiveness or "image of effectiveness" and perceived performance or "apparent" clinical response. Positive results produce loyalty, negative results are a major incentive for trying other antibiotics. The "test" may not be scientific. If the patient gets better, the antibiotic prescribed gets the credit; if the patient gets worse, the drug is blamed.

For respiratory and ear infections, penicillin is seen as highest in effectiveness; second place is shared by both the erythromycins and tetracyclines.

(B) Diagnostic indications include clinical evaluation of the pathogen and culture and sensitivity tests (which may be particularly attractive to the "problem solver").

(C) Safety is one of the major considerations in choice of an antibiotic. Its importance rises when the condition treated is not severe; when almost equally effective drugs are available which differ mainly in relative safety; or when treating patients vulnerable to side effects of a particular group of drugs.

Penicillin is seen as one of the most dangerous of all antibiotics in I.M. form (anaphylactic dangers), but is also perceived as one of the safest drugs for the non-allergic individual because of freedom from toxicity in large doses.

Erythromycin is seen as replacing tetracyclines because of its image as one of the safest of modern antibiotics.

Tetracycline is seen as having danger to children and pregnant women and is sometimes generalized as being dangerous to all patients. Pediatricians, in particular, may avoid its use. Most frequent side effects are browning and staining of teeth, interference with bone formation, and photosensitivity reactions.

Of the several remaining determinants, it is particularly interesting to note the importance of the detailman in the antibiotic field because the characteristics of this field include: 1) a vast number of drugs available, 2) the opportunity to play an influential role in sub-classes of antibiotics where no differences between brands are perceived by the physician, 3) contradictory competitive claims which increase the burden of choice by the physician and may increase his reliance upon the detailman whom he trusts, and 4) the importance of product knowledge in a field where the possible fatal consequences of prescribing or failing to prescribe are clearly seen by the physician. Most of the physicians in the groups valued visits from their detailman and felt he provided a helpful service, particularly by helping the physician maintain high comparative product visibility, actionable memory, and therapeutic suitability for the specific antibiotic brands promoted.

The availability of antibiotic drug samples helps influence the prescription practices of physicians even when samples are not being used to make an economic contribution to patient therapy. For the doctor, samples are seen as providing an immediate three-dimensional reference library of drugs, dosages, bottle sizes, colors, etc., as well as enabling him to assist his patients and also engage in "trial and error" therapy.

IV. DETERMINANTS AFFECTING CHOICE OF ILOSONE

The physicians' study reveals that Ilosone is not differentiated from other erythromycins by most physicians. It shares the dominant image characteristic of all erythromycins in regard to main uses, safety, efficacy, and spectrum. There is only a minority awareness and belief in Ilosone's advantages of absorption, blood levels, and acid stability. In terms of market impact, however, this lack of brand differentiation is counterbalanced by an even smaller minority awareness and concern about Ilosone's associations with liver toxicity. Among the relatively small group of physicians with awareness of Ilosone's liver toxicity side effects, there are two basic reactions:

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Physician attitudes regarding Ilosone, as outlined, suggest certain marketing implications which are summarized below:

(A) Ilosone is not substantially differentiated from other erythromycins. Thus, Lilly can promote Ilosone as an erythromycin which conveys safety. However, there exists a responsibility to adequately inform those physicians who are unaware of the infrequent side effects. A delicate balance is required so as not to raise unnecessary concern among those physicians who are not generally concerned about the jaundice problem.

(B) The relatively low overt concern regarding Ilosone's side effects may be taken as evidence for a positive attitude regarding the detailing of this product by the sales force.

(C) Selective detailing may be required to avoid the discussion of Ilosone with any physician who is aware of and concerned about liver toxicity side effects. Where there is any awareness of Ilosone's liver toxicity associations, the known availability of a "safe alternative like Erythromycin" is competitively decisive.

(D) By not attempting to further differentiate Ilosone from other erythromycins, Lilly may capitalize on its strong reputation in the antibiotic field to increase Ilosone use as total erythromycin use increases. We should also continue our efforts to position Ilosone as an effective alternative to penicillin for the penicillin-sensitive and as an alternative to tetracylines because of freedom from teeth and bone side effects.

In contrast to the above marketing implications, we recognize the possibility of an alternative strategy which would further attempt to differentiate Ilosone from oher erythromycin brands. In light of this research study and its description of the current market in which we operate, we would anticipate the need for clinical data that effectively demonstrate, in the mind of the physician, superiority of Ilosone over other erythromycin brands. It may be that the effort, resources, and time necessary to establish a broad and believable series of clinical data would not yield significantly greater results than efforts aimed at a strategy of non-differentiation as outlined above. Thus, prior to any major strategic decisions, further economic analysis may be required to determine the potential gains versus risks of both marketing strategies.

V. DETERMINANTS AFFECTING CHOICE OF V-CILLIN K

V-Cillin K is positioned in the antibiotic field as one of the improved, modern oral penicillins about halfway between "old" penicillin G and the newer synthetic penicillins. Physicians perceive superior absorption and acid stabiilty for V-Cillin K compared to other penicillins, and particularly in relation to penicillin G. V-Cillin K is seen as a safer alternative than penicillin I.M., and a

more effective alternative than oral penicillin G. Except for extrinsic factors such as detail men or company loyalty, V-Cillin K does not seem to be differentiated from or preferred over other penicillin V's and VK's. While V-Cillin K is perceived as being more expensive than penicillin G, it is considered a slightly less expensive penicillin than the new synthetics.

V-Cillin K's most favorable perception of efficacy by favorers was characterized as being "almost like an injection of penicillin—rapid action in 15 to 30 minutes." Most physicians were latently aware of its superior absorption claim, but acted as if this were either not believed or not clinically significant. Even users had difficulty comprehending how V-Cillin K works and how it really is better.

The above characteristics of V-Cillin K attitudes tend to confirm our previous thinking and indicate to us that we have been following the correct course of marketing action which has contributed to the higher V-Cillin sales level. Specific marketing implications are summarized below:

(A) We should continue the strategy which translates higher blood levels into clinical advantages, stressing superior therapeutic response, and suggesting some kind of inevitable functional sequence by which superior acid stability *leads to* better absorption, which *leads to* higher blood levels, which *produces* greater antibacterial activity.

(B) We should continue to position V-Cillin K as a *potent* alternative to penicillin I.M. which is relatively free of risk of anaphylaxis.

(C) Lilly's name and its associations with integrity and antibiotic reliability should continue to be used as major advantages in reinforcing the believability and acceptability of the V-Cillin K product claims.

Senator NELSON. Then on February 15, 1972, marketing letter No. 17. This was sent to the detail men:

Gentlemen:

Re: Mail promotion of Ilosone.

During the month of February, two letters will be sent to each of your key and important G.P.'s, osteopaths, and pediatricians.

The first mailing will stress b.i.d. therapy, the double-strength dosage forms, and the advantages of Ilosone over other erythromycins. A sample request card will be included. These reply cards will be forwarded to you so that you can deliver the samples.

The second mailing will stress the advantages of a twice-a-day regimen and again mention our new dosage forms and the unique features of Ilosone. A business reply card will be included, offering a lossproof key chain (see attachment). The number engraved on each key chain is permanently recorded in Indianapolis. These service items will be forwarded to you for personal presentation to the requesting physician.

We hope this mailing program will help identify or reconfirm earlier identification of physicians in your territory who have an interest in Ilosone and, therefore, represent potential for target detailing efforts.

Very truly yours,

ELI LILLY AND COMPANY.

And the attachment is a key chain.

I ask you, do you think you can compete with that "educational" program?

Mr. SEGGEL. I think the answer is, we are going to try.

Senator NELSON. I think the whole educational effort is almost a disaster in the face of detailing and in the face of promotion that is being done by the drug companies. I don't see much success, other than the fact that we are forceably removing drugs from the marketplace. That is one way to keep doctors from prescribing ineffective drugs. But with respect to promotion of drugs for improper use, I really don't think this country is making much headway, do you?

Mr. SEGGEL. Our efforts are increasing—again, I emphasize that I am talking of the very recent past. And I think it is too early to say how successful we will be, but——

Senator NELSON. I have another study done this year by Dr. Paul Stolley of Johns Hopkins in which 95 percent of the physicians in the sample prescribed some drugs for the common cold. As I recall it, 60 percent of them were prescribing antibiotics, which are not indicated for this purpose. This study, entitled: "Drug Prescribing and Use in an American Community," by Paul D. Stolley, M.D., Marshall Becker, Ph. D., Louis Lasagna, M.D., and others, appeared in the Annals of Internal Medicine, April 1972. Included is the following paragraph:

It is equally apparent that a large amount of drug prescribing and drug costs are for common, benign, and self-limiting illnesses (for example, the uncomplicated common cold). United States national marketing research data also indicate that most physicians (about 95 percent) will issue one or more prescriptions to a patient whom they diagnose as having the "common cold," and almost 60 percent of these prescriptions will be for antibiotics.

I should read the last sentence:

Data are not available to determine what proportion represent bacterial complications of an illness that was originally viral.

But that would appear to be misprescribing for a substantial percentage of those cases for the common cold, would it not?

Mr. SEGGEL. It would sound like it. But I am not a physician myself. Dr. Finkel?

Dr. FINKEL. I don't think that there is any question that antibiotics are misused when used for treatment of viral infections.

Mr. BRANDS. Mr. Chairman, may I add to Dr. Stolley's study. In one paper, "The Relationship Between Physician Characteristics and Prescribing Appropriateness," I think his finding in this study is something that can be used by the universities and by the Federal Government in the education as well as the continuing education of physicians. His study will be most useful for future actions in influencing a physician in rational drug prescribing. He listed some characteristics in this paper. If you do not have it, I will be glad to submit it.

Senator NELSON. What is the title of that?

Mr. BRANDS. "The Relationship Between Physician Characteristics and Prescribing Appropriateness."

Senator NELSON. We have it.

Mr. GORDON. There is another study that was done by Charlotte Muller which appeared in the American Journal of Public Health, December 1967, in which she refers to Dr. Furstenberg's study of:

A one percent sample of over 100,000 prescriptions written by 159 physicians rendering care under the public welfare medical care program in Baltimore, Maryland. He found that 55 percent were for proprietary preparations and identified the actions as pointless waste of the program's money since less expensive official preparations listed in the official sources were quite suitable.

I ask that the study be put into the record.

Senator NELSON. What is the total amount of Federal money and State money spent on drugs in the medicaid program?

Mr. SEGGEL. It is around a half a billion dollars.

Senator NELSON. That is Federal and State, or just Federal?

Mr. BRANDS. This is both.

Senator NELSON. That is 50–50, is it?

Mr. RICHTER. It is about 55 percent Federal overall.

Senator NELSON. So the total amount spent on drugs under the medicaid program is about $400,000 annually?

Mr. RICHTER. $500 million.

Senator NELSON. $500 million annually?

Mr. RICHTER. Yes.

Senator NELSON. How much is spent on drugs and medication?

Mr. SEGGEL. We have the figures here.

Senator NELSON. And what is the cost share on medicare?

Mr. BRANDS. On medicare hospitalization it is $541 million. Medicaid, which includes both inpatient and outpatient care, is $485,400.

Senator NELSON. How much of that total bill is Federal appropriations?

Mr. BRANDS. All of medicare and about 55 percent of medicaid is Federal money. Thus, the total bill would be between $750 million and $800 million.

Senator NELSON. Annually?

Mr. BRANDS. Annually, yes, sir.

Senator NELSON. Has that cost been rising in the past 3 years? What is the change? What was spent when the program started?

Mr. BRANDS. I don't have those figures.

Mr. RICHTER. I have some figures here on medicaid.

Mr. GORDON. I have the figures that you gave to us. Federal contributions to medicare was $541 million, and then for medicaid, $485 million.

Senator NELSON. That is the figure you just gave us.

Mr. GORDON. So between the States and Federal Government, it is one and a half billion, is that correct?

Senator NELSON. Are these figures that you gave of medicare $541 million, and medicaid, $485 million, both the Federal and State contribution?

Mr. BRANDS. Yes, sir.

Senator NELSON. And the Federal contribution you said was around $755 million?

Mr. BRANDS. Fifty-five percent of the total of medicaid.

Mr. SEGGEL. I made a rapid calculation, and it would come out to over $700 million Federal total for medicare and medicaid.

Senator NELSON. And the total expenditure for medicare and medicaid are something over a billion dollars, a billion one hundred million?

Mr. SEGGEL. That is right. About 45 percent of the medicaid is State.

Mr. GORDON. This is confusing. That $485 million for medicaid that you have here is the Federal contribution, is it not?

Mr. RICHTER. That is the total.

Mr. GORDON. Federal and State?

Mr. SEGGEL. We can review the figures, Mr. Chairman, and submit them for the record.

Senator NELSON. Let's be sure the record is correct.

Mr. SEGGEL. Yes, sir.

Senator NELSON. It is Mr. Gordon's thought that the total was a billion and a half or thereabouts.

Mr. GORDON. I have a table here, XXV, estimated Federal, State and local government expenditures for prescription drugs under DHEW sponsored health care programs. And I have $1.487 billion.

Senator NELSON. That is the figure shown on the chart. I think we had better get it straightened out for the record in any event.

Mr. SEGGEL. I may just have the Federal portion here. I am not sure; I will have to check that.

Mr. BRANDS. Mr. Chairman, 55 percent or $480 million is the Federal portion, the 55 percent.

Mr. GORDON. So for both Federal and State it comes to about $1.5 billion, is that correct?

Mr. BRANDS. That is right.

Senator NELSON. Go ahead now that we have that straight for the record.

Mr. SEGGEL. I would now like to discuss our direct purchasing policies and procedures. All centralized drug purchasing is by generic name with specifications for the finished drug product. Drugs in the direct care programs are purchased by generic name to obtain the lowest cost consistent with no sacrifice in quality when the product is produced by more than one manufacturer.

The Medical Supply Service Center at Perry Point, Md., is a mandatory source of supply for the Department's direct care programs. It generally does not purchase or stock a drug product unless there is a saving for the ultimate user of that drug product, as compared to purchasing it from the Veterans' Administration Depot, under the Federal supply schedule contracts or in the open market. However, it is also a service center as the name implies. As you are aware, most drug products are not dispensed to the patient in the quantities available commercially. They have to be counted or measured by the pharmacist in the sizes necessary for the length of treatment of the patient's condition. This counting and measuring are time consuming at the local hospital and clinic. One of the services provided at the center is prepackaging drug products in various sizes for the hospitals and clinics. This is done by machines. This service saves considerable manhours at the health facilities.

Mr. Chairman, with your permission, I would like to skip the detail, unless you wish to go into it, concerning how we handle competitive bidding.

Senator NELSON. That is all right.

Mr. SEGGEL. This will be in the record.

The Department policy in the bidding process when the cost is estimated at $5,000 or over is to advertise in the Commerce Business Daily, giving details of the product on which a bid is requested. A closing date is listed in the advertisement. When bids are received, they are opened on a specific date at a specific time. The lowest bidder is awarded the contract unless there is reason to believe his product will not meet specifications. If there is a tie bid and one of the bidders with the tie bid is a small manufacturer, the small manufacturer will be awarded the contract.

When the cost of a drug product being considered for bid is between $2,500 and $5,000, bids are mailed to manufacturers that have requested to be placed on the bidding list and to others that manufacture

the product. The bid is awarded in the same manner as described above.

For purchasing a quantity of drug products for which the estimated dollar value is less than $2,500, quotations are solicited from various manufacturers. The manufacturers selected for quotations are those which have previously bid or quoted on the same or similar products.

In order to ensure economy, the lowest bid or quotation received is compared with the current market price and the price schedules of the Veterans' Administration, the Defense Personnel Supply Center and the Federal supply schedule before the purchase is made.

The procedures and policies of the Department for centralized purchasing are in accordance with the overall Federal policies of the General Services Administration.

The Department has mandatory sources of supply in order to coordinate its direct procurement of drug products with other Government agencies. These mandatory sources in order of priority are:

(1) HSMHA Medical Supply Service Center: (2) Veterans' Administration; and (3) Federal supply schedule.

The Medical Supply Service Center also purchases drugs from the Defense Personnel Supply Center for central stocking and distribution to the Department's hospitals and clinics. The center requests usage information on individual drug products which are consolidated for centralized purchasing considerations. Immunizing agents are purchased by the Veterans' Administration for the Department's Center for Disease Control, and the Defense Personnel Supply Center purchases drugs for the Division of Emergency Health Services. The Department's Medical Supply Service Center supplies drugs to other Government agencies such as the State Department, Peace Corps, Justice Department, Job Corps, and the District of Columbia.

Grantees of the Department have been permitted to purchase drug products from General Services Administration sources of supply. However, the General Services Administration published a proposal in the Federal Register on June 1, to revise the current policy and prohibit the use of the General Services Administration and other Federal sources of supply by recipients of Federal grants. Comments will be received up to July 31, 1972.

DHEW Outlays for Drugs

I would like to briefly review expenditure data on DHEW direct drug purchases and reimbursements to community pharmacists for drug products in the Department's direct care programs and the reimbursement for drug products to hospitals and community pharmacists under the medicare and medicaid programs. The program operated under the National Immunization Act for providing certain immunizing agents to the States and the purchases of the Division of Emergency Health Services for stockpiling drugs for national or other emergency use are included in the cost figures as direct purchases. Some grant programs, such as under section 314(e) of the Public Health Services Act and the Community Mental Health Centers Act, provide grants as a lump sum for the total operation and the cost of the drug component is not broken out separately. As a result, the drug costs in these programs are not included in the figures.

The cost of drugs for hospitalized patients under each of the reimbursement programs was estimated on a percentage basis of the total hospitalization cost. The cost of drugs for outpatients under the medicaid program is the Federal share of the total cost which averages at about 55 percent nationally.

With the qualifications noted above, the Department expended an estimated $1,046,420,000 for drug products in direct purchasing and reimbursements in fiscal year 1971. Over 1 billion of this amount represents estimates for drug reimbursed through medicaid and medicare.

The Department expended $14,067,000 for the direct purchase of drugs. Of this amount, $5,058,000 was expended for vaccines for distribution to the States. These vaccines were purchased for the Department by the Veterans' Administration. $1,146,000 were spent for drugs for the emergency stockpile, and purchased by the Defense Personnel Support Center.

We cannot provide estimates of the dollar value of drugs purchased by specific therapeutic categories for medicare, medicaid, the grant programs of 314(e) and community mental health, and the reimbursements for the direct care programs for hospitalized patients. For the other Department programs, a large part of the nearly $4 million outlay for oral contraceptives includes $3,687,000 for the Department's family planning program. Outlays for biologicals were $5.3 million, and for anti-infectives were $2.1 million. No other category exceeded $1 million.

Drugs worth $1,038,000 were purchased centrally by the Medical Service Supply Center of Health Services and Mental Administration, including $350,000 through bids and quotations $657,000 from the Defense Personnel Support Center and a small amount from the Veterans' Administration Depot. The Medical Service Supply Center not only purchases centrally for the Department's programs but it purchases drugs and medical supplies for other Federal departments and agencies. In fiscal year 1971, the Medical Service Supply Center had sales of these drugs and other medical supplies of $2,467,000. Of this amount, $1,597,000 in drugs and medical supplies were supplied to programs within the Department and $870,185 were supplied to other Federal agencies and the District of Columbia. This service to other agencies is provided in the act which established the Medical Service Supply Center.

The total dollar volume of the 50 leading centrally purchased drug products was $345,754. This dollar volume includes only those drugs purchased from manufacturers and does not include any drugs purchased from the Defense Personnel Supply Center. The 50 leading centrally purchased drugs were purchased from 32 manufacturers of which 16 were small manufacturers. Thirty-nine drug products were purchased from small manufacturers at a cost of $173,206.

The routine reports generated under the medicare and medicaid programs do not contain information as to the specific drug products or their dollar volume of expenditures for either hospitalized patients or ambulatory patients. However, both programs are planning and studying methods by which such data may be obtained. With the magnitude of the health programs under medicare and medicaid a system to routinely gather this data would of necessity have to be computerized.

I would like to skip some more that we were just talking about and the portion concerning disbursements and move on to "Continuing Research Efforts" on page 14 of our prepared statement.

Senator NELSON. Your figures under the title "Outlay for Drugs," they are correct, are they not?

Mr. SEGGEL. I take it they are. And you have them in tabular form, I think, in the Secretary's response to your letter back in the late winter or early spring. And so I will proceed with the section on "Continuing Research Efforts."

As you know, we have been supporting several projects aimed at improving the provision of effective and more rational prescribing of drugs. As a prime example, the National Center for Health Services Research and Development has a contract with the San Joaquin Foundation for Medical Care to obtain data which will be used in determining the specifications for a model drug utilization review program. Information presently being obtained by the foundation provides, at predetermined intervals, four profiles of drug use as follows: Drug profile of all drugs prescribed; the patient profiles of drug use; the prescribing profile of physicians; the dispensing profiles of drug use. Information to be obtained in the contract will describe drug prescribing and use practices in nursing homes and extended care facilities, the activities of the drug utilization review committee, the internal control process, and a retrospective analysis of drug use data to determine the incidence of potential interactions between drugs.

The San Joaquin Foundation for Medical Care Services, review and pays the claims for the care provided for about 45,000 title XIX medicaid patients in four counties in California.

The information obtained through the contract will serve to improve the efficiency of the existing program of reviewing the dispensing and use of prescription drugs at the foundation. The contract is scheduled to be completed at the end of 1972.

And this will be used, if it turns out as we anticipate as more or less a model in terms of demonstrating what can be done throughout the medical community, and the health care community.

Now, to the subject of practitioner education and information.

The Department also supports practitioner education and provides practitioners with information which can improve their choice and use of drug therapy. Public Law 92–157, which is the new Health-Manpower Act, has a special project section part of which deals with the training of physicians and pharmacists in clinical pharmacology. The program is administered by the Bureau of Health Manpower Education and has a current budget for all special projects activity of $53 million.

One purpose of the special projects program is to place increased emphasis on clinical pharmacology for physicians. The bureau has 34 proposals from medical schools for improved programs in clinical pharmacology. The authority for providing capitation grants to medical and pharmacy schools includes a requirement for the teaching of clinical pharmacology in the universities.

Pharmacists in these clinical programs are working closely with physicians on drug therapy and advising them on adverse reactions, drug interactions, and alternate drug therapy.

In addition to the lists sent to some 6,000 agencies and interested parties, which I have previously mentioned, the Food and Drug Administration publishes periodically the FDA Drug Bulletin to provide timely information to physicians on actions, uses and labeling of drug products. The latest issue dated May 1972 contained the final labeling approval for oral hypoglycemic drugs, methadone for heroin addiction, and others. These bulletins provide to the extent possible unbiased scientific information to assist the physician in his drug therapy. About 600,000 copies of each issue of the Drug Bulletin are mailed to physicians, pharmacists, dentists, third and fourth year medical students, State and national medical and pharmacy associations and medical and pharmacy journals.

The pharmacists in the Department's hospitals publish newsletters containing information on drug use and costs on drugs in a particular category for distribution to physicians and nurses. Many pharmacists in hospitals throughout the country publish periodically information on the use of drugs in the treatment of disease for distribution to physicians.

The Food and Drug Administration on May 4, 1972, proposed detailed plans to clarify and formalize the agency's policy on public disclosure of information. FDA is a major depository of original, scientific, and technical information relating to drugs, foods, and other products.

The Food and Drug Administration files contained vast amounts of scientific data which have been developed over the years to prove safety and effectiveness for a variety of drugs and other products. Much of these data can help eliminate duplication of costly scientific research if it is more widely known and applied. However, there are valid reasons why some of the vast technical information in our files should remain confidential. It is not our intention to make public any data from any manufacturer that would give competitors an unfair advantage or reduce incentives for future research.

Mr. GORDON. What do you mean by unfair competition, unfair advantage? How do you determine whether competition is fair or unfair?

Mr. SEGGEL. Well, the point is that we don't want to give away any trade secrets, I guess that is the general term used, and thus vitiate the advantage that a given company gains from its own research and development.

Mr. GORDON. That is covered by the law anyhow and it would include the processes and the methods of manufacture.

Mr. SEGGEL. Yes.

Mr. GORDON. But you talk about giving an unfair advantage to competitors.

Dr. FINKEL. The clinical trials themselves are frequently rather sophisticated, and were developed under a contract with consultants, so that firms frequently feel that the clinical protocols which they have developed are confidential information.

Mr. GORDON. Generally, the firms have a patent, which gives them a 17-year monopoly. Is this going to give them a perpetual monopoly?

Dr. FINKEL. I believe after the drug is approved for marketing that the clinical data on the basis of which the drug was approved will be made public, also the preclinical data, unless the firms can show

good cause as to why this information should be considered confidential.

Mr. GORDON. And what do you consider "good cause"?

Dr. FINKEL. Well, I really can't answer that immediately other than one of the examples I just cited. Our proposal is now awaiting comment and has not yet been finalized.

Senator NELSON. This question has been raised here before.

To put it in its sharpest focus, take the case of a drug on which there was a patent, and the patent has expired. Is it the position, then, of HEW that the information on manufacturing processes, and so forth, is still to be kept unavailable from the public or the manufacturers?

Dr. FINKEL. Yes, the manufacturing processes are still considered confidential, but any other firm wanting to market that drug would be required to submit only an abbreviated New Drug Application to establish bioavailability with the marketed drug, except that certain cases would require a full application.

Senator NELSON. Does that get at the problem, similar to the chloramphenicol case? Chloramphenicol was marketed by the Parke, Davis Co. under the trade name of Chloromycetin for quite some time. When the patent expired, three other chloramphenicols came into the marketplace, and then Parke, Davis did some studies on its own chloramphenicol as well as the others in the marketplace, and demonstrated that the blood level achievement of the three products was different. Their charts showed that the blood level of the Chloromycetin achieved a much higher level very quickly, whereas the blood level of the other three or four products, whichever it was, I have forgotten, didn't achieve as high a level but extended apparently over a longer period.

The FDA then decided that they wouldn't permit the marketing of the others unless they achieved the same blood levels. They did not do any studies, and as far as I know nobody did, that demonstrated that that blood level achievement of Chloromycetin was more effective in the treatment of disease for which it was used than the others, but for purposes of consistency in the use of the drug, I suppose, they wanted them to be the same.

As I said, we had testimony in which the FDA said that there were no studies to prove that one was more effective against the target organism than the other. But let us suppose it was a significant factor. Once the patent has run out, since the Congress, the public, has given the company 17 years to protect them and make a profit on the research, shouldn't all information, then, be available to all manufacturing firms respecting this drug, especially since this involves the health of the public?

Dr. FINKEL. Since that episode and another one with tetracyclines which was uncovered by the Pfizer firm, we have required bioavailability studies for all antibiotics, so that they are all required to conform to an acceptable level.

Senator NELSON. Are you requiring that the originator of the drug in its application submit bioavailability studies?

Dr. FINKEL. Yes.

Senator NELSON. And is that public information?

Dr. FINKEL. It will become—usually it is a matter of public information, because it is included in the package insert as to what the blood levels are and when they are reached. So, that anybody can duplicate the products pharmaceutically.

Senator NELSON. You say this is an administrative ruling?

Dr. FINKEL. This has become the accepted mode of writing a package insert for antibiotics, after we developed a class label for some antibiotics. For example, all tetracyclines have the same package insert, all penicillins, all erythromycins. As a part of the description of the product and its action, the blood levels achieved with these drugs are included.

Senator NELSON. When did that start?

Dr. FINKEL. When we started to publish the efficacy ratings for the antibiotics, we would publish a class label at the same time.

Mr. GORDON. Do you have a requirement to include the dosage response curve—in other words, at what point is it effective, or do you just have a blood level produced by the drug?

How high a blood level do you need in order to make it effective?

Dr. FINKEL. First of all, the original antibiotics have all had clinical trials to establish whether the blood levels being achieved are in fact clinically effective. But in addition, by doing in vitro studies with the antibiotic disks with the organism that is cultured, one can tell how sensitive organisms are to the antibiotic and approximately what concentration of antibiotic is required to kill the organism in the human. So it is a little bit easier to study antibiotics than it is other things.

Mr. SEGGEL. Although we have indicated that there are certain data we have not made public, it is however our intention to require that each manufacturer justify any request for confidentiality of information given FDA—past, present, or future. This proposal will result in a far greater amount of information being made public, and should be of great value to formulary committees.

Examples of information which would generally be made public under this proposal include:

Correspondence or summaries of discussions with company officials, Members of Congress, or the public; internal operating manuals; informal enforcement actions; and all completed reports of FDA testing and research.

Information which will generally be retained as confidential includes:

Manufacturing methods, formulas, trade secrets, commercial and financial information; active investigatory files compiled for law enforcement purposes; internal FDA correspondence; and FDA correspondence with other Government agencies.

Mr. Chairman, we are pleased to have been afforded the opportunity to appear before your committee to describe the Department's current policies and efforts to obtain greater economies and health benefits from prescription drug outlays.

The completes my general statement, and I would be glad to answer any further questions you may have.

Senator NELSON. I guess we have raised this question peripherally at least. But just for the record, let me repeat it.

In preparation for these hearings, on January 6 of this year I asked the Department of Health, Education and Welfare for data on drug expenditures. The following information was requested:

(1) A list of the 50 most prescribed drugs under medicare, and (separately) medicaid programs for the latest fiscal year available, preferably 1971.

(2) Total expenditures by the Department of Health, Education, and Welfare under the medicare, and (separately) the medicaid, programs for each of these drugs for that year.

(3) The prices paid by HEW for each of these drugs in medicare and medicaid programs during that year.

On April 7 the Department answered these three questions as follows:

The Department is unable to provide a list of the 50 most prescribed drugs under the medicare and medicaid programs, the total expenditures and the prices paid for these drugs. The reporting systems do not provide for a compilation of the frequency or the total amounts of drug usage and prices paid by individual drug products.

Now, these products are costing the Federal Government and the State and local governments approximately $1.5 billion a year.

Don't you think we ought to know what the money is being spent on, and whether the situation is as it is in the State of Mississippi, where it would appear that a substantial percentage of the expenditures are for ineffective drugs, or drugs like Darvon Compound 65, which was rated as an irrational combination, or unnecessary drugs?

Don't you have to do individual studies of this kind by State?

Why can't it be done in the medicare program? Aren't all those drugs dispensed in an institutional situation in medicare?

Mr. SEGGEL. Yes, that is right.

Senator NELSON. All of them; is that right?

Mr. SEGGEL. Those are the only ones that are reimbursable in medicare.

Mr. OLDER. Under the medicare program, cost reports, the cost by departments rather than the individual items in that department.

For example, we have costs for the pharmacy department in the hospital, but we don't have the individual costs of the drugs that were dispensed. We have program validation teams that review some of those costs, and they review them from the point of view, at least at present, of whether the costs were reasonable, and whether the proprietors of the hospital had used prudent buying procedures in purchasing these drugs.

Senator NELSON. But you do not know what money was spent on what particular drug products?

Mr. OLDER. No.

Senator NELSON. So you don't know how much money is being spent on ineffective, unnecessary, unacceptable, or excessively expensive drugs; is that correct?

Mr. OLDER. At this time we don't. We do know the costs of the Department. And we do know that when we find these costs are out of line, the review teams will compare the costs of certain specific drugs to see how the costs compare with what they could have been purchased for, either at the wholesale level or at the retail level, but we do not know the amount spent for each specific drug.

Senator NELSON. How do you expect to find out whether or not substantial amounts of money are being wasted on unnecessarily expensive drugs or irrational combinations or something else?

Mr. OLDER. We will follow the publication of the ineffective or the possibly effective drugs, and rule those out, and they will be excluded from reimbursement. For a drug that is ineffective, for example, there will be no reimbursement.

Senator NELSON. How will you do that when you don't know what the drug money is being spent on?

Mr. OLDER. This will be performed by our intermediaries who review the reports and the data supplied by the hospital. They will have to be informed, as they will be, of the drugs that are ineffective, and they will have to review the records to make sure that these are not part of the drugs that are being paid for.

Mr. SEGGEL. Mr. Chairman, this goes to the point I was making before about the difficulty of administering a regulation prohibiting the purchase of "possibly effective" and "ineffective" drugs through the reimbursement machinery. It is just that at this point in time we don't have a system by which you can zero in on the individual drugs or to make any kind of analysis that is meaningful across the board in terms of totals. But it is something that we are studying.

It would obviously involve extensive computerization, I assume, to get into that kind of data. This is a huge program covering the whole health care system of the country.

Senator NELSON. That is the pressing problem. As more and more of the taxpayer's money is being spent in this field, there is going to be an increase in demand that the money be spent on the most effective drugs in the most economical way. I don't know of any way you can control that unless you establish some procedures. What about the question of establishing a formulary in the medicare program? Medicaid might be more difficult. But why don't you, at least in medicare programs, establish a formulary and purchase from the formularies? Every good hospital in the country has a formulary, and if the practice is well followed in the hospital, the doctor who wants to prescribe something that isn't on the formulary has to justify it.

Why couldn't you do that in the medicare program, other than the standard answer that we get all the time, that the local doctors won't like it?

Mr. SEGGEL. I think we can certainly consider that. And at this point I would assume that under medicare we would, under such a plan, have to relate to every hospital and require as a condition of reimbursement the establishment of such a formulary. And then the question would be whether we would police that, so to speak, or exercise surveillance over it.

Your question before on medicaid went to that point. And what I would like to do is to say that we hope to get these drugs off the market—that is, the "ineffectives." The "possibly effectives" will either go off or go up in the scale; it is a self-liquidating proposition.

Beyond that, to get into the question of what is good for an individual patient, I am not sure how much the Federal Government should get into it and through what methods.

Senator NELSON. It isn't only the question, really of ineffective drugs; the question is the one of expense. There is a tremendous difference be-

tween the cost of the same compounds marketed under different names. What do you do about that? Is the taxpayer going to pay $20 a hundred for a tablet because the doctor prescribes it by a brand name although it may be available at a dollar under a different name, brand or generic?

Mr. SEGGEL. As Mr. Older indicated, they are attempting through their intermediaries to exercise controls on those costs. And there are studies going on as to ways and means by which we can improve the process.

Do you want to add to that, Mr. Older?

Mr. OLDER. No, except that I would like to say that, as you indicated, a good hospital has a formulary. There is certainly no difference in the kind of drugs that are prescribed for medicare patients or for other patients. We have a specific requirement in the medicare law that we are not to interfere with the practice of medicine. And we would have difficulty certainly in saying to a doctor that he should not have prescribed any particular drug or medicine. But this can be said by committees in the hospital where the doctor gets the criticism or the suggestions from his peers.

Senator NELSON. Well, when the Defense Supply Agency purchases drugs it asks for a bid under a generic name. And all you have to do is look at the difference between what the Defense Supply Agency will pay for a product and what the same company is selling to the retail pharmacist for 50 times or 100 times as much as Defense Supply Agency pays.

In one case they are in a competitive bid situation, and in the other place they are being prescribed by brand name. Perhaps you may be worried about the charge that you would be interfering with the practice of medicine. But don't forget that you are interfering with the taxpayer by permitting the use of a very expensive product when its equivalent is in the marketplace, and there is no doubt about its equivalency, aren't you?

Mr. OLDER. I think our only attack there is our prudent buyer concept; would a prudent buyer pay $20 for it when he could buy it for a dollar? And that is something that our intermediaries consider in inquiring about costs in the hospital.

Senator NELSON. Are you taking specific drugs and checking the costs in this way?

Mr. OLDER. Yes, in certain cases. In our regional offices we have program validation teams that go in and see how the intermediary is doing and how the hospitals that they service are doing in implementing medicare rules. And part of this study is to see, for example, what the cost of a pharmacy department is. And in checking that we will take certain drugs and compare the costs paid by the hospital against the costs that they could have paid as a prudent buyer.

Now, it could be as a by-product of that question as to whether generic drugs should have been purchased instead of name brands. We don't have a requirement, however, that says specifically that you have to buy generic drugs.

Senator NELSON. No, I don't think anybody is suggesting that. But you should look at the bids that are made to New York City, the Defense Supply Agency, the State of Illinois, and the State of California, and identify the bidders.

I have referred to the case of prednisone a number of times because the "Medical Letter" reviewed it. A brand name company offered it to New York City at $1.20 a hundred but lost the bid to a company that bid 45 cents a hundred. The same company that bid the $1.20 a hundred to New York City was selling to the pharmacist across the street at $17.90 a hundred on the same day by brand name.

It was being prescribed by brand name because the doctor was used to that name. And so you have that company charging the druggist $17.90 a hundred, with the patient paying $30 to $35 a hundred, while that same company is offering to sell in open competition the same drug, the same brand name, not at $17.90 a hundred, but at $1.20 a hundred. The question is, should the taxpayers be paying $17.90 a hundred, when the same firm is trying to sell it at $1.20 at competitive bids to the city of New York? This is the kind of problem we are going to confront constantly as we start expanding our expenditure of public moneys in this field. A billion and a half dollars is a lot of money for drugs. And that is just the beginning, it won't be long before we will be spending $3 billion in medical care programs paid for by the Federal Government.

But the taxpayer isn't going to stand for the idea of spending four, five, and 10 times as much for a drug than the equivalent which is available to the Defense Supply Agency on competitive bid, just because a brand name identification moves the doctor to write that prescription in that way.

I don't think the taxpayer is going to stand for that very long. It raises a big problem. I don't see that it is easy to answer. But it is going to have to be answered at some stage.

With respect to Darvon, all the testimony—unrefuted—is that it is not a drug of choice. It is a mild analgesic. The Defense Department was spending about $4.5 million when it could have bought aspirin for less than $180,000, at a saving of over $4 million. What had developed was that at the military hospitals this drug was being widely prescribed routinely, although everybody agreed that it wasn't the drug of choice.

Well, should the taxpayer be paying more than $4 million extra just because it is preferred by a physician using public moneys at a military hospital contrary to the unanimous opinion of the clinical experts on this drug? That is the question.

So then when you say to the Defense Department, well, certainly in a military situation you can establish a formulary, they are very worried about that, because that makes the physician mad at the local level. If you can't have a rational system of prescribing drugs in the military services, if you can't do it there you can't do it any place else.

I don't have any more questions.

Mr. GORDON. Why can't you issue a formulary, a list of drugs, with respect to Medicaid, and state that we will reimburse for these drugs, and none other? What is wrong with that?

Mr. SEGGEL. Mr. Richter?

Mr. RICHTER. We, of course, don't have such a requirement now.

Mr. GORDON. In a way you have that requirement, because that memorandum issued by the Surgeon General states that we are not going to reimburse for certain types of drugs.

Now, that is a negative way of putting it. Why not put it in a positive way, we will reimburse for these drugs and none other?

Mr. SEGGEL. I think it is a matter of the way you administer that program, to what extent the Federal Government will lay down those kinds of requirements. As I say, we are putting our bets on the regulatory process, and the process of continuing education, if you want to call it that, when you are getting to the practitioners as well as the people at large. And we hope to get a lot of mileage out of that, although the Senator is somewhat skeptical.

Mr. GORDON. Perhaps you can do it by buying on a central basis, that is, you order drugs by direct purchase. You don't even have to touch the drugs at all. You order it from the company, the company ships directly to the drug stores, and the Government pays the drug firm. The drug store dispenses the drug. The Government receives the bill from the druggist for his services.

Mr. SEGGEL. It would obviously involve some additional administrative machinery. I believe there is a study going on on that.

Mr. BRANDS. This particular method was discussed. I don't think that it has gone much further than the discussion stage. I think you would run into problems with this because your community practitioner would have to keep separate stock. If he had Government stock on hand for his medicaid patients or medicare patients, and then he had stock for his private patients, there would be a lot of confusion because of switching back and forth. In addition, it would be terribly hard on the practitioner. What the savings would be, I do not know. But I think that it would be most difficult for all concerned to administer by central purchasing and distribution.

Mr. GORDON. Yes, but it is also difficult to be spending one and a half billion dollars on drugs when we don't even know what we are spending for and what we are paying for it.

Mr. BRANDS. I agree with you. But I think a study like the San Joaquin study may develop a method whereby we can keep our finger on what is going on better than we can right now. I think that we are looking for waste and methods to improve the system and keep track of what is going on.

Senator NELSON. Just so there wouldn't be any misunderstanding, I don't claim to have the answer, and suggest that if you have the answer we would be glad to take it. I simply say that it is becoming a very serious problem as to which we have to find some sensible, reasonable answer.

If every institution at least had a good formulary that was scientifically designed, and an internal program of enforcement of that formulary, basically your problem would be solved, and it is handled at the local level. As you know, lots of institutions do have that kind of a system, and more of them are developing it. And from an institutional standpoint perhaps that problem will be resolved at some stage at least in general hospitals. I don't know how you do it in, say, in nursing homes, where you don't have the same critical collection of scientific expertise to develop the formulary.

Thank you very much.

You will submit those statistics on the drugs?

Dr. FINKEL. Yes.

Senator NELSON. Our next witness is Mr. James Campbell, Assistant Administrator for Program and Management Services, Agency for International Development.

Mr. Campbell, the committee welcomes you today. You have some associates with you.

Mr. CAMPBELL. Yes.

Senator NELSON. Would you identify your associates for the reporter so that we will have the record straight.

STATEMENT OF JAMES F. CAMPBELL, ASSISTANT ADMINISTRATOR FOR PROGRAM AND MANAGEMENT SERVICES, AGENCY FOR INTERNATIONAL DEVELOPMENT; ACCOMPANIED BY LESLIE GRANT, DEPUTY GENERAL COUNSEL; SEYMOUR BARONDES, CHIEF, COMMODITY ELIGIBILITY AND PRICE BRANCH, OFFICE OF CONTROLLER; AND RAYMOND TORREY, CHIEF, INDUSTRIAL RESOURCE DIVISION, OFFICE OF PROCUREMENT

Mr. CAMPBELL. Yes, sir.

I have with me Mr. Leslie Grant, Deputy General Counsel, Mr. Seymour Barondes, Chief of the Commodity Eligibility and Price Branch, Office of our Controller; and Mr. Raymond Torrey, Chief, Industrial Resource Division, Office of Procurement.

Senator NELSON. Your statement will be printed in full in the record. You may present it as you desire.

Mr. CAMPBELL. Thank you, Mr. Chairman.

Senator NELSON. The Agency appeared before in 1970, about a year and a half ago.

Mr. CAMPBELL. Yes, sir.

Thank you, Mr. Chairman. We welcome this opportunity to discuss the AID pharmaceutical program.

Dr. Hannah, the Administrator of AID, has asked me to testify on his behalf. About a year and a half ago I took over the responsibilities formerly held by Governor Lane Dwinell, who previously appeared before your committee on the same subject.

In our appearance before this committee in August 1970 we described, in general terms, the regulations governing the procurement and pricing of commodities financed under the various programs administered by the Agency, with particular reference to pharmaceuticals. As a result of the discussion at that hearing and our recognition of the peculiar characteristics of the pharmaceutical industry, the Agency promulgated, on December 31, 1970, special, more stringent restrictions that pharmaceutical suppliers must meet for their products to be eligible for AID financing.

At a hearing before the committee in February 1971, we described, in some detail, these new standards. We stated our policy aim to you at that hearing as follows:

> Formulation of the new standards with their more stringent criteria enables us to continue to finance pharmaceuticals with some assurance that the interests of all parties in procuring essential and suitable items at reasonable costs are safeguarded.

We believe that the experience since December 31, 1970, has fulfilled our expectations, and hopefully yours. AID has continued to

make funds available to developing countries for financing private sector purchases of vitally needed, safe, and efficacious bulk pharmaceuticals at prices which in general compare favorably with prices paid by buyers in sales not financed by AID.

I should like to recapitulate briefly the four special pricing standards that pharmaceuticals must meet to qualify for AID financing. Prices paid to U.S. suppliers are limited to the lowest price resulting from any of the following:

(1) the world market prices plus 10 percent;

(2) the lowest price at which the generic product is available from the United States;

(3) the lower price at which another product can be obtained when experts indicate the lower priced product to be substantially equivalent; and

(4) the lowest price charged in any export sale by the supplier for the same product. Under this latter standard a supplier may exclude the lowest priced 5 percent of his sales volume in his calculation of his lowest price.

On April 5, 1971, rule (4) was modified to make it inapplicable to sales by a supplier of a nonpatented item to a buyer not affiliated with the seller. This change was made so that suppliers could sell nonpatented items at world market prices despite the fact they may have made more than 5 percent of their sales of the item to affiliates at prices below world market prices.

Under Section 604(f) of the Foreign Assistance Act of 1961, as amended, AID is required to approve each proposed transaction in writing as eligible for AID financing. This is the mechanism by which we have enforced the new standards on a preaudit basis. In our judgment these price standards have proved effective. As you know, under rule (3), the Agency made 16 high-priced drugs ineligible for financing. None of these drugs have been financed since December 31, 1970. We are also on the alert to see whether additional drugs should be added to the list of 16.

Mr. GORDON. Would you name those drugs, please?

Mr. CAMPBELL. I have a list of them which I will be very happy to give to you. I can submit it to you now.

Senator NELSON. It will be submitted for the record.[1]

Mr. CAMPBELL. Rule (1) which relates to world market prices on which you have asked us to comment, has been effective. Suppliers have reduced their prices to meet the requirements of this rule. Where they have refused to do so, it has been our policy not to make AID funds available.

Mr. GORDON. Can you give some examples of that?

Mr. CAMPBELL. Yes, sir.

Senator NELSON. You have compared the prices?

Mr. CAMPBELL. I have prepared a list of examples for you of price reductions achieved under the new rules and I would like to make that part of the record.

Senator NELSON. And that shows the prices that they were charging prior to the new rules, and the prices since?

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[1] See pp. 8751–8752.

Mr. CAMPBELL. Yes, sir, the prices previously financed or requested and the prices approved under the special rules, two columns.

Senator NELSON. Thank you. That will be admitted in the record at the appropriate place.

Mr. CAMPBELL. Most pharmaceutical suppliers have cooperated with AID in adjusting their prices to comply with restrictions imposed by the special rules. In a number of instances, suppliers have submitted applications for approval of AID financing for transactions involving prices higher than permitted by the rules. When these applications have been disapproved, suppliers have submitted amended applications with prices which met our requirements.

Senator NELSON. Do you have examples of that?

Mr. CAMPBELL. Yes. They are included in the examples that we have just submitted.

The Agency has accomplished savings of about $100,000 in these transactions. Much of the savings accomplished, however, cannot be measured because most suppliers, cognizant of our rules have submitted transactions for AID approval which in the first instance met our price standards.

The total FAS value of AID-financed pharmaceuticals in our commercial import program in calendar year 1971, was $8.8 million. Of this amount, $4.2 million were for drugs going to Pakistan, $1.9 million for India, $1 million to Africa, and $1.7 million for drugs going to all other countries. As a consequence of the hostilities between India and Pakistan, all AID commodity financing was suspended for these two countries as of December 6, 1971. This has brought commercial imports of pharmaceuticals under the AID program, at the present time, to a virtual halt. In addition to the financing of unfinished pharmaceuticals in the commercial import program, AID also provides funds for family planning projects and for our missions or importing governments who receive their requirements under formal bidding or through procurement by the Department of Defense or GSA.

In 1971, we financed a wide range of pharmaceuticals with particular emphasis on anti-infectives, vitamins and serums, toxoids and vaccines. The items which we financed within these categories are generally items in which U.S. suppliers are known to be competitive in world markets. Vitamins are a good example of our strong competitive position in world markets.

A number of large pharmaceutical manufacturers have dropped out of the AID program because of the special restrictive rules. These are companies whose major activity in the AID program was in the sale of one or more of the high-priced 16 drugs no longer eligible. None of these companies indicated a willingness to reduce the prices of these high priced drugs to a level that would be acceptable to AID.

Mr. GORDON. Can you tell us more about some of these companies that did not indicate a willingness to reduce the prices and they dropped out of the program? Could you give us a list of them for the record?

Mr. CAMPBELL. We can either name them now or submit the list. There are very few.

Mr. GORDON. Go ahead.

Mr. BARONDES. Bristol Myers is one company that has dropped out, and Squibb is another. Schering Corp. is another. Abbott Laboratories has virtually dropped out. Merck and Co. has dropped out except for vaccines. One or two others have also dropped out.

Mr. GORDON. Thank you.

Mr. CAMPBELL. Pharmaceutical suppliers are still subject to the general pricing rules applicable to all AID financed commodity exports. Basically, these rules provide that a U.S. supplier may not charge more than the prevailing market price in comparable export sales from the United States nor may he charge more than the price he generally charges in his own comparable export sales from the United States. Where we determine that a supplier has violated these rules, it is our customary procedure to secure refund of the overcharges from the supplier.

We previously submitted to the committee details on refunds received by AID. In addition to the $2,000,059 that had been refunded as of July 31, 1970, 12 pharmaceutical companies have since that time paid or agreed to pay refunds totaling $950,357.39. Two claims totalling $117,914.47 have been referred to the Department of Justice for collection since July 31, 1970.

Senator NELSON. When you say "where we determined that a supplier has violated these rules," you mean since the new rules were instituted, you are talking about cases of violation since then?

Mr. CAMPBELL. No, sir; I have reference to the general rule that we have, not the new rules that apply specifically to pharmaceuticals.

Senator NELSON. What is the general rule?

Mr. CAMPBELL. This is the rule that a U.S. supplier may not charge more than the prevailing market price in comparable export sales from the United States, or may charge more than the price he generally charges in his own comparable export sales from the United States.

Senator NELSON. But that rule wasn't in effect a year and a half ago when you testified, was it?

Mr. CAMPBELL. Yes; it was, it had been in effect, sir. This is a general rule for procurement by AID. It has been in effect for many years.

Senator NELSON. I thought the figures that we had at that time—I don't have them before me—indicated a large number of cases where they were charging much more than the world market prices.

Mr. CAMPBELL. Mr. Barondes?

Mr. BARONDES. Under the new rules where we hold suppliers to approximately the world market price there should not be any claims, because transactions will not be approved for AID financing if proposed prices are higher than world market prices. So, we won't have any claims under the new rules. But most of these claims represent transactions that took place under the old rule where pharmaceutical suppliers charged even higher prices than those allowed under the more lenient rules that are generally applicable.

Senator NELSON. These are refunds to whom?

Mr. BARONDES. The refunds are payable to AID.

Senator NELSON. Are those AID expenditures, or were these foreign government expenditures?

Mr. BARONDES. They are AID disbursements under loans made to these various countries. Generally when the refunds are received by AID, the money is made available again to those countries who put up the local currency to bring in these pharmaceuticals.

Mr. CAMPBELL. In other words, the money is eventually returned to the country to make a purchase.

Mr. GORDON. How many cases of overcharge did you have last year? You don't have to tell us now. You can submit it for the record, giving the names of the firms.

Mr. BARONDES. We did submit, I think, last time a list of all companies against whom we had claims where we either collected, or we had not yet collected.

Mr. CAMPBELL. We have a list here that we can submit for the record—it is complete—of the overcharges.

The list of claims previously referred to the Department of Justice is already in the record. Two claims totaling $343,821.83 are unpaid. Discussions between AID and the two suppliers involved are continuing.

Since pharmaceutical prices charged by AID suppliers must meet both the pricing criteria applicable to all AID financed commodities and the more restrictive criteria of the special pharmaceutical rules which are applied on a preaudit basis, we anticipate that no further refund claims will be required in this product area.

In making our determinations as to the appropriate prices for pharmaceuticals under the current standards we utilize all sources of information available to us. A prime source of information is the pharmaceutical industry itself. Other sources of information are price lists of foreign suppliers, actual export sales from the United States and other countries in which AID restrictions limiting the source of supply do not apply.

No other U.S. Government agency has a concern comparable to that of AID with export prices of unfinished drugs. Price information from other agencies usually does not reflect commercial export prices of drugs and is therefore not particularly helpful to AID. AID has cooperated with other agencies seeking export price information, particularly HEW. We believe that AID financed prices compare favorably with prices in purchases by other agencies.

You also have asked that we describe the actions taken in regard to pronouncements by the FDA and other medical experts on the lack of merit on many drugs.

AID does not finance drugs which the U.S. Food and Drug Administration has found to be either unsafe or ineffective.

In February 1971, we discussed the FDA's authority to approve drugs on the basis of both safety and effectiveness. In exercising this authority, FDA has established four classifications for the drugs it evaluated:

(1) Drugs classified as "effective" are those which are supported by substantial evidence of effectiveness;

(2) Drugs classified as "probably effective" are those which are supported by some evidence but additional evidence is required before they can legally be classified as "effective";

(3) Drugs classified as "possibly effective" are those which are supported by little evidence of effectiveness; and finally,

(4) Drugs classified as "ineffective" are those drugs which lack acceptable evidence of effectiveness.

Under AID policy, pharmaceuticals in finished dosage form are normally eligible for financing only for use in specific projects in the AID receiving countries. Only unfinished pharmaceuticals, or ingredients,

are normally eligible as commercial imports financed with AID program funds. This requires that we apply the FDA rulings in two different situations:

First, as they apply to drugs in finished dosage forms, and second, as they apply to ingredients which we finance as commercial imports for processing into finished products after their receipt by the importer in the receiving country.

With respect to the finished products purchased by or for other governments for specific projects, all "ineffective" drugs are ineligible for AID financing including any new drugs added to the "ineffective" list by FDA.

The application of FDA rulings to the eligibility of ingredients is complicated by the fact that FDA reviews finished products only. This means that the lists of finished products must be examined to determine how they affect the ingredients which AID finances. Since a great many finished products consist of more than one active ingredient, we reviewed the FDA lists to identify the ingredients which were found unacceptable by FDA in any finished dosage form or combination.

These ingredients have been added to our list of products which are ineligible as commercial imports. This precaution assures us that drug ingredients found ineffective in any finished product are ineligible for AID financing in either finished or unfinished form.

Because manufacturers of drugs classified as "possibly effective" are given a 6-month period in which to make them acceptable to FDA as "effective" or have them classified "ineffective" by the FDA, we do not make them ineligible until FDA has reached a final decision on them. We provide current lists of "possibly effective" drugs to our missions, and through them, to the importing governments for their use in selecting products best suited to their needs. In the commercial sector, AID has not financed items on the "possibly effective" list.

Mr. Chairman, this concludes my prepared statement. If you have any further questions on AID financing of pharmaceuticals, my associates and I will endeavor to answer them.

Senator NELSON. Can you explain that figure you gave earlier of saving $100,000 on page 4, "The Agency has accomplished savings of about $100,000 in these transactions," what do you mean by these transactions?

Mr. BARONDES. These are those transactions where the drug manufacturer has come in with a specific price, and we have rejected that price as being in excess of that permitted under the guidelines. They have then come in with a new application at an acceptable price. So there are these few transactions where we can actually measure the precise dollar savings. And that comes to a hundred thousand. We think more often than not the manufacturers, knowing that their prices have to be in line with the new standards, have come in with acceptable prices.

Senator NELSON. So, your savings are much greater than that.

Mr. BARONDES. Oh, yes.

Senator NELSON. Have you made any computation as to what savings have been based upon the new practices vis-a-vis previous years when much higher prices were being paid?

Mr. BARONDES. Well, we would estimate that that hundred thousand could be at least tripled to get a more realistic figure. In addition to that, of course, there are the 16 expensive drugs financed in previous

years that have now been made ineligible. In previous years we paid about a million dollars a year for these drugs.

To the extent that we don't finance those expensive drugs at all and the countries can buy either cheaper drugs or something else which may be of greater value vis-a-vis the price paid, you could say the million dollars is also a saving. So, we estimate overall about $1.3 to $1.5 million in savings, which is fairly substantial percentage of a rather small program.

Senator NELSON. Is this an annual saving you are talking about?

Mr. BARONDES. This would be an annual savings, yes.

Senator NELSON. Thank you very much, gentlemen. We appreciate your taking the time to come here.

Mr. CAMPBELL. Thank you very much, sir.

(The information follows:)

Sixteen high-priced drugs ineligible for A.I.D. financing

Generic name	Brand name
Chlortetracycline.	Aureomycin.
Doxycycline.	Vibramycin.
Methacycline HCL.	Rondomycin.
Demethylchlortetracycline.	Ledermycin, Declomycin.
Rolitetracycline.	Bristacin, Syntetrin, Velacycline.
Oxytetracycline.	Terramycin.
Chlorcyclizine.	Histantine.
Cyproheptadine HCL.	Periactin.
Dexchlorpheniramine Maleate.	Polaramine.
Triamcinolone.	Aristocort, Ledercort, Kenacort.
Dexamethasone.	Decadron.
Paramethasone.	Haldrone.
Betamethasone.	Celestone, Valisone.
Methylprednisolone.	Medaprin, Medrol.
Propoxyphene.	Darvon.
Ethoheptazine.	Zactane, Zantirin, Equagesic.

DETAIL OF SIGNIFICANT EXAMPLES OF REDUCED PRICES UNDER AID'S SPECIAL RULES AS COMPARED WITH PRICES REQUESTED BY SUPPLIERS OR PREVIOUSLY FINANCED BY AID

Supplier and product	Prices previously financed or requested per kilo	Prices approved under special rules per kilo
Wyeth Labs:		
Bicillin All-Purpose	$160.00	$39.90
Indochlorohydroxyquinolone	23.10	10.00
White Cross Labs: Phenacetin	2.58	1.60
U.S.V. Pharmaceuitcals: Inositol NF	13.55	11.45
Sandoz-Wander:		
Pheniramine Maleate	40.80	30.00
Phenobarbitol	9.50	7.92
A. H. Robins: Methocarbamol	24.22	14.00
American Cyanamid: Ethambutol	100.00	88.00
Eli Lilly: Erythromycin Estolate	150.00	110.00
Lakeside Labs:		
Mepenzolate (Cantil)	350.00	285.00
Pipenzolate Bromide	1,130.00	700.00
S. B. Penick: Neomycin Sulfate	35.00	32.75
Abbott Labs: Erythromycin Ethylsuccimate	253.00	178.50
E. R. Squibb: Nystatin	[1] 51.00	[1] 33.00
Cyanamid: Acetazolamide	53.00	17.00
Warner Lambert: Methenamine Mandelate	4.09	2.93
Upjohn: Sulfamethizole	17.05	[2] 12.00
Cyanamid: Sulfamethoxypyridine	35.25	19.78
Schering: Chlorpheniramine Maleate	100.00	[2] 32.40
Cyanamid:		
Tridihexethyl Chloride	480.00	130.00
Trihexyphenidyl	1,700.00	303.00

[1] Per BOU.
[2] Price financed by another company.

REFUND CLAIMS ASSERTED BY A.I.D. AGAINST PHARMACEUTICAL SUPPLIERS

SUPPLEMENT TO CLAIMS INFORMATION FURNISHED TO SENATE SUBCOMMITTEE ON MONOPOLY ON JULY 31, 1970—AS OF MAY 31, 1970

TABLE I.—CLAIMS ON WHICH REFUNDS HAVE BEEN RECEIVED

Supplier	Date of claim	Amount of overcharge
Alcon Laboratories	June 9, 1970	$2,355.36
American Hoechst	Sept. 28, 1970	33,598.15
F & S International Ltd	Apr. 21, 1970	40,000.00
Eli Lilly	Apr. 22, 1971	221,366.39
Merck & Co., Inc	Mar. 24, 1971	63,688.80
	May 20, 1970	59,535.00
	May 20, 1970	9,336.00
Merck, Sharp & Dohme (I.A.)	Mar. 24, 1971	112,878.00
	May 20, 1970	179,654.09
	May 20, 1970	23,769.00
Parke-Davis	June 1, 1971	1,050.00
	Apr. 5, 1971	17,740.37
E. R. Squibb & Sons	Dec. 17, 1971	47,413.21
Upjohn Inter American	Apr. 20, 1971	[1] 108,665.70
U.S.V. Pharmaceutical Co	Apr. 1, 1971	855.00
Bristol-Meyers	Apr. 6, 1972	[2] 28,452.32
Total (12 companies) (16 claims)		950,357.39

[1] Settlement provides for deferred payment of $71,977.42 portion of this amount during 1972.
[2] Refund agreed to.

TABLE II.—CLAIMS REFERRED TO THE DEPARTMENT OF JUSTICE

Supplier	Date of claim	Amount of overcharge
Amfre-Grant, Inc	Apr. 5, 1971	$94,507.21
E. Tosse & Co	Mar. 9, 1970	23,407.26
Total (2 companies)		117,914.47

TABLE III.—CURRENT CLAIMS UNPAID AS OF JUNE 20, 1972

Supplier	Date of alaim	Amount of overcharge
American Cyanamid Co	Dec 8, 1971	$125,248.96
Wyeth Laboratories	July 1, 1970	218,572.87
Total (2 companies)		343.821.83

(Whereupon, at 12:15 p.m., the committee adjourned, subject to call of the Chair.)

APPENDIXES

APPENDIX I

EXHIBITS PROVIDED BY THE FOOD AND DRUG ADMINISTRATION

STATEMENT

BY

CHARLES C. EDWARDS, M.D.

COMMISSIONER OF FOOD AND DRUGS

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE

THE

SUBCOMMITTEE ON MONOPOLY

SENATE SELECT COMMITTEE ON SMALL BUSINESS

MAY 9, 1972

Mr. Chairman and Members of the Subcommittee:

We appreciate the opportunity to discuss with this Committee today some of the problems in drugs and drug use in this country, to discuss some of the reasons for the existence of these problems, and to describe for you the progress we have made over the past two years toward their resolution. We will also, as requested, review for you the findings of the Drug Efficacy Study, the impact it has made on therapeutics in this country and the present status of our implementation programs.

Before discussing the Drug Efficacy Study and its effects on therapeutics, it might be helpful to review with you some general aspects of drug use and some current problems we see in therapeutics in this country.

There are currently approximately 35,000 prescription drug products and several hundred thousand OTC drug products on the American market.

Each year a multibillion dollar effort is made to market, promote, and sell these products. In some OTC products approximately 30 percent of receipt of sales is spent in promotion and in the prescription drug area expenditures on promotion approach in magnitude those on research. Despite the contention that advertising and promotion is educational, most of the drug promotion we see is designed primarily to sell, to motivate the physician to prescribe and the consumer to buy.

In part, due to the influences of such promotional efforts these drugs are being increasingly prescribed and such use is increasing rapidly. The American public is currently receiving over two billion prescriptions per year and it is estimated that within four to five years this may increase by 50 percent to three billion prescriptions per year. In no area is this increase more dramatically evident than in the case of psychotropic drugs where in 1969 over one billion doses of amphetamines and two and one-half billion doses of barbiturates were used. The magnitude of other psychoactive drug use is reflected by the fact that some five to six billion doses were distributed in 1969 representing a 65 percent increase in the use of these drugs over a four year period.

We have a rapidly growing, frequently troublesome, occasionally tragic, and to a large extent needless and avoidable problem on our hands in the misuse of drugs in America.

Since most physicians want to serve their patients well and do what is best for them it seems reasonable to assume that where poor therapeutics is being practiced it is at least in part due to poor communication to the physician of the information he needs to do a better job.

If the physician had balanced information, honestly pointing out the limitations and actions of a drug, its beneficial and adverse effects and when it should or should not be given, he would have the information necessary to make the most rational therapeutic decisions. Too often at present, this needed information is not readily available to him.

Since drugs are being massively prescribed and since there is risk as well as benefit inherent in their use it is imperative that the profession and the public have available the information necessary for their rational use so that the greatest possible benefit can be attained. Adequate communication of such information is vital.

A brief review of how physicians currently obtain drug information will help us understand why some of our current problems came about and what must be done to correct them. The practicing physician is currently communicated with in six major ways: Through detail men, advertising of the pharmaceutical industry either in journals or through direct mail, medical journal articles, colleagues, medical meetings and the labeling of the drugs he uses.

A number of recent studies suggest that most of the physicians canvassed had obtained much of their information about a new drug from drug manufacturers and their representatives whose interest understandably is to make the doctor use it. Other recent studies indicate that it is very difficult for detail men, who are salaried and sometimes paid commissions to sell a product, to be sources of truly balanced and objective information on drugs which the practicing physician needs to make intelligent therapeutic decisions on his patients' behalf. It must be stated at this point however that a number of firms are engaged in major efforts to improve detailing with balanced presentations.

Approximately $500 million a year are spent in prescription drug promotion. The large number of drugs marketed, the conflicting claims that each one is better than the others, the emphasis on brand names, the rapid introduction of new products that are always said to be better than the old ones, extensive detailing and the sheer bulk of advertisements in the mails, the media and in the medical journals -- all combine to give the doctor and the public a sense of frustration and confusion.

Other sources of drug information which are made available to the physician can also be improved. These include the scientific evidence for drug efficacy and the labeling information on the drugs he uses. Drug labeling is especially important since it sets the legal limits for drug promotion and advertising. The final report of the Drug Efficacy Study addresses itself to an appraisal of both and here I quote from the report. "The Drug Efficacy Panels expressed concern and surprise about the generally poor quality of the evidence of efficacy of the drugs reviewed and the poor quality also of the labeling of those drugs." The panels found that there was little convincing scientific evidence to support many of the cited indications for use of drugs that are currently in good standing in medical practice and criticized the labeling of about two-thirds of the drugs they evaluated as failing in their primary purpose of providing the physician and the pharmacist with balanced authoritative and objective guides to prescribing or dispensing the drugs in question.

Thus, too much of the "communication" currently being beamed to the physician is either scientifically inadequate, lacks fair balance, is incomplete, inaccurate, and occasionally misleading. Physicians are the target of an over $500 million effort to sell them something. This amounts to an expenditure of approximately $4,000/physician/year for drug promotion. Over 35,000 prescription drug products, most with different trade names are clamoring for his attention. How can the physician be expected to know these drugs or to know that the several hundred antihistamines, the many coronary vasodilators, adreno-corticoids, tetracyclines, anticholinergics, and thiazide diuretics, are basically the same with little or no significant advantage one over the other. After all no one manufacturer could reasonably be expected to tell him this. This present "communication overkill" of today with its resultant confusion is exactly what the already overburdened physician does not need and it certainly does not serve the public.

What can be done to improve this situation? Before the situation can be remedied, a number of preliminary steps must be completed:

1. The physician must be made aware of the extent of present problems which exist both in therapeutics and in the communications he receives.

With the publication of the FDA Drug Bulletin, beginning in July 1971, the Food and Drug Administration launched a new and, we believe, an effective means of communicating a variety of types of drug information to over 600,000 physicians, dentists and other health professionals. The Bulletin is being mailed to physicians on a periodic and continuing basis. The Bulletin is being used to explain certain policies, to announce our approval of new drugs for marketing as well as our approval of new uses of previously marketed drugs, to relate the questionable effectiveness or ineffectiveness of drugs, to caution about newly recognized hazards of "old" drugs, or to warn against subpotency of drugs. We are submitting a copy of each Bulletin for the record. Of course, we will be pleased to answer any questions concerning them.

2. More understanding is needed of the problems inherent in drug evaluation. Summaries of the information on which a judgment was made by this agency to approve a drug for marketing should be available and used by physicians. As you know, the Bureau of Drugs is the world's largest repository of original drug information. The communication of this information to the medical profession can help improve therapeutics and also help eliminate wasteful duplication of costly scientific research. Our recent proposal on Freedom of Information will

help bring about needed access to the information in our files without taking unfair advantage of manufacturers or reducing incentives for future research.

3. We must study much more thoroughly how a physician can be reached and assisted to use drug information in order to build the most effective communication system beamed to him. We have a number of studies underway which will help us delineate this process.

4. We need to establish and make available to the physician a source of objective, balanced, accurate, nonpromotional timely information which is regularly and continually available to him and designed especially with the interests of himself and his patient in mind. This must include any new information which becomes available on newly discovered, beneficial, or adverse effects from marketed drugs. To meet this need, we are now developing plans for a National Drug Experience Reporting System which will provide information on adverse reactions observed by physicians, on the epidemiology of drug usage, on intoxications and drug abuse, and on interactions observed during the intensive monitoring of selective groups of in-patients and out-patients. This approach will permit more careful monitoring of new drugs during the post-marketing phase, promote identification of rare

adverse effects more rapidly, and should encourage more careful drug use by physicians and patients. It will also place FDA in a position to provide a valuable consultative service to physicians and other agencies of the Federal Government.

We are also calling on industry to join in our efforts to gather and make available this kind of information to the practicing medical community.

In the meantime, a number of other steps are being taken:

1. Ineffective drugs and formulations which cannot be rationally used are being removed from the market or reformulated. Only those drugs for which scientifically adequate evidence of efficacy is available will remain.

2. Labeling is being improved and those drugs remaining will be labeled simply but accurately with a fair balance of information. In a recent speech to the Pharmaceutical Manufacturers Association, I stated that ideally, the package insert should tell the physician in the fewest possible well organized words what the most knowledgeable expert, if consulted, would tell him about that drug--<u>When</u>, <u>Why</u>, and <u>How</u> to use it and <u>What</u> result he may reasonably expect. This information will reflect fair balance from the <u>scientific</u> point of view, not the commercial and not the regulatory. Let me be more specific; it is wrong

to allow material in the package insert merely for the purpose of promotion rather than information. It is equally wrong to delete essential facts simply because they provide a basis for promotion. It is wrong to overstate the efficacy of a drug or to be so vague and general about documented indications for its use as to encourage improper use. It is equally wrong to make it read as though a rarely reported side effect is common.

I firmly believe that the sole purpose of package literature is to inform the physician. It is, therefore, my hope that we will be able to effect widespread revision of package literature, well organized, easily read and understood, with essential information in fair balance for the physician.

3. Where appropriate, class labeling will be employed for like drugs to avoid confusion on the part of the physician. This can be of significant aid to him in sorting out the thousands of drugs available on the market. Many of the antihistamines, anticholinergics, diuretics, antibiotics, analgesics, and corticosteroids could fall into such class labeling and some are already so labeled.

4. We are hoping the medical literature will be improved with less duplication of previously published material and with more reports of adequate and well-controlled clinical trials which have been carefully assessed by editorial boards before publication.

5. We are working to get true balance or full disclosure in all medical advertising so that this $500 million effort becomes primarily educational, and accurately and fully presents a drug's advantages and disadvantages.

6. Detailing, as a part of advertising, will also have to achieve true balance and full disclosure. It is realized that this will be difficult to achieve and to monitor but it must be done.

7. Finally, we are working to make the general public more knowledgeable and active in the area of drugs. They should be more adequately informed of the hazards as well as benefits inherent in drug use. The fully informed citizen would be unlikely to accept Chloromycetin for a cold or some other powerful and potentially hazardous agent for a minor complaint. Likewise, an adequately informed populace would be less likely to press a physician for drug therapy when his professional judgment led him to recommend against it.

In summary, the problems that currently exist are not the fault of any one group. Correction of the problems will require the combined efforts of all involved -- the Federal Government, the professional community, industry, and the public.

I would like to conclude with a report of the present status of the Drug Efficacy Study. Before doing so, as Commissioner I would like to publically commend the dedicated professional staff of the Bureau of Drugs who have worked so diligently to implement this very important study.

By July 1 of this year, we will have completed and published in the Federal Register our evaluation of all 3,000 drugs which were in the Drug Efficacy Study. During 1971, 142 drugs named in Federal Register announcements as "lacking substantial evidence of effectiveness," and 367 "related" drugs were effectively removed from trade channels, 64 by recall. To date, 452 ineffective drugs specifically covered by the publication of 102 final orders in the Federal Register are off the market. This has resulted in the removal from the market of 1473 additional related drugs. Of the 452 ineffective drugs specifically mentioned in the Federal Register statements, 338 were fixed combinations, and of the 1473 related drugs removed from the market, 1345 were fixed combinations.

In the months ahead, the drug industry will be carrying out, and the FDA will be assessing, the studies necessary on drugs which currently lack adequate evidence of efficacy. Drugs which are unable to provide adequate evidence of effectiveness will, as required by law, be removed from the

market. This has already been done on many fixed-dose combinations. In the months ahead, as the results of this study reach more elements of our society, there will be a major impact on the public, the medical profession, the drug industry, and Government. In the end, much that is good will come from this study to the ultimate benefit of the medical profession and the public. The panels of the NAS-NRC have clearly and objectively pointed out the problem that faces us in the drug area. One of the great strengths of the study is that it has been a constructive joint effort of the medical profession and the Federal Government.

Procedures set up by this administration will allow a fair and equitable resolution of these problems in the months ahead. No precipitant actions will be taken and whatever actions are taken will be guided by detailed and fair analysis of adequate scientific data.

A new and high standard has been established for establishing proof of drug efficacy and for the evaluation of combination drugs through our new regulations on adequate and well-controlled studies and our combination drug policy. This alone should be a major factor in improving therapeutics in this Country. In time, ineffective drugs and irrational formulations will be removed from the market.

The effective drugs remaining will be clearly and accurately labeled so that physicians will have available to them the balanced information they need for rational drug use. Where possible, this information will be derived from adequate and well-controlled clinical studies.

To fulfill our obligation to keep physicians fully informed about drug efficacy, we will require all drug labeling and advertising to disclose the efficacy ratings of the products involved while required studies are being done to determine their efficacy. We have also taken appropriate steps to keep other Federal and State agencies informed of our actions in the Drug Efficacy Study Implementation.

In the months ahead, a number of drugs will fall by the wayside and many others will establish the evidence of efficacy required by law. A massive project such as this cannot be completed without arousing some emotions. Our policy in this and all matters facing the agency is clear, "We do have an emotional commitment, a simple one; this is to take the emotion out of our work. We are not interested in any kind of confrontation, in political or bureaucratic victories; we are moving very swiftly toward relationships based not on crusades or rhetoric but on matters of equity and justice and effectiveness."

With the great deal of critically important work which lies ahead of this agency in the drug area, we recognize our responsibility to take all steps necessary to assure the soundness of our scientific judgments and the efficiency of our operations. To accomplish this, we have taken the following steps:

1. In the past two years, we have not only strengthened our own internal staff, but we have called upon the expertise of the medical and scientific community to assist us in strengthening our scientific reviews.

2. Today, a total of 260 experts serve on 26 Advisory Committees, and another 200 advisors will be added to this total as the over-the-counter (OTC) expert review panels are organized. In addition, the Bureau of Drugs expects to add five new advisory groups in the coming fiscal year. Just this past week, the first meeting of the National Drug Advisory Committee was held in Washington. This newly-formed group is intended to serve as the top policy drug advisory committee to the Food and Drug Administration.

3. We are taking a number of steps to eliminate the time, cost, and delay that may affect New Drug Applications. First, we have set up a Task Force to help detect any faults in our internal procedures; we have matched this in recent weeks with a major contract to conduct an extensive study of these same internal FDA procedures. With industry and with academic help, we are developing guidelines for clinical research. These guidelines will, we hope, assist individual investigators as well as industry to more clearly understand what FDA expects -- and to gain this understanding during the workup of a New Drug Application. We have this year established a pilot plan for joint Industry-FDA conferences at designated points, points during the investigational stage of new drugs and again prior to submission of New Drug Applications. The purpose is to speed the overall process by earlier understanding, better information, and, hopefully, fewer signal changes in mid-stream, and also to improve the overall quality of the scientific information generated about a drug.

4. We are planning new strategy for sorting out IND's to differentiate between individual physician research and complex commercial investigations. Both should benefit. We are tightening internal quality controls through mandatory 90-day review of all working NDA's. We are soliciting new ideas from industry, from academia, from professional societies and from within FDA through conferences such as that recently concluded at Airlie House near Washington.

5. We are asking major FDA Advisory Committees for ideas and review of criteria for judging efficacy; for example, the amphetamines. We have now completed the assignment of a statistician to every NDA review team to insure the statistical quality and completeness of every submission. This has major implications because it means still another specific check and balance for data quality. We are taking necessary steps to simplify as much as possible the approval of "me-too" drugs through the Abbreviated NDA procedures.

Let us sum up: We now have 10 years of invaluable experience under Kefauver-Harris. It is no exaggeration to say that this has been the most dramatic period of progress in the drug area in FDA's 66-year history. It has been a tough but useful period of on-the-job training for FDA and industry alike. Many problems remain but much progress has been made toward the goal of better drugs and better therapeutics for the American people.

DRUG BULLETIN

THE DRUG EFFICACY STUDY

FIXED COMBINATION PRESCRIPTION DRUGS

ORAL HYPOGLYCEMIC AGENTS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

June 23, 1971

Dear Colleague:

The Bureau of Drugs of the Food and Drug Administration is probably the worlds largest clearinghouse of drug information. One of our responsibilities is to make this important information available to practicing physicians.

As one means of fulfilling this responsibility, we are initiating a regular series of drug bulletins which we hope will be helpful by providing accurate, objective, timely drug information to you for use in your medical practice.

This first FDA DRUG BULLETIN is concerned with policy matters of great significance to physicians, dentists, pharmacists and other members of health professions. The Drug Efficacy Study conducted by the National Academy of Sciences represents a national audit of the scientific evidence presently available as testimony to the marketing claims of 80 percent of today's prescription drugs. The present issue also contains statements on the current status of fixed-ratio combination drugs, and oral hypoglycemic agents.

Future issues of FDA DRUG BULLETIN will contain a greater proportion of information about matters of direct clinical import. We hope to use this means to inform you about significant new drugs prior to their marketing and also bring to your attention new information about drugs which are already in use.

We want to be helpful to the health professions in any way we can and we welcome your comments and suggestions.

Yours very truly,

Henry E. Simmons, M.D., M.P.H.
Director
Bureau of Drugs

THE DRUG EFFICACY STUDY

Within the next 90 days, prescription labeling and promotional material on about 80% of currently prescribed drugs will display a rating of the drugs' efficacy for certain of the claimed indications.

The action is being taken by FDA in the belief that the prescribing physician must know the scientific status of a given drug's efficacy in order to exercise the best possible clinical judgment in choosing drugs for patients.

This section attempts to explain the aims and procedures of the National Academy of Sciences' Drug Efficacy Study (DESI) which led to this development.

BACKGROUND

The DESI program stems directly from requirements of the Federal Food, Drug, and Cosmetic Act. Beginning in 1938, this law required preclearance of new drugs by FDA for safety. The Drug Amendments of 1962 (Kefauver-Harris) required that effectiveness as well as safety of drugs be established prior to marketing. The amendment provided that this proof of efficacy be in the form of "substantial evidence." This evidence was defined by the Congress as ". . . adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have."

Therefore, since 1962, the FDA has reviewed all new drug applications for both safety and effectiveness. But the 1962 amendments also required that all drugs marketed between 1938 and 1962 and tested only for safety, now be evaluated for effectiveness as well.

Some 4,000 drug products fell into this category and efficacy evaluation for all of them obviously posed an enormous task.

To accomplish this task within a reasonable time, FDA went to the National Academy of Science for assistance. The Academy assembled 30 panels with some 200 medical and scientific specialists described in its 1969 report as "predominantly physicians with academic affiliations for the obvious reason that these best met the legal qualification of 'experts qualified by scientific training and experience to evaluate the effectiveness of the drug(s) involved.'"

The National Research Council — research arm of the National Academy of Sciences — developed guidelines for the study. In the course of its work, NRC consulted manufacturers, professional and scientific organizations and other interested parties.

The 30 study panels of the Academy considered information gathered from all these sources, including FDA files and the scientific literature. On the basis of this information, panel members were able to make informed judgments.

The panels classified each of approximately 16,000 therapeutic claims for the more than 4,000 drug formulations into the following categories:

Effective: substantial evidence of effectiveness;

Probably effective: additional evidence required to rate the drug "effective";

Possibly effective: while additional evidence for an "effective" rating might be forthcoming, as it stands there is little evidence of effectiveness, and in the absence of substantial evidence, the claim is considered inappropriate;

Ineffective: lack of substantial evidence of efficacy;

Ineffective as a fixed combination: even though one or more of the components might be effective if used alone, not acceptable in fixed dosage combination for reasons of safety or because of lack of evidence of contribution of each component to claimed effect;

Effective but: with an appropriate qualification. This difficult group is under reconsideration by NAS/NRC and FDA.

Each drug received a rating. FDA was given the first rating report in October 1967; the last report in May 1969.

SIGNIFICANCE TO THE PHYSICIAN

The Efficacy Study revealed that about 60% of all therapeutic claims reviewed lacked adequate evidence of efficacy under the law. Overall, the NAS experts reported a "deplorable situation" in the generally poor quality of labeling and of evidence submitted in support of efficacy claims.

Many efficacy presentations submitted by manufacturers consisted of reports of uncontrolled observations and testimonial-type endorsements. There was a "conspicuous" lack of substantial evidence based on well-controlled investigations by experienced investigators.

The panels specifically criticized the labeling of about two-thirds of the drugs they evaluated. They found too many package inserts to be "poorly organized, repetitive, out-of-date, evasive and promotionally oriented." The majority were found to fail in their purpose of providing the physician and the pharmacist with authoritative and objective guides to prescribing or dispensing the drugs in question. This point takes on added significance because official labeling sets the boundaries for permissible advertising and other promotion.

THE FDA RESPONSE

In each case, the FDA's conclusions, based on the NAS/NRC recommendations, are published in the *Federal Register,* a daily official journal of the Federal Government. As soon as the FDA judgment is published, manufacturers of drugs with claims rated less than effective have several options open to them short of product withdrawal. They may choose:

- to develop necessary scientific data to substantiate current claims;
- to eliminate or modify questionable claims, or
- to reformulate the product.

When the choice is to develop additional data, the manufacturers have six months for "possibly effective" claims and twelve months for "probably effective" claims. During these periods, manufacturers may request extension of time based on development of a satisfactory protocol for study of disputed claims. The drug may remain on the market in the interim if there are no questions of safety. FDA is well aware that the studies will take time and will not insist on unreasonable time limits in any case.

Overall, the Agency is determined to better meet the need to reach practicing physicians and other professionals with all pertinent information on what is being proposed and accomplished under the Drug Efficacy program. Furthermore, the law requires that the labeling of prescription drugs bear full disclosure of all material facts to the prescribing physician. On the basis of this double incentive, FDA is issuing regulations requiring that all labeling and all promotional material carry a prominently placed "box" characterizing the claims for any given drug which have been judged "probably" or "possibly" effective.

FDA recognizes that drugs of questioned efficacy will be available by prescription while evidence of effectiveness is still incomplete. Such a status will be temporary, and drugs in this category either will become "effective" as soon as appropriate evidence permits, or removed from the market if this evidence is not forthcoming.

CONCLUSION

The Drug Efficacy Study has been the most thorough review ever attempted of drugs available to the physician. When the study is fully implemented, the physician should be able to prescribe any marketed drug secure in the knowledge that its efficacy has been judged on the basis of acceptable scientific evidence.

FIXED COMBINATION PRESCRIPTION DRUGS

The Drug Efficacy Study focused attention on questions of efficacy peculiar to combination drug products. In its 1969 *Final Report to the FDA Commissioner,* the National Academy of Science stated:

> "It is a basic principle of medical practice that more than one drug should be administered for the treatment of a given condition only if the physician is persuaded that there is substantial reason to believe that each drug will make a positive contribution to the effect he seeks. Risks of adverse drug reasons should not be multiplied unless there be overriding benefit. Moreover, each drug should be given at the dose level that may be expected to make its optimal contribution to the total effect, taking into account the status of the individual patient and any synergistic or antagonistic effects that one drug may be known to have on the safety or efficacy of the other.
>
> "On these grounds, multiple therapy using fixed dose ratios determined by the manufacturer and not by the physician is, in general, poor practice."

This general opinion of combination drugs is shared by other expert bodies. The Council on Drugs of the American Medical Association in a letter accompanying the recent first edition of *AMA Drug Evaluations* says:

> "The effects of drugs are intrinsically so complex that it is generally advisable to administer multiple agents separately in order that the dosage and frequency of administration of the individual drugs may be varied in accordance with a patient's requirements. Therefore, most fixed-ratio combinations listed are not recommended. This reflects a long-standing policy of the Council."

FDA COMBINATION POLICY

The FDA is not opposed to combination drug products; it recognizes that many are safe and effective and provide important advantages to patient and physician.

For a combination to be approved under the law there must be substantial evidence that each active component contributes to the claimed effect of the product, a requirement since 1962. If this requirement is satisfied, two or more drugs may be combined in a single dosage form when, in good medical practice, they would be given concurrently and when putting them together in the same product in no way detracts from their safety and efficacy. Such a combination product should provide appropriate dosage for a significant patient population that can be defined in the labeling. A special case of this general rule is the addition of an ingredient that enhances the safety or effectiveness of the principal active component or minimizes its abuse potential.

ORAL HYPOGLYCEMIC AGENTS

SULFONYLUREAS

Following review of the findings of the University Group Diabetes Program (UGDP) on tolbutamide by FDA and several professional groups, FDA published last year* recommendations on the use of oral agents in the treatment of diabetes mellitus. The INDICATIONS AND WARNINGS section of the labeling of all sulfonylureas is now changed to read as follows:

INDICATIONS:

"Diet and reduction of excess weight are the

* FDA Current Drug Information, October 1970.

foundation of therapy of diabetes mellitus and when the disease is adequately controlled by these measures, no other therapy is indicated.

". . . . . (Name of Drug) . . . . . is indicated in the treatment of adult-onset, non-ketotic diabetes mellitus which cannot be adequately controlled by diet and reduction of excess weight alone and when, in the judgment of the physician, insulin treatment is not feasible."

WARNINGS:

". . . . . (Name of Drug) . . . . . has been shown to lower excess sugar in the blood when administered in appropriate dosage to selected diabetic patients; this finding constitutes the basis of its use in such patients. Because the adult-onset, non-ketotic diabetes population is the only group in which adequate studies have shown the utility of the drug in the management of the condition, the use of *(Name of Drug)* should be limited to these patients as described in the indications section above.

"Twelve university medical clinics comprising the University Group Diabetes Program conducted a long-term prospective study designed to evaluate the efficacy of hypoglycemic drugs in the prevention of vascular complications in adult patients with recently diagnosed non-insulin dependent diabetes.

"All patients received diet instructions and, in addition, were randomly assigned to different treatment schedules (fixed dosages of tolbutamide, fixed dosage of insulin, variable dosage of insulin, or placebo). At the end of an eight-year period, the death rates from cardiovascular disease were 12.7% or 26 out of 204 patients in the tolbutamide group, and 4.9% or 10 out of 205 patients in the placebo group, whereas the cardiovascular death rates in the two insulin groups were similar to the rate in the placebo group. The reasons for the higher cardiovascular mortality in the tolbutamide group are not clear. These studies provided no evidence that the combination of diet and tolbutamide in the fixed dosage, as used for these mild non-insulin dependent diabetics, was more effective than diet alone in prolonging life. The findings suggested that tolbutamide and diet may be less effective, at least insofar as cardiovascular mortality is concerned, than diet alone or than diet and insulin.

"Although the UGDP study considered only one sulfonylurea, tolbutamide, drugs of this class are sufficiently alike in effects that the physician should be aware of the above results when prescribing any of them."

Full information of all labeling changes is now being sent to physicians directly from the manufacturers. Physicians are urged to familiarize themselves as soon as possible with the new labeling.

PHENFORMIN

As of May 1971, the University Group Diabetes Program (UGDP) discontinued the use of phenformin in their study because of increased mortality in the phenformin-treated group. The FDA is currently reviewing this data in conjunction with other expert groups. Physicians will be informed of any necessary changes in phenformin labeling when this review is complete. In the interim, physicians should be aware of this development in following the current labeling for this drug.

FDA
OCTOBER 1971

DRUG BULLETIN

METHOTREXATE: USE IN PSORIASIS

SPECTINOMYCIN FOR ACUTE GONORRHEA

PROBLEM WITH DIGOXIN

ISONIAZID: LABELING CHANGES

FDA APPROVES BONE CEMENTS ■ FAT LABELING ■ ADVERSE DRUG REACTION REPORTING

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METHOTREXATE: ITS USE IN PSORIASIS

Psoriasis has for ages challenged the physician's therapeutic resources. A recurrent disease, it is characterized by exacerbations and remissions which sometimes are difficult to control with conventional therapies.

Some cases of psoriasis which are severe, disabling and resistant to conventional therapy have been effectively treated with the anti-metabolite drug, Methotrexate.

The Food and Drug Administration and the FDA's Advisory Committee on Dermatology have reviewed a series of clinical investigations and based on the recommendations of the Advisory Committee, the FDA has concluded that Methotrexate is safe and effective for the treatment of certain cases of psoriasis.

The FDA-approved directions for use in these cases will soon be available from the manufacturer, Lederle Labs., and should be reviewed carefully before the drug is used in the treatment of psoriasis.

The labeling of Methotrexate restricts its use in psoriasis to severe, disabling, proven cases recalcitrant to more conservative treatment and makes the following recommendations:

– screening of patients by all appropriate parameters to exclude administration of Methotrexate to pregnant women and to patients with preexisting renal, hepatic, or hematopoietic disease;

– screening of patients to disclose any preexisting infections that might be activated by use of an immunosuppressive agent; and

– ensuring the availability of facilities for close medical and laboratory supervision of patients receiving the drug for psoriasis. Supervision should include CBC, urinalysis, serum creatinine, liver function studies, and liver biopsy, if indicated.

Methotrexate should be used only by physicians who are thoroughly familiar with the severe adverse effects, including deaths, associated with the use of anti-metabolite drugs. Deaths that have occurred during Methotrexate treatment for psoriasis usually have been preceded by signs and symptoms of bone marrow aplasia (e.g., hemorrhagic enteritis). Patients should be fully informed of the risks involved and closely monitored. The drug should be discontinued promptly in the event of developing renal or hepatic toxicity.

Methotrexate has been marketed for 18 years as an important representative of anti-neoplastic chemotherapy. Use of an anti-neoplastic drug for treatment of an incurable dermatologic condition must be carefully weighed by the physician after consideration of the risks and benefit to his patient.

Methotrexate should be used only when other, less toxic drugs have failed to bring improvement to patients disabled with severe psoriasis. Please note that the drug is to be dispensed to patients *by physicians only.*

SPECTINOMYCIN FOR ACUTE GONORRHEA

FDA recently approved spectinomycin* for marketing. The drug is indicated only in the treatment of acute gonorrheal urethritis, proctitis, and cervicitis, when due to susceptible strains of *Neisseria gonorrhoeae.* This antibiotic, a product of *Streptomyces spectabilis,* is active against most strains of *N. gonorrhoeae* in a minimum inhibitory concentration varying between 7.5 and 20 mcg./ml. Cross resistance of *N. gonorrhoeae* between spectinomycin and penicillin has not been demonstrated.

Because of its high degree of efficacy and the long-term experience with penicillin, it is still considered the drug of choice for gonorrhea unless the organism is not sensitive to penicillin or the patient is allergic to penicillin. In addition, penicillin should be used when syphilis, suspected or confirmed, is concurrent with gonorrhea. Spectinomycin has no activity against syphilis. It should not be administered to children or during pregnancy.

Spectinomycin is administered only by intramuscular injection. It is rapidly absorbed. The antibiotic is not significantly bound to plasma protein. Spectinomycin can be administered safely to patients who are hypersensitive to penicillin.

For further details, including dosage, consult the package insert.

*"Trobicin", The Upjohn Company.

DRUG QUALITY CONTROL: PROBLEM WITH DIGOXIN[1]

In a recent monitoring program on digoxin tablets, the FDA's National Center for Drug Analysis reported that 47% of the batches investigated did not comply with the requirements of the USP monograph, chiefly because of failure in the content uniformity test. In one of the worst examples, NCDA found digoxin tablets containing twice the declared quantity of active ingredients. The same bottle contained tablets with 60-70% of the declared quantity. The manufacturers agreed to recall the violative lots. A follow-up program on digoxin tablets is underway, and the Bureau of Drugs is monitoring production to assure content uniformity of individual tablets.

On the basis of the digoxin findings, and other studies of diverse pharmaceutical products containing high potency drug substances in relatively low concentrations, FDA has concluded that direct tests for content uniformity are essential. Testing of bulk formulation material has proved unreliable as a measure of uniform content in individual dosage units. When such procedure is used, it is still possible for many of the tablets punched from the formulation mass to fall far outside permissible potency limits.

The significance of this finding to the prescribing physician is obvious: If a previously well-digitalized patient displays signs of under or over-digitalization, the problem may be with the drug rather than with the patient. Certainly, this possibility should be borne in mind when such signs appear.

The Food and Drug Administration is working to eliminate the problem of variable potency and its Bureau of Drugs has undertaken extensive investigations. In establishing the National Center for Drug Analysis, the Bureau has significantly expanded its capacity for gauging the quality of drug control in general. As a result of the Center's marked success in developing automated methods of analysis and applying them to individual units of dosage forms, NCDA is now able to focus attention on problem situations involving deviations from content uniformity requirements.

[1] Adapted from a paper delivered at the Mid-Year Meeting of the National Association of Pharmaceutical Manufacturers, February 14, 1971, at Washington, D.C., by Daniel Banes, Ph.D., Director, Office of Pharmaceutical Research and Testing, Bureau of Drugs, FDA.

ISONIAZID: LABELING CHANGES

In 1970 following the discovery of active tuberculosis in several employees on Capitol Hill in Washington, D.C., a large number of individual employees were placed on isoniazid for prophylactic purposes. Several developed jaundice. There were two deaths from hepatitis. This precipitated new consideration of the hepatic side effects of isoniazid. An intensive review of isoniazid followed. Involved in this review were the National Center for Disease Control, the FDA's Advisory Committee on Anti-Infective Agents, the American Thoracic Society, and the National Tuberculosis and Respiratory Disease Association.

Available evidence could not support a conclusion that the two Capitol Hill deaths were caused by isoniazid. However, it did become evident that reports of hypersensitivity reactions such as hepatic dysfunction were more frequent than had been generally recognized.

As a result of the review of isoniazid, changes have been made in the package insert. These changes have the support of the agencies identified above.

FDA urges your attention to the new "Warnings" statement in the package insert. It is evident that careful and periodic monitoring of the patient is advisable to permit earlier identification of the signs and symptoms of liver toxicity. At the first sign of hypersensitivity, including hepatitis, all drugs should be stopped. If isoniazid is reinstituted, it should be in small and gradually increasing doses to determine whether the manifestations are drug-induced. Preventive treatment for tuberculosis should be deferred in individuals with acute hepatic disease.

The package insert should be consulted for further guidance. A Guest Editorial, "Isoniazid and the Liver," follows.

GUEST EDITORIAL

ISONIAZID AND THE LIVER

The discovery in 1951 of the antimycobacterial property of isonicotinic acid hydrazide (isoniazid, INH, INA) introduced into the therapeutic armamentarium one of the most effective tools ever known for the control of an infectious disease. In addition to efficacy it possessed the features of low toxicity, cost, and ease of oral administration with concomitant patient acceptance.

In the ensuing years the therapeutic value of isoniazid in the treatment of active tuberculosis has been proven abundantly in world-wide clinical use.

Soon after its introduction, studies suggested that it also possessed prophylactic potential. Extensive trials have clearly established that it is very effective in preventing tuberculosis infection from becoming active disease. In high risk groups morbidity has been consistently reduced by 50-75% over an extended period of years. As a result its prophylactic administration has become widespread. Its paucity of untoward reactions has been considered one of its outstanding advantages.

In the past few years, there has appeared to be an increasing number of instances of isoniazid-associated liver dysfunction.

Recently an Ad Hoc Committee on Isoniazid and Liver Disease, appointed by the U.S.P.H.S. Center for Disease Control to study data on isoniazid-associated liver disease and to advise on its future use as preventive treatment against tuberculosis, presented its report.

In brief, the committee concluded that liver disease can occur in patients receiving isoniazid but that the risk is very small—varying from 0 to 10 cases per 1,000 patients per year. The committee felt that no changes are warrented in the present use of the drug in treating active tuberculosis; and that the present program of isoniazid preventive treatment and the guidelines for selection of recipients should not be modified at this time. However, the report did recommend that all preventive therapy candidates and recipients should be carefully screened and monitored at monthly intervals to detect incipient liver dysfunction. The report detailed the surveillance procedures.

In reaching a judgment as to whether or not to place a patient on preventive therapy the physician must weigh the risk of possible hepatic damage—the order of this has been mentioned above—against the risk of the development of active disease. The latter varies considerably in various high risk groups. In household contacts it is about 1 in 30 during the first year after discovery of the index case; there is a similar risk in recent converters of any age; and in persons with previously known, but now inactive tuberculosis who have not had adequate chemotherapy, the annual risk is about 1 in 75. One must also consider that while the risk of liver damage is present only during the year of preventive therapy, the risk of developing active tuberculosis in the absence of chemoprophylaxis remains a lifetime matter with hazard not only to the individual but to his family and close contacts—and thus to the community—health and cost-wise.

Isoniazid remains a powerful and very effective antituberculosis agent which merits continued therapeutic and prophylactic use even though liver dysfunction can be associated with its use. The individual and the community advantages of its use overbalance the rare possible untoward reactions.

Gordon M. Meade, M.D.
Formerly Medical Director,
American Thoracic Society

FDA APPROVES BONE CEMENTS

The Food and Drug Administration announces approval of New Drug Applications for Methyl, Methacrylate* for cementing in place total hip replacement prostheses.

This approval makes available a significant new therapy for disabled patients. A significant number of such patients can now be at least partially rehabilitated through judicious use of this new material in orthopedic surgery.

The drug will be available for restricted use as specified in the package insert. (The manufacturer will mail each orthopedic surgeon a copy of this insert.)

The Food and Drug Administration wishes to express its appreciation to the American Academy of Orthopaedic Surgeons for help and cooperation during the approval process. Special appreciation also is due the orthopedic surgeons who served on the FDA's Ad Hoc Advisory Committee. Further, the FDA wishes to compliment the Academy on its current program to develop training courses in 23 centers to assist orthopedic surgeons in the proper use of this new drug.

*Surgical Simplex P Bone Cement and Surgical Simplex P Radiopaque Bone Cement, Howmedica

FAT LABELING

FDA is taking major initiatives to improve nutritional labeling of food products. Some of these efforts are of particular interest to physicians.

Of most interest, perhaps, are proposed changes in fat labeling. FDA has proposed regulations requiring product labels to give the name, source, and amount of fat content, and, on some foods, the amount and kind of fatty acids present. Under this proposal, such uninformative labeling as "shortening" or "vegetable oil" would be stopped.

FDA is proposing the fat labeling regulations to provide information to interested consumers and their physicians. The Agency is not recommending changes in dietary habits; neither is it taking sides in any medical discussion.

A related step by FDA is designed to make it possible for buyers to determine from the label the nutritional value of the food he is buying.

Several types of labels are being tested to measure effectiveness from the consumer's point-of-view. From these tests should come necessary information to evaluate consumer understanding, acceptance, and use of nutrient labeling.

ADVERSE DRUG REACTION REPORTING

The development and use of increasingly potent drugs has been accompanied by a significant incidence of adverse reactions. Recent reports indicate that as many as 5 percent of admissions to hospital medical services involve drug reactions and 15 percent of hospitalized patients suffer an adverse reaction during their stay.[1]

The Food and Drug Administration is taking steps to improve its adverse reaction surveillance and information programs. An initial move will be the appointment of an expert advisory committee to guide agency plans for improved methods of information gathering and dissemination to the medical profession.

The FDA also needs help from practicing physicians through voluntary reporting of adverse drug reactions. To aid participating physicians, a short reporting form has been prepared and pretested successfully at a number of major medical meetings, including a recent AMA meeting (Please see proposed form accompanying this Bulletin. When ready, a supply of forms will be mailed to practicing physicians.)

All physicians are urged to help; all physicians will share the results. But only insofar as the individual physician shows interest and participates will these results be meaningful. All information will be held in confidence. Later

issues of the FDA Drug Bulletin will include progress reports on the Agency's drug reaction surveillance program.

[1]National Academy of Sciences: Report of the International Conference on Adverse Reactions Reporting Systems. Washington, D.C., 1971, page 1.

DRUG EXPERIENCE REPORT *(IN CONFIDENCE)*			Form Approved OMB No. XXXXXXX
PATIENT INITIALS *(Optional)*			DATE OF REACTION ONSET
SUSPECTED REACTION(S)			
SUSPECTED DRUG(S); TRADE/GENERIC NAME *(Manufacturer's name, if possible)*			
DISORDER OR REASON FOR USE OF DRUG(S) *(Optional)*	ROUTE	TOTAL DAILY DOSE	DATES OF ADMINISTRATION
OTHER DRUGS TAKEN CONCOMITANTLY			
COMMENTS *(Optional)*			
PHYSICIAN'S NAME, ADDRESS, AND ZIP CODE			

FD PROPOSED FORM

FDA
NOVEMBER 1971
DRUG BULLETIN

DIETHYLSTILBESTROL CONTRAINDICATED IN PREGNANCY

DRUG'S USE LINKED TO ADENOCARCINOMA IN THE OFFSPRING

We wish to bring to the attention of all physicians, hospitals, and medical personnel an important possible toxic effect of diethylstilbestrol reported for the first time in April 1971 by Herbst, et al[1]. From their studies the authors concluded that maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed. The authors studied eight cases of adenocarcinoma of the vagina in patients born between 1946 and 1951. The malignancies were identified and treated between 1966 and 1969. In seven of the eight cases, there was a history of maternal use of diethylstilbestrol. Because this type of malignancy in young girls had rarely been reported previously, the authors conducted a retrospective investigation in an attempt to find factors that may be associated with such malignancy in this age group. Four matched controls were established for each patient and the data obtained were subjected to statistical analysis. A statistically significant relationship was observed for three variables: diethylstilbestrol given during pregnancy (p=.00001), bleeding in that pregnancy (p=less than .05) and prior pregnancy loss (p=less than .01). It is obvious that the most significant of the variables is the administration of diethylstilbestrol during pregnancy.

Since publication of this study, five additional cases of this malignancy associated with the maternal use of diethylstilbestrol have been reported by Greenwald, et al[2]. Dr. Herbst, in a recent communication to FDA, has reported an additional 15 cases associated with use of this drug, bringing the total number of known cases to 27. It must be emphasized that this type of epidemiologic study defines only an association and not necessarily a cause-and-effect relationship. Further studies are underway to clarify the significance of these findings.

In the meantime, the FDA is initiating the following precautionary actions:

1. All manufacturers of DES or closely related congeners (dienestrol, hexestrol, benzestrol, promethestrol) are being notified that appropriate changes will be required in the labeling for such drugs. This change will consist in the listing of pregnancy as a contraindication to the use of diethylstilbestrol and the other above-mentioned compounds.

2. All other estrogens will be required to have the following WARNING in their labeling: "A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy."

3. Epidemiological studies are being initiated to determine the true incidence of this disease in young women, the number at risk, the characteristics of patient populations with this malignancy, and the probability of a cause-and-effect relationship.

Both FDA and the medical profession face a responsibility to help determine whether this reported association constitutes a cause-and-effect relationship. We ask that all physicians consider appropriate steps to assist FDA case-finding and to protect any patients who might be at risk.

It may be possible to trace the offspring of those mothers who received DES during pregnancy. All physicians should be especially alert for young women whose mothers may have received hormonal therapy during pregnancy, particularly those young women who may be experiencing irregular vaginal bleeding. The association should be a routine consideration for physicians whose practice includes young women.

This is a previously unsuspected health problem. Further information is essential to the FDA and to the medical profession. We ask your help in reporting any cases you encounter for entry in a case registry.

1. Herbst, et al – Adenocarcinoma of the Vagina – New England Journal of Medicine – Volume 284, Number 16 (April 22, 1971).

2. Greenwald, et al – Vaginal Cancer After Maternal Treatment with Synthetic Estrogens – New England Journal of Medicine, Volume 285, Number 7, (August 12, 1971).

FDA will take every possible step to insure that you are kept abreast of new information as soon as it can be gathered and analyzed.

For your convenience, an adverse reaction reporting form is printed in this bulletin. FDA will forward a supply of forms to each practicing physician as soon as they are printed. Facsimile forms are acceptable.

DRUG EXPERIENCE REPORT
(IN CONFIDENCE)

Form Approved
OMB No. XXXXXXX

ΓIENT INITIALS *(Optional)*

DATE OF REACTION ONSET

PECTED REACTION(S)

ECTED DRUG(S); TRADE/GENERIC NAME *(Manufacturer's name, if possible)*

RDER OR REASON FOR USE OF DRUG(S) *(Optional)*

ROUTE	TOTAL DAILY DOSE	DATES OF ADMINISTRATION

ER DRUGS TAKEN CONCOMITANTLY

ENTS *(Optional)*

ICIAN'S NAME, ADDRESS, AND ZIP CODE

OPOSED FORM

FDA
DECEMBER 1971
DRUG BULLETIN

HEXACHLOROPHENE AND NEWBORNS

HEXACHLOROPHENE AND NEWBORNS

A number of recent studies have raised serious questions concerning the toxicity of hexachlorophene preparations used for total body bathing of newborn infants. A summary of three such studies follows:

1. Fifty newborn infants, bathed daily with a 3% hexachlorophene product, showed hexachlorophene blood levels of .009 to .646 micrograms/ml. on the day of hospital discharge. No obvious toxic symptoms were noted in the newborns. (Curley, A., et al. Lancet, Aug. 7, 1971.)
2. Rats fed hexachlorophene to achieve mean hexachlorophene blood levels of 1.21 micrograms/ml. showed brain changes characterized by cerebral edema limited to the white matter, and cystic spaces of the brain believed produced by fluid accumulation. (Gaines, T.B., Kimbrough, R.D. Paper read at the 10th annual meeting of the Society of Toxicology, Washington, D. C., March 7-11, 1971. See also Kimbrough & Gaines, Arch. Environ. Health 23:114-118, Aug. 1971.)
3. Newborn monkeys washed daily with 3% hexachlorophene for 90 days showed mean hexachlorophene plasma levels of 2.3 micrograms/ml. When they were sacrificed, the white matter of the brain, particularly the cerebellum, brain stem and all parts of the cord, showed lesions consisting of cystic spaces like those described above. (Studies submitted by Winthrop Laboratories to FDA on November 18, 1971.)

These studies challenge the safety of hexachlorophene bathing of infants, a practice which has been widely advocated as effective prophylaxis against nursery epidemics of staphylococcal skin infections. A critical review of the studies on which this claim is based indicates that whereas there is no doubt that hexachlorophene bathing decreases skin colonization of gram-positive organisms, there is a lack of substantial evidence that hexachlorophene washings by themselves prevent staphylococcal disease or show antibacterial activity against gram-negative organisms. Hospitals are known to operate nurseries safely without the use of this product.

The FDA has been in close contact with the Committee on Fetus and Newborn of the American Academy of Pediatrics regarding these findings. In light of these findings and since other methods of control of infection are available, we have jointly concluded that the use of hexachlorophene for total body bathing of infants in hospital nurseries or at home is not recommended. In its place the committee recommends the following procedures:

> "At present we recommend dry skin care, washing with plain soap and water or tap water alone for skin care of the newborn infants. It should be emphasized that the most important factor in the transmission of infection from infant to infant is hand contact. This can be minimized by scrupulous hand washing before entering the nursery as well as just before and just after handling each infant. Either an iodophor preparation or 3% hexachlorophene emulsion is recommended."

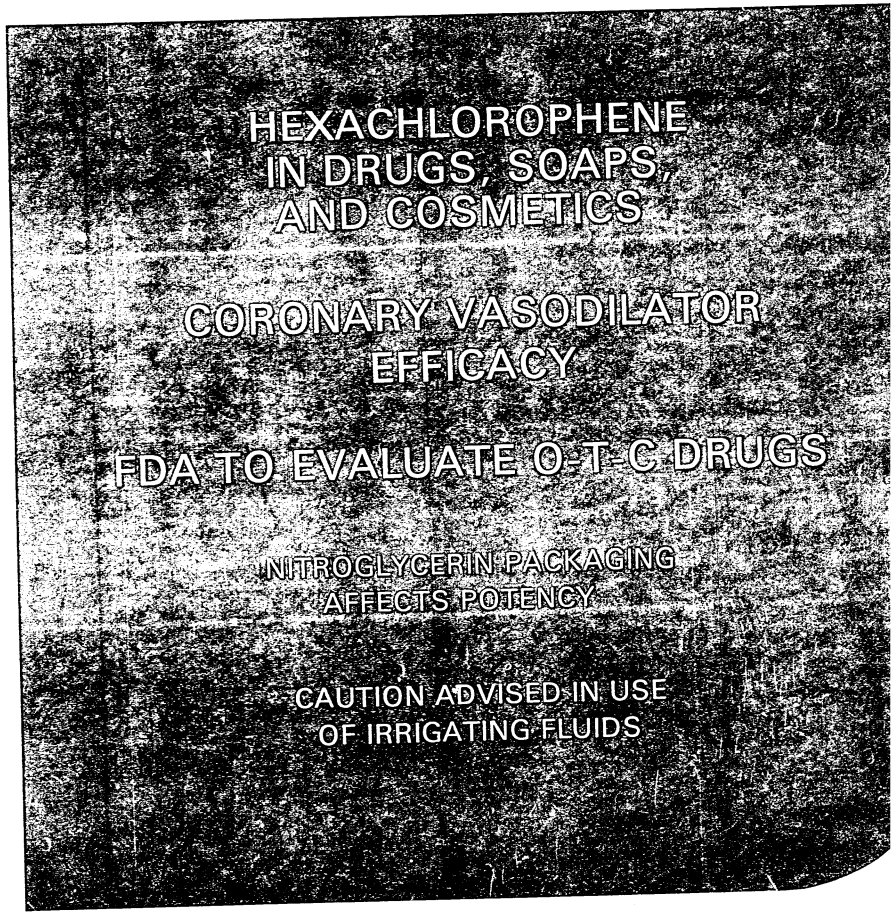
The labeling of 3% hexachlorophene products is being amended to advise against their use for total body bathing.

The effectiveness of 3% hexachlorophene for other uses has been studied by the Food and Drug Administration and the National Academy of Sciences. On December 8, 1971, FDA published NAS Drug Efficacy Study evaluations rating such products effective for use as bacteriostatic skin cleanser (including surgical scrub). They are rated possibly effective* for use in the treatment of impetigo in newborns and of other staphylococcal skin infections, and in the treatment of cradle cap and in helping to clear acne. They are found to be lacking in substantial evidence of effectiveness for use in the relief of pruritus ani, for the broad claim as a vaginal douche, in the treatment of chronic eczema, in irrigating or cleansing wounds and burns, and as an "aid to personal hygiene".

Further studies will be necessary to determine the ultimate usefulness of hexachlorophene preparations.

*A rating of possibly effective means that there is little evidence of effectiveness for the given indication. Substantial evidence of the effectiveness of drugs is required by law. The responsibility for substantial evidence of effectiveness of a drug rests with the manufacturer.

FDA
FEBRUARY 1972
DRUG BULLETIN



HEXACHLOROPHENE IN DRUGS, SOAPS, AND COSMETICS

Hexachlorophene is widely used as an antibacterial component in a large number of products such as lotions, ointments, powders, soaps, shampoos and deodorants. It is used in such products because of its bacteriostatic action against gram-positive organisms, especially staphylococcus strains. It offers no protection against gram-negative infections, and its antibacterial activity depends on repeated use.

Hexachlorophene is readily absorbed into the blood stream from normal skin, including that of newborns, and especially from abraded and burned skin. The toxicity of hexachlorophene appears to be related to its concentration in the blood, and this concentration increases with the amount of exposure to hexachlorophene. The margin of safety between toxic and nontoxic blood levels in humans and animals appears to be narrow.

In a recent study, baby monkeys developed brain edema when bathed daily for 90 days with 3% hexachlorophene. *Misuse* of hexachlorophene products in humans such as application on burn surfaces or use in vaginal packs, has resulted in central nervous system toxicity and death.

Daily human use of lower concentrations of hexachlorophene in deodorant soaps or hand scrubs, which may produce chronic blood levels of approximately 1.5 mcg/ml, is not known to produce toxicity, even after long-term use.

In the past two decades there has been a rapidly expanding use of hexachlorophene. To protect consumers from any potential hazard resulting from such increased exposure to hexachlorophene, FDA has proposed new action to limit its inclusion n drugs and related products. The Agency also has ıcted to ensure that in the future all antibacterial ıgents intended for chronic daily use have been ıdequately evaluated for safety and efficacy. A ummary of FDA proposed action follows:

1. Hexachlorophene may not be used in cosmetic products, except as a preservative in levels up to 0.1%, and then only when other suitable preservatives are not available.
2. When hexachlorophene is a component of drugs which have approved new drug applications, the drug label must read "Caution: Contains Hexachlorophene. For external washing only. Rinse thoroughly." The hexachlorophene level may not exceed .75%.
3. Drugs containing hexachlorophene in levels over .75% must bear the prescription label.
4. A panel of experts is being consulted to determine the safety, efficacy and appropriate labeling of all over-the-counter drugs — such as bar soaps — offered for routine, daily use as antibacterial agents.

The proposed action in no way restricts physician-directed use of hexachlorophene products, including the use of 3% hexachlorophene as a surgical or disinfectant scrub. The action does, however, reflect FDA concern that there should be medical justification for the addition of antibacterial agents to readily available consumer products.

The new proposals cited above supplement an FDA warning against total body bathing of infants and adults with products containing HCP in 2% and 3% concentrations (see FDA Drug Bulletin dated December 1971).

Comments on the FDA proposals should be sent prior to March 7, 1972, to the Hearing Clerk, Department of HEW, Room 6-88, 5600 Fishers Lane, Rockville, Maryland 20852.

CORONARY VASODILATOR EFFICACY

Long-acting coronary "vasodilators," widely-prescribed in the management of angina pectoris, will require extensive study as a result of a National Academy of Sciences/National Research Council report questioning the quality of evidence on the drugs' effectiveness.

The NAS/NRC panel, after evaluating all available evidence about the drugs, concluded:

- Isosorbide dinitrate tablets, when administered by the *sublingual* route, are "probably" effective for the treatment of attacks of angina pectoris and for prophylaxis in situations likely to provoke such attacks.
- The same drug, isosorbide dinitrate tablets, is only "possibly" effective for the same indications when administered *orally* (swallowed).

- Extended action or conventional oral dosage forms of pentaerythritol tetranitrate, trolnitrate phosphate, and mannitol hexanitrate – alone or in combination with other drugs – are "possibly" effective for the treatment or prevention of anginal attacks.
- Sustained action nitroglycerin tablets are "possibly" effective for the treatment or prevention of anginal attacks.

At this point, it is well to restate what these NAS/NRC ratings mean. *Probably effective* signifies that *for a particular indication,* the available evidence indicates that a drug probably accomplishes its proposed effect, but that additional evidence is required before the drug can be deemed "effective" beyond reasonable doubt. *Possibly effective* signifies that little evidence of effectiveness *for the given indication* has been obtained. The possibility that adequate supporting evidence might be developed should not be ruled out, however.

FDA recognizes that these drugs are widely regarded by physicians as safe and useful in the management of angina pectoris in some patients. It also recognizes the difficulty of designing and executing controlled clinical studies for anti-anginal drugs. For these reasons, the Agency will allow manufacturers sufficient time to complete the required studies and the drugs will continue to be marketed during that time. FDA will keep physicians informed as the studies develop.

On the basis of the NAS/NRC panel's conclusion, physicians may wish to reevaluate the role of long-acting coronary vasodilators for their patient.

NITROGLYCERIN PACKAGING AFFECTS POTENCY

A recent FDA assay survey of nitroglycerin tablets suggests that improper packaging has a crucial bearing on the drug's stability and potency.

The assay involved nitroglycerin tablets stored in a pen-shaped plastic container provided by pharmacies as a convenient means of carrying several days' supply. Dispensers containing the drugs were left standing at room temperature for 1-, 2-, and 3-day periods.

The nitroglycerin was found to have decreased to about 50%, 30% and 20% of initial potency after being left in the dispensers for these periods. FDA has requested recall of the dispensers.

The assay led FDA to conclude that unexplained patterns of therapeutic response by patients to nitroglycerin therapy may be caused by the manner in which the drug is packaged. Physicians should consider this possibility when evaluating patient response to the drug.

To avoid rapid loss of potency, nitroglycerin should be kept at all times in tightly-sealed glass vials. Physicians and pharmacists may wish to tell patients this when prescribing and dispensing the drug.

CAUTION ADVISED IN USE OF IRRIGATING FLUIDS

Recent bacteriologic sampling programs of commercially produced irrigating solutions with screw cap closures have revealed microbial contamination of the glass thread area and the cap components in some of the lots tested. Occasionally, the fluids themselves have been found to be contaminated. No human health problems have been reported.

The FDA is now working with the manufacturers of these products to develop a closure system which can be used for such fluids and which will be free of this potential problem. Physicians and hospital personnel will be kept advised.

In addition to usual aseptic technique, the following precautions are recommended when using such solutions with screw top closures:

- Do not use intravenously;
- Do not strike bottle caps to open; discard if not opened easily;
- Do not replace caps;
- Use solutions immediately on opening. Discard unused portion.

FDA TO EVALUATE O-T-C DRU

S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20852

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IMPORTANT PRESCRIBING INFORMATION
FROM CHARLES C. EDWARDS, M.D.,
COMMISSIONER OF FOOD AND DRUGS

FDA DRUG BULLETIN

February 1972

FDA DRUG BULLETIN

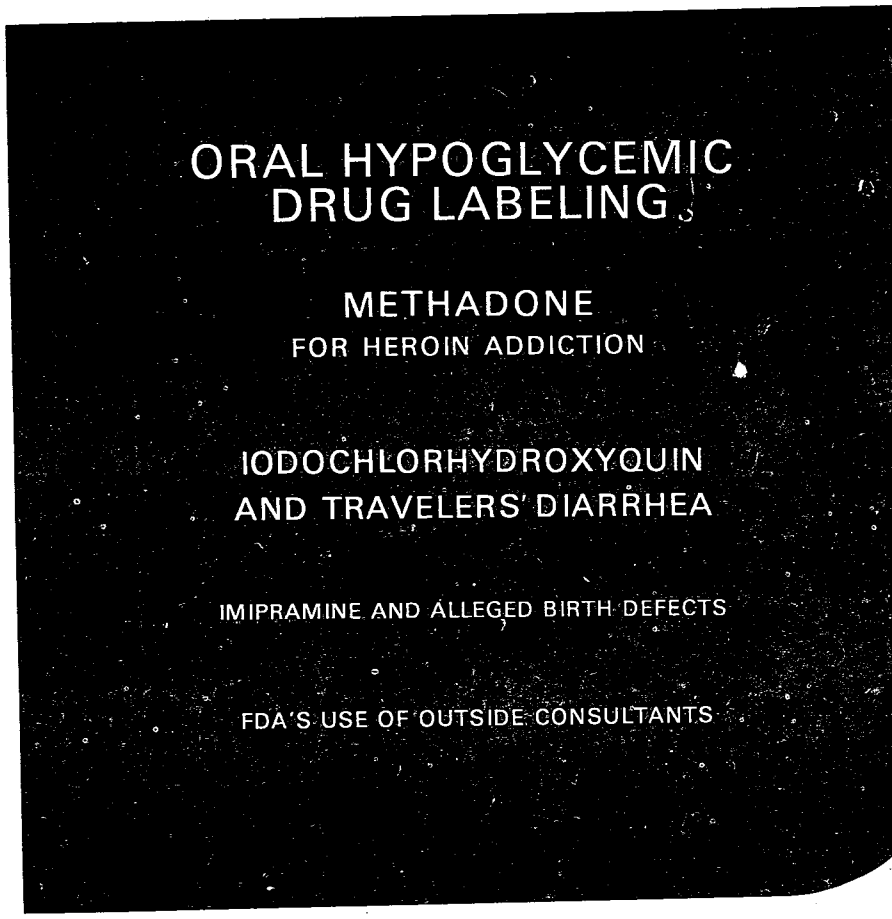
News and Reports of Interest to Practicing Physicians and Allied Health Professionals, Issued by the Food and Drug Administration, Department of Health, Education, and Welfare. Comments are invited. All correspondence should be addressed to the Assistant to the Director for Medical Communications, Bureau of Drugs, BD-40, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852

FDA TO EVALUATE O-T-C DRUGS

The Food and Drug Administration has embarked upon a major scientific and regulatory program designed to assure that all over-the-counter drugs are safe, effective, and accurately labeled for the relief of minor illnesses and discomfort.

Responsibility for evaluating the over-the-counter drug products on a class-by-class basis will rest with expert panels, to be appointed by FDA. Each panel will consist of physicians with extensive knowledge of the drugs involved. A National Drug Advisory Board, chaired by Food and Drug Commissioner Charles C. Edwards, M.D., will supervise the evaluation.

The basic scientific undertaking will take two to three years to complete. Meanwhile, FDA is continuing implementation of the National Academy of Sciences review of efficacy of prescription drugs (see Drug Bulletin, July 1971). The aim of both programs is to assure physicians and the public of the safety, efficacy and accurate labeling of all marketed drugs.


FDA
May 1972
DRUG BULLETIN
ORAL HYPOGLYCEMIC DRUG LABELING
METHADONE
FOR HEROIN ADDICTION
IODOCHLORHYDROXYQUIN AND TRAVELERS' DIARRHEA
IMIPRAMINE AND ALLEGED BIRTH DEFECTS
FDA'S USE OF OUTSIDE CONSULTANTS

FINAL LABELING APPROVED FOR
ORAL HYPOGLYCEMIC DRUGS

The most recent labeling for the sulfonylurea drugs and for phenformin, approved by the Food and Drug Administration, provides that these drugs are indicated in the treatment of adult-onset, non-ketotic diabetes mellitus only when the condition cannot be controlled adequately by diet and reduction of excess weight alone.

The labeling includes a **SPECIAL WARNING** which says:

Diet and reduction of excess weight are the foundations of initial therapy of diabetes mellitus. When the disease is adequately controlled by these measures, no hypoglycemic drug therapy is indicated.

Because of the apparent increased cardiovascular hazard associated with oral hypoglycemic agents, they are indicated in adult-onset, non-ketotic diabetes mellitus only when the condition cannot be adequately controlled by diet and reduction of excess weight alone, and when, in the judgment of the physician, insulin cannot be employed because of patient unwillingness, poor adherence to injection regimen, physical disabilities such as poor vision and unsteady hands, insulin allergy, employment requirements, and other similar factors.

This labeling and therapeutic regimen for diabetes mellitus are consistent with the therapeutic recommendations of the American Diabetes Association and the Council on Drugs of the American Medical Association, with which FDA consulted on the evaluation of the University Group Diabetes Program (UGDP) study.

The long-term UGDP study provided the basis for the labeling. That study suggested that the use of the sulfonylurea drug tolbutamide and the biguanide drug phenformin were associated with a greater incidence of cardiovascular mortality than diet alone, or than insulin plus diet.

Although the specific sulfonylurea drug studied by UGDP was tolbutamide (Orinase), the conclusions apply equally to all sulfonylureas — Diabinese, Dymelor, Orinase and Tolinase — because of their close chemical relationship. Of the biguanides, only DBI-TD was studied by UGDP, but the conclusions apply to DBI and Meltrol as well.

Further studies are being undertaken to shed additional light on the role of sulfonylureas and phenformin in the management of diabetes mellitus.

The "indications" section of the labeling approved recently by FDA for all oral hypoglycemic drugs says:

Oral hypoglycemic drugs are indicated in the treatment of adult-onset, non-ketotic diabetes mellitus only when the condition cannot be controlled adequately by diet and reduction of excess weight alone.

Because of the increased cardiovascular hazard which appears to be associated with oral hypoglycemic agents, the drugs should be used only after full consideration of the special warning.

FDA'S USE OF OUTSIDE CONSULTANTS

All four of the Food and Drug Administration decisions described in this Drug Bulletin were made only after the Agency consulted experts outside the Federal Government.

The use of non-Government experts as consultants on major medical judgments reflects FDA's commitment to base important regulatory decisions on the best available scientific evidence.

Fourteen advisory committees made up of 112 medical experts meet regularly with FDA's medical staff in the Bureau of Drugs to discuss important issues. Additional committees are now being formed. The overall direction of the Agency's regulation of prescription and over-the-counter drugs is influenced by a National Drug Advisory Council.

These committees supplement FDA's medical capabilities. FDA believes that the use of outside consultants, combined with the expertise of FDA's own physicians, leads to sound and well-balanced medical regulatory actions.

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METHADONE FOR HEROIN ADDICTION

FDA plans to sanction increased use of methadone as a substitute for heroin. Maintenance treatment of patients 18 years and older with oral dosage forms of methadone will be available at about 450 Drug Addiction Centers throughout the United States. Each Center is being inspected by health officials and is subject to FDA approval.

To control illicit traffic in methadone, the drug will be available only in approved Centers and hospital pharmacies. Accurate record-keeping for the drug will be required. These restrictions do not prohibit use of methadone in the treatment of severe pain or for detoxification of addicts in hospitals.

Methadone taken by mouth prevents heroin withdrawal symptoms and, in general, controls the intense desire or need for heroin. Addicts who stay on methadone maintenance programs are often able to return to a normal life pattern.

FDA's decision was made after consultation with the National Institute of Mental Health and the Justice Department's Bureau of Narcotics and Dangerous Drugs, and was endorsed by The Special Action Office for Drug Abuse Prevention of the White House. FDA also had the advice and opinion of many other groups, such as the AMA's Council on Mental Health. The consensus is that current evidence on the safety and effectiveness of methadone is sufficient to permit its use for narcotic addiction in adults.

IODOCHLORHYDROXYQUIN AND TRAVELERS' DIARRHEA

The Food and Drug Administration recommends that iodochlorhydroxyquin (Entero-Vioform) not be given to prevent "travelers' diarrhea."

FDA's conclusion is based on recent findings in Japan, Australia and Sweden implicating iodochlorhydroxyquin as the cause of a frequently severe neurologic complex, subacute myleo-optic neuropathy (SMON). Evidence is not yet available to confirm this association, but it appears that too-long-continued dosing with iodochlorhydroxyquin may be a major factor in SMON.

There is no acceptable evidence that other halogenated hydroxyquinolines, chiniofon and diiodohydroxyquinoline (Diodoquin), are effective in the treatment or prevention of "travelers' diarrhea."

Travelers to areas where hygiene and sanitation are poor may be able to prevent diarrhea by eating only recently peeled or thoroughly cooked foods, and by drinking only boiled or bottled water, bottled carbonated soft drinks, beer or wine. Tap water used for brushing teeth or for ice in drinks may be a source of infection. The cause of the diarrhea is uncertain.

Most tropical disease specialists believe iodochlorhydroxyquin is ineffective for "travelers' diarrhea." Labeling of the product cites only intestinal amebiasis as an indication.

IMIPRAMINE AND ALLEGED BIRTH DEFECTS

Recent alarm about possible implication of imipramine (Tofranil), an anti-depressant drug, in birth defects (amelia and phocomelia) appears to be without firm foundation. A report of an association between imipramine given pregnant mothers and congenital deformities in their offspring came from Australia in early March.

The Australian Department of Health recently informed FDA that it regards as inconclusive the data on which the report was based. In addition, the Department of Health and Social Security in London told FDA that during the eight years the British Committee on Safety of Drugs has been in operation, only one report of congenital abnormality of a limb associated with imipramine has been received. Amelia and phocomelia occasionally occur without known association with drugs.

FDA-approved imipramine labeling in use since 1965 contains the following warning: "Safe use of imipramine during pregnancy and lactation has not been established; therefore, in administering the drug to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results. There have been clinical reports of congenital malformation associated with the use of this drug, but a causal relationship has not been confirmed."

CHAYET & FLASH,
Boston, Mass., October 7, 1971.

COMMISSIONER OF FOOD AND DRUGS,
Department of Health, Education, and Welfare,
Washington, D.C.

DEAR SIR: I am herewith transmitting a petition relative to the Food and Drug Administration's actions based on the agency's acceptance of and extrapolations from the conclusions of the University Group Diabetes Program.

I would appreciate a prompt reply to this petition and would hope that in any case, one could be received within 30 days.

I anticipate that the petition will be printed in the Federal Register in the usual course. Kindly address your reply to me at the above address.

Very truly yours,

NEIL L. CHAYET.

PETITION OF COORDINATING COMMITTEE OF THE COMMITTEE ON THE CARE OF THE DIABETIC TO COMMISSIONER OF FOOD AND DRUGS

(From the office of Neil L. Chayet, Esq., Chayet & Flash, 15 Court Square, Boston, Mass.)

COMMISSIONER OF FOOD AND DRUGS,
Department of Health, Education, and Welfare,
Washington, *D.C.*

DEAR SIR: This petition is submitted with respect to (1) the issuance of recommendations contained in the October, 1970 FDA Current Drug Information Bulletin entitled, "Diabetes Prescribing Information" and (2) the recommended changing of the INDICATIONS AND WARNINGS section of the labelling of all sulfonylureas as stated in the June 23, 1971, FDA Drug Bulletin.

Attached hereto, in quintuplicate and constituting a part of this petition are the following:

A. The FDA Current Drug Information, October, 1970 (marked Appendix A).

B. Relevant excerpts from FDA Drug Bulletin dated June 23, 1971 (marked Appendix B).

C. Written communications of Robert F. Bradley, M.D. and the Committee on the Care of the Diabetic to the FDA. (marked Appendix C).

D. A statement of the grounds upon which your petitioner relies for the action requested herein (marked Appendix D).

The recommendations which are the subject of this petition have been made by the Food and Drug Administration (FDA) as a result of the report of the University Group Diabetes Program (UGDP). This report has been the subject of intense controversy since its conclusions were made known both because of the unprofessional manner in which the conclusions originally became known, in the lay press, as well as the irreparable flaws of its methodology, and the major inconsistencies in the conclusions. The report, which suggested that tolbutamide is no more effective than diet alone in the treatment of mild adult-onset diabetes, is insupportable in the light of impartial scientific inquiry, and the Food and Drug Administration, by embracing its conclusions, has intruded into the practice of medicine, placing the physician who continues to prescribe tolbutamide for the treatment of maturity-onset diabetes in jeopardy and causing great concern on the part of more than a million diabetics and their physicians who have regularly used this drug.

This petition is grounded in three fundamental principles:

1. Regardless of the validity of the UGDP study, it is the contention of your petitioners that the Food and Drug Administration's legal mandate is solely the regulation of drugs as to safety and efficacy and not the control of medical or scientific practices; furthermore, the FDA should not engage in the establishment of an official governmental policy in respect to the practice of science or medicine. We believe this to be as true for the treatment of diabetes as it would be in relation to such procedures as cardiac surgery or kidney and heart transplants.

2. The government should particularly refrain from taking a partisan position and establishing a "government line" in an area of medicine and science in which extensive controversy and debate exists among qualified scientists and/or physicians. In the present situation such a position has been taken despite the absence of corroborating studies which have reproduced the UGDP findings, an essential criteria in the establishment of scientific principles. Even if the UGDP study were beyond reproach, which the statement marked "Appendix D" will show it is not, the FDA should not adopt the singular position of one group if contradicting positions are advocated by other qualified scientists and physicians. With respect to the UGDP findings, strong controverting data and extensive comment, disagreement and experience among a large body of extremely well qualified scientists exists and is a matter of scientific record. Furthermore, in this situation the FDA has ruptured its own rule of fair balance in failing to present the other side of the issue in its mailings and statements, even as it has itself taken sides in the issue.

3. The single study upon which the FDA bases its action has been criticized on professional, scientific, clinical, statistical, and other grounds. Furthermore, FDA action did *not* properly reflect the criticisms and recommendations of its own medical advisory panel on the subject. In effect, despite repeated requests for over a period of a year from many different sources, the basic data of the study remain unavailable to the scientific community and the recent report on phenformin [1] presents an inadequate amount of protocol material to enable adequate scientific evaluation. The 6/23/1971 FDA Current Information Bulletin nevertheless made the general statement that "although this study considered only one sulfonylurea, tolbutamide, it raises serious questions as to the ultimate place of all antidiabetic agents in the treatment of diabetes mellitus."

This petition for a reversal and clarification of the FDA's positions as stated above is thus grounded not only on the basis of the fundamental principle of the separation of science and state, but also on the fact that legitimate scientific controversy exists and the UGDP study has been controverted by a large and leading body of specialists in the field as being more than just erroneous. In point of fact, the FDT has sought in this situation to regulate therapy on the basis of an experiment which is based on faulty methodology, which has disregarded many essential recommendations related to the true *therapeutic* application of the agents under study, and in doing so has extrapolated without valid statistical basis, thus flying directly in the face of the caveat of the authors of the UGDP study themselves, to wit:

"It should be noted that any conclusion reached in this study pertains only to the type of patient studied and to the specific hypoglycemic agents and dosage schedules used. Extrapolation of findings obtained in the UGDP to other dosage schedules of the same drug or to other chemically related hypoglycemic agents not included in this study must be made on a judgmental and nonstatistical basis." [2]

In addition, it was recently reported that Dr. Christian R. Klimt, the statistical coordinator of the UGDP study, stated that a similar trial of diabetic oral agents, which he will be conducting in Yugoslavia under FDA auspices, will employ a flexible dosage regimen and be confined to a symptomatic diabetic population. [3] The use of fixed dosage and asymptomatic patients are two of the serious limiting factors in the UGDP study (see Appendix D). This action by the statistical coordinator indicates the merit of the most serious criticism which has been levelled at the UGDP report.

It has also been reported that the protocol in regard to the double blind technique may not have been followed in every partcipating clinic for all patients (see Appendix D, Part 2).

Lastly, it should be noted that the conclusions of the study have been specifically rejected by the Canadian Food and Drug Directorate, the Canadian Diabetes Association, the British Committee on Drug Safety, the British Diabetes

[1] "Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes," JAMA, August 9, 1971.
[2] "University Group Diabetes Program," *Diabetes* 19, Supp. 2, 1970.
[3] Drug Trade News, August 23, 1971.

Association, the German Ministry of Health, the German Diabetic Society, and the Swedish government.

Failure to grant petitioner's requests will result in a continuance and aggravation of damage which has already been perpetrated by the dissemination of these recommendations already made and the suggested labelling changes. As a result of actions taken by the Food and Drug Administration, an undetermined number of patients stopped taking medication on their own or were taken off the medication by their alarmed physicians and subsequently became symptomatic.

Failure to grant these requests will cause further irreparable harm to more than a million patients, particularly to their relationship with their physicians and to their personal psychic stability so essential in a disease such as diabetes.

Failure to grant the request will perpetuate the unjustified damage done to a large number of physicians and research scientists in the field of diabetes with respect to their standing in the public view as well as in the medical and scientific communities.

The Food and Drug Administration has taken a partisan position in an area of valid and continuing medical and scientific discussion and debate. This is a serious error both in principle and in fact. The Food and Drug Administration identification with a controversial study which has been subject to extensive criticism is particularly unfortunate.

It must clearly be recognized that the government has no role as a partisan in valid continuing scientific controversy.

Your petitioners, in reliance on the statement contained in Appendix D of this petition, respectfully request that the following steps be taken immediately:

(1) That the recommendations contained in the October 1970 Food and Drug Administration Current Drug Information Bulletin, entitled "Diabetes Prescribing Information" be immediately rescinded and that notice of such rescission be distributed in exactly the same manner as the Bulletin was distributed.

(2) That the recommendations which would change the Indications and Warnings section of the labelling of all sulfonylureas as stated in the June 23, 1971 Food and Drug Administration Drug Bulletin be rescinded and that notice of same be distributed in exactly the same manner as the Bulletin was distributed.

(3) That the Food and Drug Administration use its best efforts to restore the confidence of patients in their physicians who use tolbutamide and the sufonylureas generally.

(4) That pending corroboratory studies the Food and Drug Administration refrain from making any further recommendations related to hypoglycemic substances based on the University Group Diabetes Program and that any actions related to the UGDP studies avoid debatable extrapolations and clearly indicate the study's deficiencies and the controversial nature of its implications. And that any references be made in the context of fair balance as above stated.

(5) That the Food and Drug Administration repudiate all other recommendations, statements, mailings or communications of any kind which have been distributed to the medical and scientific communities, to the lay press, or to the general public based on the UGDP study and that the Food and Drug Administration use its best efforts to widely disseminate such repudiation.

(6) That the Food and Drug Administration make available to your petitioners and other qualified researchers the baseline data of the University Group Diabetes Program; such baseline data shall include the total patient record of each patient included in the study.

(7) That in accord with its policy of fair balance, the Food and Drug Administration disseminate with equal effort, emphasis and frequency, the results of all other studies reported by qualified researchers as well as clinical opinions of outstanding diabetologists which disagree with or controvert UGDP study and the conclusions extrapolated therefrom.

(8) That your petitioners be provided with full and complete answers to the following questions:

(*a*) By virtue of what statute, regulation, rule, or other legal authority does the Food and Drug Administration establish therapeutic regimens by stating preferences—i.e., first, diet; second, insulin and third, oral agents—in its Bulletins marked Appendix A and Appendix B of this petition?

(*b*) Why did the Food and Drug Administration ignore the views of the majority of its own Advisory Committee on Diabetes, a committee that was composed of four diabetologists, two biostatisticians and a biochemist? That majority was not willing to accept the conclusions of the UGDP report.

(9) That any other relief be granted that the Food and Drug Administration may deem meet and proper to fulfill the spirit and letter of this petition.

Respectfully submitted.

ROBERT F. BRADLEY, M.D.,
Medical Director, Joslin Clinic, Boston, Mass.
HENRY DOLGER, M.D.,
Professor of Clinical Medicine, Mount Sinai School of Medicine, City University of New York, New York, N.Y.
PETER H. FORSHAM, M.D.,
Chief of Endocrinology, Professor, Department of Medicine, University of California Medical Center, San Francisco, Calif.
HOLBROOKE S. SELTZER, M.D.,
Chief of Endocrinology, Professor of Internal Medicine, Veterans' Administration Hospital, University of Texas, Southwestern Medical School, Dallas, Tex.
NEIL L. CHAYET, Esq.,
Attorney for the Committee.

(Note.—Appendixes supplied by the FDA were too voluminous to be incorporated in this volume, and were retained in Committee files.)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., June 5, 1972.

NEIL L. CHAYET, *Esq.*,
Chayet & Flash,
Boston, Mass.

DEAR MR. CHAYET: This is in response to your petition filed on behalf of the Coordinating Committee of the Committee on the Care of the Diabetic, requesting the Food and Drug Administration to rescind its decision to require new labeling for oral hypoglycemic agents. We have considered both the submission filed on October 7, 1971, and the additional material filed on January 10, 1972.

We have considered your petition in two parts. The petition first questions the legal authority of the Food and Drug Administration to require the labeling in question on the ground that this regulates the practice of medicines. This aspect of the petition is considered in Part I below. The petition then questions the scientific reliability of the UGDP Study and argues that it is not adequate support for the proposed labeling. This aspect of the petition is considered in Part II below, as supported by Appendix A and its attachments.

I. THE LEGAL ISSUES

Your petition contends that, because FDA's legal authority extends solely to the regulation of the safety and effectiveness of drugs, and not to the control of medical or scientific practices, the Agency may not legally require the use of labeling for oral hypoglycemic agents which limits their recommended use to selected cases under specified circumstances. You also argue that such labeling would violate the statute by failing to state that there is a large body of opinion contrary to this proposed labeling. Each of these arguments is considered separately below.

A. *The legal status of the package insert.* Your first argument, that FDA is without legal authority to require the labeling in question, misconceives the scope of the Federal Food, Drug, and Cosmetic Act, as intended by the Congress.

Section 502(a) of the Act states that a drug is misbranded if its labeling is false or misleading in any particular. Section 201(n) of the Act further states that, in considering whether labeling is misleading, the Food and Drug Administration must take into account the extent to which the labeling fails to reveal facts material in the light of other representations or material in the labeling, with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use contained in the labeling or that are customary or usual. Both of these provisions were included in the statute as enacted by Congress in 1938.

During 1938–1962, Section 505 of the Act also required submission to FDA of a new drug application (NDA) which FDA could permit to become effective if the safety of the drug was demonstrated. In 1962, Congress amended this law to require explicit FDA approval of both safety and effectiveness for every new drug. Section 505(d), as added to the statute in 1962, provides three relevant bases for refusing to approve an NDA: insufficient information to determine whether the drug is safe for use under the conditions set out in the proposed labeling, a lack of substantial evidence that the drug will have the effect it purports to have under the proposed labeling, or that based on a fair evaluation of all material facts the labeling is false or misleading in any particular.

It is true that, throughout the debate leading to enactment of the 1938 Act, there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice, and references to the understanding that the bill did not purport to regulate the practice of medicine. Congress recognized a patient's right to seek civil damages to the courts for malpractice, and declined to provide legislative restrictions upon the medical profession. The legislative history of the 1962 Amendments confirms this Congressional intent. The legislative debate indicates that Congress did not intend to regulate the practice of medicine as between the physician and the patient.

It is equally clear, however, that Congress did intend that FDA determine those drugs for which there exists substantial evidence of safety and effectiveness and which thus will be available for prescribing by the medical profession, and what information constitutes truthful and accurate full disclosure about the drugs to permit the physician to prescribe them safely and effectively. As the law now stands, therefore, the Food and Drug Administration is charged with the statutory responsibility for judging the conditions under which a drug may safely and effectively be used and for approving labeling that fully conveys this information to the physician. The physician is then charged with the professional responsibility for exercising his judgment in prescribing the available drugs in the light of the information contained in their labeling.

The basic question, therefore, is whether there is adequate scientific basis for the labeling with which your petition is concerned. If there is such a basis, there is no question but that FDA has the legal authority, and indeed is obligated by law, to require the labeling of all oral hypoglycemic agents to be changed to reflect that information. It similarly follows that, if the labeling must be so changed, FDA is obligated under the Act to inform physicians and the public, through such media as the FDA Drug Bulletins, about this important change in labeling.

You express concern that the failure of a physician to follow a package insert may render him liable for malpractice. The package insert is not intended either to preclude the physician from using his best judgment in the interest of the patient or to impose liability if he does not follow the package insert. Although package inserts, along with medical texts and expert opinion, may constitute evidence of the proper practice of medicine, they are not controlling on this issue.

The Food and Drug Administration recognizes that the physician must retain his professional judgment in prescribing drugs in the best interest of the individual patient and that a rigid rule cannot be imposed for all situations. A physician should also recognize, however, that the package insert represents a summary of all information on the conditions under which the drug has been shown to be safe and effective by adequate scientific data submitted to the Food and Drug Administration.

We are concerned that you and others misconceive the legal responsibilities of FDA, the status of the package insert, and the responsibilities of a physician when he concludes not to follow the conditions of use approved by the Food and Drug Administration through the package insert. We hope that the above explanation clarifies the situation from the legal standpoint.

B. *Fair balance.*—Your second legal argument is that, assuming that the scientific evidence on the use of oral hypoglycemic agents is equally divided, or at least that there is substantial scientific evidence and opinion on both sides of the issue, FDA should require the labeling to reflect both positions in order to achieve fair balance.

When the Federal Food, Drug, and Cosmetic Act was enacted in 1938, evaluation of drug safety and effectiveness was relatively unsophisticated as compared with today. It was largely the opinion of individual physicians who had tried

the drug on patients that determined whether the product would be considered safe and effective. Congress therefore included in the 1938 Act a provision under Section 201(n) which provided that differences of opinion with respect to the effectiveness of a drug could be handled by stating both sides of the issue in labeling.

Since 1938, enormous progress has been made in the methodology for evaluating both the safety and the effectiveness of a therapeutic agent. Congress therefore concluded in 1962 that unsubstantiated expert opinion could no longer suffice to establish the effectiveness of drugs, and that in the future controlled clinical studies would be required. The concept of using the package insert to debate the proper medical use of a drug was thus replaced by a requirement that the drug be proved safe and effective by the most rigorous scientific standards available.

Congress has delegated to the Food and Drug Administration the legal duty of determining whether substantial evidence exists to prove the safety and effectiveness of drugs. While these determinations often involve close questions, they are questions that are required by law to be resolved definitively, and they cannot be avoided. Because of the importance of the issues involved, we often consult outside experts, advisory committees, and professional organizations. In the vast majority of instances, including this one, the decisions on safety, effectiveness, and labeling comport with the weight of medical and scientific opinion.

It must be recognized that there is probably no statement in any package insert for any drug on which at least one, and perhaps more, individuals could not be found to raise questions that they believe important and significant, backed up by at least some kind of literature reference or opinion. The Food and Drug Administration is required, however, to determine the conditions of use under which the drug has been proved safe and effective by substantial evidence. This requires the Food and Drug Administration to act as an independent arbiter on medical issues, and means that inevitably its decisions will not meet with unanimous scientific agreement.

Unless this is done, the welter of conflicting and confusing statements that would be found in package inserts would overwhelm the practicing physician and create chaos for the public. It is not the function of the package insert to present all sides of an issue. This is properly done in textbooks and journal articles, and in scientific discussion. The function of the package insert is to set out, in relatively concise terms, a summary of the conditions for use, based upon the best scientific evidence presented to the Food and Drug Administration about the drug. Except perhaps in rare instances where there is substantial evidence on both sides of an issue, therefore, it is inappropriate to utilize the package insert to present all aspects of the evidence relating to safety and effectiveness, or otherwise to debate medical questions.

We do believe in testing the validity of our determinations through the normal process of scientific debate and peer review, as well as through the statutory appeal processes. Where we are shown to be in error, we have not been slow to correct that error.

It would be the rare situation where there is substantial evidence that both proves and disproves the safety or effectiveness of a drug, and thus justifies equal consideration in labeling. Certainly, that is not the situation involved here. In virtually all cases, including this one, analysis of the available data and information leads to a reasonably reliable determination one way or the other. It is therefore our opinion that there is no basis for requiring or permitting the labeling of oral hypogycemic agents to present a variety of view-pointn on the safety and effectiveness of these drugs, since to do so would abdicate the legal responsibility of the Food and Drug Administration and result in highly confusing and misleading labeling.

II. THE MEDICAL ISSUES

Your petition questions the scientific reliability of the UGDP Study on a number of grounds, the argues that it is not adequate support for concluding that, in the treatment of diabetes, diet alone should first be used, and then insulin, and then the oral hypoglycemic agents. We have carefully reconsidered this matter in the light of the arguments contained in your petition. Our position on the validity of the UGDP Study, on the weight that should be given to that and other studies, and on the labeling that will be required as a result of the available scientific evidence relating to safety and effectiveness of diabetic treatment methods, is set out in full below.

A. *The scientific reliability of the UGDP Study.*—Appendix D of your petition challenges the statistical methodology of the UGDP Study. Other highly qualified experts have defended the UGDP methods and analysis. Their explanations, findings and conclusions are set forth in detail in Appendix A to this response.

Doubtless there are weaknesses in the UGDP Study, as there are in most complex clinical studies. A number of criticisms have been directed at the design and methodology of the Study; these are described and addressed in Appendix A. Despite the merit of some of these and perhaps other criticisms, the UGDP Study presents the best medical evidence available at this time on the cardiovascular hazards of oral hypoglycemic drugs.

Your petition presents only one side of the medical literature on the UGDP Study. We have attached to Appendix A additional articles and editorials which strongly support the reliability of the UGDP Study and reject the conclusion that it should not be given serious consideration. The AMA Council on Drugs has stated:

"Although some flaws exist in the UGDP study it clearly demonstrates that every effort should be made by the physician to control the symptomatic maturity-onset diabetic with diet alone. Should this fail, treatment with insulin oral hypoglycemic agents should be undertaken. If oral hypoglycemic agents are selected for therapy, the results of the UGDP study should be kept in mind. Therefore, the consideration of treatment with oral hypoglycemic agents should be secondary to the use of insulin."

The Ad Hoc Editorial and Advisory Committee on the American Diabetes Association has similarly concluded that:

"In adult onset diabetes with hyperglycemia and glycosuria, symptomatic or not, and in the absence of a ketosis a trial with an appropriate diet should come first. If this does not establish satisfactory control insulin is to be preferred to other therapeutic agents because it is more uniformly effective in controlling hyperglycemia and the UGDP study indicated that it may be safer."

Your petition states that the results of the UGDP Study are not available and therefore not subject to the usual critcial review. We have been assured that the UGDP personnel will honor any reasonable request for data and information.

Finally, you state that FDA acted against the advice of its own advisory committee in accepting the results of the UGDP Study. A review of the minutes of the ad hoc committee convened to discuss this subject in May 1970 indicates that this was not the situation. A copy of those minutes is also attached to Appendix A.

In short, we see no basis for ignoring the findings of the UGDP Study. They must be given very serious consideration by the Food and Drug Administration and the medical profession.

B. *The weight accorded to the UGDP and other studies.*—There now exists substantial evidence of the safety and effectiveness of three different treatment methods for adult-onset diabetes: (1) diet and reduction of excess weight, (2) diet plus insulin, or (3) diet plus oral agents.

From the standpoint of safety, there is overwhelming evidence that diet and reduction of excess weight is preferable to any form of drug therapy. It is well known that drugs have side effects, and that insulin and the oral hypoglycemic drugs clearly produce side effects not attributable to diet alone.

Where diet alone is not adequate to control diabetes, a choice must then be made between insulin and the oral agents. Although the UGDP Study constitutes strong evidence that insulin is safer than the oral agents, because of a lower incidence of cardiovascular death, it cannot yet be said that this has been proven conclusively.

Your petition appended reports by Keen et al., and Paasikivi, presumably to indicate no cardiovascular danger from prolonged tolbutamide therapy. Careful review of these reports reveals that they cannot be considered comparable to the UGDP Study, and thus that they are insufficient evidence to negate the findings of the UGDP Study. (A discussion of these studies may be found on pp. 19 and 19a of Appendix A.) Nor are we aware of any other existing data that justify rejection of the findings of the UGDP Study.

C. *The product labeling required to reflect the available evidence on the safety and effectiveness of diabetic treatment methods.*—As a result of our analysis of the available data, we are requiring product labeling to reflect the following information.

Indications: Oral hypoglycemic drugs are indicated in the treatment of adult-onset, non-ketotic diabetes mellitus only when the condition cannot be controlled adequately by diet and reduction of excess weight alone.

Because of the increased cardiovascular hazard which appears to be associated with oral hypoglycemic agents, the drugs should be used only after full consideration of the special warning.

Special warning: Diet and reduction of excess weight are the foundations of initial therapy of diabetes mellitus. When the disease is adequately controlled by these measures, no hypoglycemic drug therapy is indicated.

Because of the apparent increased cardiovascular hazard associated with oral hypoglycemic agents, they are indicated in adult-onset, non-ketotic diabetes mellitus only when the condition cannot be adequately controlled by diet and reduction of excess weight alone, and when, in the judgment of the physician, insulin cannot be employed because of patient unwillingness, poor adherence to injection regimen, physical disabilities such as poor vision and unsteady hands, insulin allergy, employment requirements, and other similar factors.

Since the association of tolbutamide and phenformin with increased cardiovascular hazard is shown by strong evidence although not yet conclusive proof, it must be reflected in labeling by a warning which clearly states that insulin should be used in preference to oral agents where that is feasible, because of benefit-risk considerations.

This new evidence of an increased risk is placed in a Special Warning section, explicitly cross-referenced by a statement in the Indications section because special labeling is required to correct the current erroneous impressions of many physicians accustomed to using these drugs according to their former labeling.

A copy of the new labeling for the oral agents is attached as Appendix B.

III. CONCLUSIONS

Your petition has been extremely helpful in prompting us to evaluate and articulate our position on the labeling of drugs.

Because of the importance of the issues that you raised and that are discussed in this response, we are taking the liberty of sending a copy of this response and the attachments to all of the individuals who signed the petition or wrote to me indicating their support for it.

Finally, I again wish to thank you and all the others who participated in the petition. We welcome critical review of all of our actions. It is not just the right, but indeed the responsibility of physicians and all other citizens to petition us whenever they believe that inadequate or incorrect action has been taken, or that action which should be taken has not been undertaken. In this way, we can be helped to do a better job.

Sincerely yours,

CHARLES C. EDWARDS, M.D.,
Commissioner of Food and Drugs.

(NOTE.—Attachments supplied by the FDA were too voluminous to be incorporated in this volume, and were retained in Committee files.)

APPENDIX II

UNITED STATES GENERAL ACCOUNTING OFFICE
Washington, D.C. 20548

For release on delivery
expected at 10 am. EDT
Wednesday, May 10, 1972

STATEMENT OF
ELMER B. STAATS, COMPTROLLER GENERAL OF THE UNITED STATES
BEFORE THE
MONOPOLY SUBCOMMITTEE
SELECT COMMITTEE ON SMALL BUSINESS
UNITED STATES SENATE

on

DIRECT AND INDIRECT EXPENDITURES
BY FEDERAL AGENCIES FOR PRESCRIPTION DRUGS

We are pleased to be here today to discuss our work related to procurement and reimbursement for prescription drugs by the Federal Government and related matters.

Among the matters we will comment on are:

--Actions taken to assure that only effective and low cost equivalent drugs, when available, are procured by the Government or paid for under Government sponsored medical programs.

--Information sources used by physicians in selecting drugs.

--Use of Government specifications in the procurement of drugs.

--Quality assurance and inspection procedures of Federal agencies.

--Coordination and cooperation between Federal agencies which buy drugs.

--Procurement of drugs of foreign origin.

--Policies and practices pertaining to furnishing drugs under the Medicare and Medicaid programs.

Estimates indicate that direct Federal procurements of prescription drugs amounted to about $240 million for fiscal year 1971. Most of these procurements were made by the Defense Supply Agency, through the Defense Personnel Support Center (DPSC), and the Veterans Administration (VA).

DPSC manages about 1,100 drug items on a centralized basis and spent about $95.5 million for drugs in fiscal year 1971. The VA manages about 450 drug items on a centralized basis and procured for central stock drugs valued at $27.4 million in fiscal year 1971. The VA also administers Federal Supply Schedule contracts under which Federal agencies can satisfy their drug requirements by direct purchases from drug manufacturers. Purchases under these contracts by all Government agencies for fiscal year 1971 amounted to about $64 million. The Public Health Service centrally manages about 600 drug items and spent an estimated $14.2 million for drugs in fiscal year 1971. About 50 percent of this amount was spent under contractual arrangements made by VA.

A substantial portion of Federal expenditures for prescription drugs are indirect, consisting principally of the Federal share of the cost of drugs provided to beneficiaries under the Medicare and Medicaid programs. The Department of Health, Education, and Welfare (HEW) estimates that Medicaid expenditures for prescribed drugs for fiscal year 1971 amounted

to about $485 million, of which about $246 million represented the Federal share and the remaining $239 million the State and local share. Expenditures for prescription drugs under part A (hospital services) of Medicare for fiscal year 1971 were estimated at $541 million. No information is available on expenditures under part B (physician services) of Medicare.

Although we have not completed our work with respect to examining into the effectiveness of administration and management of Federal programs for procurement and distribution of drugs, it is already clear that standardized procedures and improved cooperation and coordination among the Federal procurement agencies currently involved in (1) procuring and distributing drugs, (2) financing the supply of drugs to beneficiaries under the Government's social programs, and (3) evaluating the effectiveness of drugs, would be beneficial in reducing costs and providing service.

ACTIONS TAKEN BY FEDERAL AGENCIES TO ASSURE THAT ONLY EFFECTIVE DRUGS ARE PROCURED AND THAT FEDERAL PROGRAMS MINIMIZE USE OF HIGH COST DRUGS

As of January 19, 1972, the Food and Drug Administration (FDA) had published 2,339 reports as to the effectiveness of drug preparations for the indications claimed in their labeling, and had reported them in the Federal Register. At that time FDA recognized that several problems pertaining to drug efficacy remained. Briefly they concerned:

--Conflicting reports relating to several drugs;

--Speeding up the progress on follow-up actions for drugs requiring evidence to be rated "effective";

--Completing compliance activities currently in process pertaining to "ineffective" drugs;

--Completing the review, which FDA expects to publish by June 30, of the remaining drug study reports; and

--Pursuing plans for evaluating the effectiveness of over-the-counter drugs.

Actions taken by the Department of Defense

As of November 18, 1971, the Defense Medical Material Review Board had initiated action to stop further procurement and to eliminate from the supply system all items that FDA had then pronounced "ineffective" or "possibly effective". Also, the Surgeons General of the military departments have emphasized through instructions to medical

organizations the DOD policy on such drugs, which became effective January 21, 1971. This policy provides that for "ineffective" items subsequently withdrawn from the market, remaining stocks are to be destroyed or other appropriate action taken to remove them from the inventory. For items categorized "ineffective" but awaiting final determination by FDA, further use of remaining stocks is suspended until the final status is announced. Pharmacy and Therapeutic Agents Committees are required to question all prescriptions for "possibly effective" items, but local procurement of such items may be made if no alternative means of therapy is available.

No "ineffective" drugs have been purchased by DPSC for central stocks since the pertinent pronouncements in the Federal Register, but we are aware of a Federal Supply Schedule purchase of one item, Darvon (32 milligram), for initial treatment of seriously underweight geriatric patients. Also, 24 procurements valued at $1.5 million have been made of "possibly effective" drug items by DPSC for central stock since the FDA pronouncements. Twenty of these buys, valued at over $1.4 million, were made before the DOD policy prohibiting further procurements of "possibly effective" drugs was issued in January 1971.

Following this Subcommittee's hearings in 1970, DOD established a committee to conduct an item by item review of drugs, chemicals, and biologicals in the Federal Supply Catalog to identify high cost, possibly ineffective, or duplicate items, and to initiate action to minimize the use of high cost drugs where lower price equivalents are available.

Items so identified were to be reviewed by the military services to determine whether they should be deleted from the supply system. As of January 1972, seven items had been deleted and 57 items had been reclassified to a status prohibiting further procurements. Included in the 57 items were seven for which lower cost equivalent drugs were available in the supply system. Based on reported unit costs and demand, annual savings in excess of $1.1 million will be realized if the deleted items are not obtained via local purchase. Specific actions to stop local purchase of such items have not been taken because it would tend to dictate the drugs physicians can prescribe.

Actions taken by the Veterans Administration

A VA circular of December 4, 1970, transmitted to hospitals and clinics a listing of "ineffective" drugs and stated that the Executive Committee on Therapeutic Agents had recommended that VA hospital therapeutics committees remove these items from their formularies. If the hospitals and clinics wished to retain any of the drugs they were required to obtain approval from the Executive Committee. This has been done for certain drugs being used for research.

The hospitals were requested to advise fee basis physicians of VA's policy on these drugs and to attempt to get them to prescribe alternatives. Information on FDA pronouncements made after December 4, 1970, has been sent by the VA headquarters to its hospitals and clinics.

The VA policy for "possibly effective" drugs is that consideration should be given to using alternative products having a higher FDA effectiveness classification. The VA purchased seven "ineffective" drugs for central stock after

FDA pronouncements appeared in the Federal Register. Procurement of six of the seven items was discontinued after the VA policy was issued on December 4, 1970. The other item was purchased for over 2 years after the FDA pronouncement because it was inadvertently excluded from the list of "ineffective" drugs issued on December 4, 1970. The VA Marketing Center has now been instructed to suspend issuance of all "ineffective" drugs and to negotiate with manufacturers for return of existing stocks for credit.

The VA continues to purchase "possibly effective" drugs, apparently because of its philosophy that it should not take actions that would unduly restrict the prescribing practices of physicians.

On January 13, 1971, VA hospitals and clinics were advised to ensure that every effort be made to treat VA patients with the most effective therapeutic agents at the most favorable prices. Also, VA hospital therapeutic committees were requested to continually review prescribing practices--with due regard to the effectiveness and fluctuating prices of drugs--as patents expire, or competitive market conditions make price advantages available. Also, the hospital therapeutic committees were advised that the purchase of high cost drugs could not be justified when equally effective, but less expensive, items are available.

Actions taken by the Department of Health, Education, and Welfare

HEW has also acted to implement the FDA procurements related to the effectiveness of drugs. The Surgeon General on December 11, 1970, established the policy that the Department would not spend Federal funds for (1) "ineffective" drugs, except under approved clinical research projects, or (2) for "possibly effective" drugs, except under approved clinical research projects or when alternate

means of therapy are not available. On January 19, 1971, the Department instructed its agencies that provide direct patient care to stop the procurement and use of such drugs and to advise contract physicians of the Department's policy.

The December 1970 policy announcement stated that the policy also applies to Government financed programs and the Federal Register of October 16, 1971, contains the proposed regulation for Medicare. The Department planned to furnish Medicare carriers and intermediaries with listings of "ineffective" and "possibly effective" drugs to be excluded from reimbursement under the Medicare program. However we understand that the Department has recently undertaken a reevaluation of whether to extend the December 1970 policy to Government financed programs.

In January 1971, the Medical Services Administration of the Social Rehabilitation Service, HEW, notified all Associate Regional Commissioners for Medical Services of the departmental policy relating to purchases of "ineffective" and "possibly effective" drugs. The Medical Services Administration stated that program regulations were being amended to implement this policy for Medicaid. As of May 1, 1972, regulations have not been issued to implement the revised Federal drug policy for Medicaid.

Since 1966 HEW has required that Federal funds be expended only for the lowest priced drugs consistent with acceptable standards of identity, strength, quality, purity, and effectiveness. Information we have obtained on the Medicaid program in four states shows usage of "ineffective"

or "possibly effective" drugs. For example under the Medicaid program we found that in Mississippi during a 7-1/2 month period in 1970-71 nearly $90,000 was paid for two prescription drugs classified by FDA as "ineffective" and one as "possibly effective". In Ohio, during 4 months in 1970, about $138,000 was spent for 43 drugs classified as "ineffective" by FDA and in Illinois and New Jersey during 2 months in 1970 about $99,000 was spent on prescriptions for 10 randomly selected drugs classified by FDA as "ineffective". See Appendix I for a summary of such drugs paid for in Mississippi, Illinois, Ohio, and New Jersey.

INFORMATION SOURCES USED BY PHYSICIANS IN SELECTING DRUGS

In the 1971 hearings, the Subcommittee expressed interest in the sources of information considered by physicians in making their selections of prescription drugs.

Two studies, one by Milton S. Davis, Ph.D. and Lawrence S. Linn, Ph.D., under a Social Security Administration grant and the other by a Professor of Pharmacy and Pharmaceutical Chemistry, University of California, shows that detail men were the most important source of information to physicians.

The American Medical Association (AMA) in 1971 published a manual entitled "AMA Drug Evaluations" to provide physicians with a convenient source of information for the sound use of drugs. This manual contains an evaluation by the AMA Council on Drugs regarding the effectiveness of drugs, information on the pharmacology and therapeutic indications of drugs, and preparations available, dosage, and generic and proprietary names.

The manual was distributed free to all members of the AMA--about 300,000, of which 170,000 are practicing physicians. Large numbers have also been purchased by the Government, pharmacists, physicians in residence and intern training, nurses, and medical students. In 1972, the AMA began a survey of 2,000 physicians to determine the extent to which this manual has been used. The AMA hopes to complete the survey in June 1972.

We understand that a second edition of the manual is scheduled for publication shortly and will include changes designed to make it more useful including dosage guidelines, ingredients of over-the-counter drugs, and additional trade name items.

GOVERNMENT SPECIFICATIONS FOR DRUGS

One requirement of an efficient supply system for prescription drugs is the development of specifications which can be used to encourage competition and assure controlled quality production of drugs with the desired therapeutic effect.

Both DPSC and VA develop specifications for items they intend to buy competitively. These items account for about 25 percent of all VA centrally managed drug items and 99 percent of all DPSC centrally managed drug items. The remaining items procured centrally by the agencies are designated for purchase from preselected sole sources. Data for preparation and development of DPSC specifications is obtained primarily from the manufacturers of drug products.

Although DPSC attempts to purchase virtually all of its drug items competitively, it has been able to do so for only about 51 percent of its approximately 1,100 drug items. The

remainder, about 535 items, have been supplied by single sources. Of these, competitive procurement of 386 is limited by patents or by FDA regulatory requirements which preclude marketing without an approved new drug application or antibiotic certification. The remaining 149 items have no apparent legal or regulatory restrictions that would preclude interested firms from submitting bids on DPSC requirements.

In 1969 and 1971 DPSC made a widespread effort to develop competition on a large number of drug items but the responses were few and disappointing.

Basically DPSC's specifications require full compliance with the product standards and requirements set forth in the United States Pharmacopeia (USP) or National Formulary (NF). But additional requirements are often included to provide assurance that items manufactured will have needed characteristics for such requirements as potency and purity, from the time of manufacture to use. Only about 50 percent of the drug items managed centrally by DPSC and 65 percent of those managed centrally by VA are monographed in the USP and NF.

The use of manufacturers' data by DPSC in the development of its specifications could result in including requirements which are not essential to producing a comparable product or which do not contribute to its medical usefulness. However, DPSC includes in its solicitation packages a Specification Analysis Sheet for potential suppliers to submit comments on the specification requirements and those that bidders claim are unnecessary or unduly restrictive are evaluated by DPSC.

We found that it was common for manufacturers to add requirements to those in the compendia (USP and NF) for products they sell to the general public. Comments by manufacturers and compendia officials and statements in professional publications explain that the additional requirements are added for controlling manufacturers' production processe and to ensure product quality and uniformity.

The DoD practice of establishing a specification for every drug item in its central supply system, while commendable for purposes of broadening and equalizing the competitive base and assuring the receipt of acceptable products, results in unnecessary technical and administrative effort when the policy extends to drug items which, because of legal or regulatory restrictions, are obtainable from only one source.

The VA, after its appearance before your Subcommittee in 1970, began developing specifications for 115 sole source items for which competition appeared feasible. We were informed on May 1, 1972, that 36 final specifications had been issued as a result of this effort.

QUALITY ASSURANCE

In our last appearance before the Subcommittee we reviewed the quality control activities of FDA, DPSC, and the VA. We have noted (1) apparent overlap of these activities, (2) the acceptable results obtained by VA from its minimal inspection efforts supplemented with the use of FDA testing services, and (3) that substantial military procurements are made each year from Federal Supply Schedules and local vendors--about $21 million in fiscal year 1970--based

only upon the quality assurance work of the FDA. We suggested in our statement that consideration should be given to assigning sole responsibility to FDA for inspecting drug contractor plants and testing products and quality control procedures.

So far as we are aware no action has yet been taken to consider the advisability and feasibility of centralizing drug inspection along these lines. The estimates of manpower requirements and administration costs, including inspection activities, involved in the DoD and VA procurement systems for drugs are provided in Appendix II.

COOPERATION AND COORDINATION AMONG AGENCIES MAKING DIRECT PROCUREMENT OF DRUGS

In our previous statement we suggested that closer cooperation between VA and DPSC could result in substantial savings in the procurement of drugs. Our subsequent review work confirms that improvements can be made.

We found little exchange of requirements data or coordination of procurements for drugs which are centrally stocked by both organizations, or those centrally stocked by one system but procured from either Federal Supply Schedule contracts or from local vendors by the other system. The VA negotiates several special contracts which exclude military activities and, in some cases, other civilian agencies from using them. The military uses Federal Supply Schedule contracts for its requirements for items in these special contracts and pays prices higher than those in the contracts. The lack of adequate cooperation and coordination has resulted in increased drug costs to the Government.

The VA has an agreement with DPSC under which it can buy drugs from DPSC for its central stocks. In fiscal year 1970 purchases from DPSC were only about $206,000. One drawback to this agreement is the add-on of surcharges by DPSC and the VA Marketing Center for drugs supplied to VA field stations. DPSC charges the VA Marketing Center its standard price (cost plus 7 percent) plus a 3-1/2 percent surcharge for packing, handling, and crating costs for medical items shipped from DPSC depots; a total add-on of 10-1/2 percent. For items shipped directly from a vendor to the VA depot, DPSC adds a one percent surcharge, for administration, to the cost of the items. The VA Marketing Center adds an 8 percent surcharge on all items bought from DPSC to recover its operating costs.

VA field stations do not order directly from DPSC because the VA requisitioning system requires the stations to submit requisitions, other than for local procurements, via the VA Marketing Center. As a result, certain drug items are purchased by the field stations from either the Federal Supply Schedule contractors or local vendors at substantially higher prices than they could obtain them from DPSC. The flow of drug items from DPSC depots or manufacturers to VA depots and then to VA field stations is cumbersome and results in extra handling and added transportation costs.

Even though the addition of surcharges discourages procurement from, or through DPSC, we found many cases where ultimate prices to the VA stations would have been significantly lower than the prices paid by these stations. For example, if VA field stations had purchased Aristocort

(8 ounce jar) directly from DPSC the cost would have been $39.85 per jar, with all surcharges, instead of $46.07 paid on the Federal price list. Total savings for this drug item alone during calendar year 1970 would have amounted to over $4,600. Further, even with the 8 percent surcharge of the VA Marketing Center a savings of $3.03 per jar would have been realized.

The military has made no formal arrangements to allow its activities to purchase from VA depots drug items which are not centrally managed by DPSC. During the period July 1, 1970, to December 31, 1971, military hospitals purchased about $550,000 of the drug Macrodantin from the Federal Supply Schedule at about $275,000 more than it would have cost to buy from VA at the contract price. This item has now been approved for inclusion in the DOD central supply system and a contract has been awarded by DPSC at prices comparable to those negotiated by the VA. But, until delivery is received under the DPSC contract, military hospitals will continue to purchase the item at the higher Federal Supply Schedule price.

Our examination of invoices and sales records for purchases totaling about $6.2 million from four manufacturers during a recent two-year period showed that the Government incurred excess costs of about $721,000 because (1) many drugs were purchased by local installations at prices which ranged as much as 100 percent higher than prices available to DPSC and VA Marketing Center, (2) prices paid for the same drugs differed between DPSC and VA Marketing Center, and (3) there were purchasing weaknesses at VA and DPSC field stations.

Our review of DPSC and VA procurement records for 43 identical drug items purchased by both agencies within 30 days of each other during fiscal years 1970 and 1971 showed excess costs of at least $246,000--split approximately equally between the VA and DPSC--resulted from the differences in prices paid for these items.

From 1964 to 1971 several studies have been made by the Defense Supply Agency and the General Services Administration, separately and jointly, to determine the feasibility of a single agency having Government-wide responsibility for management of various categories of supplies including medical materials. The studies indicated differences of opinion on the feasibility of consolidating the procurement and management of medical items. Decision on this has been deferred pending the outcome of a current study.

The Office of Management and Budget in January 1972 initiated a joint study by DOD, the General Services Administration, HEW, and VA to determine the lowest cost system or combination of systems to achieve maximum economy in meeting Government-wide needs for medical material, including drugs.

We believe that procurement costs can be reduced significantly by better cooperation and coordination between the VA and DPSC. However, the differences in their procurement practices, such as the respective volumes of procurements of brand-name and generic items, use of specifications, and inspecting and testing requirements, must be reconciled to ensure that drugs will be purchased at the lowest possible cost to the Government.

PROCUREMENT OF DRUGS OF FOREIGN ORIGIN

Studies by HEW covering world drug prices in 1970 and 1971 show that prices charged by manufacturers to druggists in the United States were generally higher than prices charged to druggists in other countries for the same drug. Recent comparative data is provided in Appendix III.

Although drugs of foreign origin are frequently priced lower than comparable drugs of domestic origin the following factors influence procurement of the cheaper drugs:

1. FDA's New Drug Application (NDA) requirements. DoD and VA normally will not procure drugs which require an NDA approval from firms which do not have them. Foreign firms sometimes do not have the required NDA approval.

2. Inability of some foreign firms to satisfy American manufacturing standards for such matters as quality control and good housekeeping.

3. Possible legal action on patent infringements.

4. Implementation of the Buy American Act (41 U.S.C. 10 a-d).

For evaluating bids or offers of foreign firms for their products against offers of domestic products, civilian agencies are required by the Federal Procurement Regulations, which implement the Buy American Act, to add to the foreign bids or offers a price differential equivalent to 6 percent, inclusive of import duties, or 12 percent, inclusive of import duties, if the low domestic bid is a small business or distressed labor area concern. Military departments generally add a price differential of 50 percent to bids or offers of foreign products, exclusive of import duties, for evaluation

purposes, when a 6 or 12 percent differential, plus import duties, does not result in a greater evaluated price for the foreign products.

The effect of adding these price differentials can be seen in a procurement of 310,464 units of tetracycline hydrochloride tablets by DPSC in April 1971. The low foreign bid was $.85 a unit, excluding duty, and the low domestic bid was $1.19 a unit. After an evaluation using the 12 percent factor plus duties, the foreign bid was still low. But, an evaluation using the 50 percent differential resulted in the domestic bidder being low and receiving the contract. After considering discount and freight, this procurement cost almost $107,000 more than it would have from the foreign source.

Because of the above influences neither DPSC nor VA normally make any special effort to develop foreign sources for their drug requirements even though prices of drugs of foreign origin, as a general rule, are lower than domestic prices. Efforts to obtain bids from foreign sources are limited to the actions normally taken to obtain bids from any source, that is, solicitations are sent to the few foreign firms on the bidders list at the time they are sent to other potential suppliers and the proposed procurements are announced in the Commerce Business Daily. The VA also sends copies of its solicitations for items to be procured competitively to publishers of a number of marketing publications.

In November 1971 VA wrote to several Canadian firms inquiring whether they marketed three specific drug items in the United States. Four of the eight replies said that the

firm did not yet have the necessary NDA approval and the others said that they did not market or manufacture the items.

Appendix IV shows the drug items procured from foreign firms in the years 1968 through 1971 by DPSC and VA.

POLICIES, REGULATIONS, AND PRACTICES PERTAINING TO FURNISHING DRUGS UNDER THE MEDICAID AND MEDICARE PROGRAMS

Medicaid

The current HEW policy for the payment for prescription drugs under the Medicaid program does not require uniform procedures and practices to be followed by the States. Also, the use of a formulary is optional, but where one is used standards for quality, safety, and effectiveness must be set and supervised by professionals. The Social and Rehabilitation Service is responsible for administering the Medicaid program.

The formulary system should be broad enough to enable physicians and pharmacists to select high quality drugs of recognized therapeutic value for the treatment of any medical situation. Approximately 20 States have attempted to control the cost of drugs in their Medicaid programs through the use of formularies. Attempts have also been made by the States to limit certain drugs in their formularies to generic names.

In November 1970 we reported to the Congress that significant savings could be available to the States and the Federal Government if physicians were to prescribe lower-priced, chemically equivalent drugs instead of higher-priced

brand-name drugs. We pointed out that the HEW Task Force on Prescription Drugs reported in December 1968 that of the 409 brand-name drugs most frequently prescribed for elderly persons in 1966, chemical equivalents for 63 of these were available at lower costs. These 63 drugs accounted for about one-fourth of the prescriptions for the 409 drugs, and the task force computed that prescribing the lower cost chemical equivalents would have resulted in annual savings of $41.4 million.

The HEW task force reported also that physicians were not always aware of low-cost, chemically equivalent drugs produced by competing manufacturers or were reluctant to prescribe such drugs until their safety and effectiveness had been proven.

Medicare

Regulations for part A of Medicare set forth two basic requirements that must be met in order for a drug or biological to be included as a covered hospital service. It must (1) represent a cost to the institution in rendering service to the beneficiary, and (2) either be included, or approved for inclusion, in the USP, the NF, the U.S. Homeopathic Pharmacopoeia, or New Drugs or Accepted Dental Remedies (except for those unfavorably evaluated), or approved by the pharmacy and drug therapeutics committee (or equivalent) of the medical staff of the hospital for use in the hospital. There are no Medicare regulations concerning the use of generic versus brand-name drugs.

Payments for drugs under part A are made on the basis of reasonable cost. Payments are audited by fiscal intermediaries under contract to the Social Security Administration in accordance with the "prudent buyer concept". Under this concept the Government pays the amount a prudent and cost-conscious buyer would pay for a given item or service.

Under part B of Medicare, coverage of drugs and biologicals is limited to those drugs and biologicals (except for insulin) commonly furnished in physicians' offices which cannot, as determined by regulations, be self-administered. Thus, a drug or biological is reimbursable under part B of Medicare only if it is of a type which is normally not self-administered.

Medicare carriers are responsible for determining whether the services in a given case are reasonable and necessary. In making its evaluation, the carrier is expected to take into account accepted standards of medical practice in its service area. Because accepted standards of medical practice vary from one area to another, the Social Security Administration has issued general guidelines leaving it to the carrier to develop more detailed guidelines which reflect accepted patterns of care in its service area.

Mr. Chairman, this concludes my statement. I shall be happy to answer any questions that you or other members of the Subcommittee may have.

APPENDIX I

LISTING OF DRUGS PURCHASED UNDER THE MISSISSIPPI MEDICAID PROGRAM DURING THE PERIOD 7-1-70 - 2-19-71 WHICH WERE CLASSIFIED EITHER AS "INEFFECTIVE" OR "POSSIBLY EFFECTIVE" BY FDA

Drug name	Classification	Date of FDA classification	Number of prescriptions	Amount paid
Antivert Tablets	Ineffective	3-27-70	13,952	$52,425
Equagesic Tablets	Possibly effective	1-10-70	4,305	20,541
Rautrax-N Tablets	Ineffective	9- 5-69	3,372	15,938
			21,629	$88,904

LISTING OF DRUGS PURCHASED UNDER THE ILLINOIS AND NEW JERSEY MEDICAID PROGRAMS DURING JULY AND OCTOBER 1970 WHICH WERE CLASSIFIED AS "INEFFECTIVE" BY FDA

Drug name	Date of FDA classification	Illinois		New Jersey		Total	
		Prescriptions	Amount	Prescriptions	Amount	Prescriptions	Amount
Alertonic	9-12-69	6,070	$26,021	637	$ 2,271	6,707	$28,292
Terramycin SF capsules	4- 2-69	3,421	18,521	656	3,571	4,077	22,092
Antivert tablets	3-27-70	4,039	17,891	851	3,120	4,890	21,011
Mysteclin F capsules	12-24-68	2,272	11,858	358	1,309	2,630	13,167
Robaxisal tablets	2-11-70	1,346	7,372	-	-	1,346	7,372
Rautrax-N tablets	9- 5-69	804	4,722	-	-	804	4,722
Rautrax tablets	9- 5-69	203	1,314	20	117	223	1,431
Panalba capsules	12-24-68	86	688	-	-	86	688
Esidrix-K tablets	9- 5-69	138	518	-	-	138	518
Panalba-KM drops	12-24-68	25	115	-	-	25	115
Total		18,404	$89,020	2,522	$10,388	20,926	$99,408

APPENDIX I

LISTING OF DRUGS PURCHASED[1] UNDER THE OHIO MEDICAID PROGRAM DURING THE MONTHS OF JANUARY, APRIL, JULY, AND OCTOBER 1970 WHICH WERE CLASSIFIED AS INEFFECTIVE BY FDA

Drug name	Date of FDA classification	Ohio	
		Prescriptions	Amount
Alertonic	9-12-69	10,009	$ 40,707
Terramycin SF Capsules	4- 2-69	2,675	17,090
Achrocidin Tablets	9-12-69	2,278	14,253
Hydropres KA Tabs	9- 5-69	2,272	12,808
Rautrax N Tablets	9- 5-69	980	7,494
Panalba Capsules	12-24-68	942	7,271
Declostatin 300 Tabs	4- 2-69	648	5,642
V-cillin Sulfa Pediatric	4- 2-69	1,316	5,183
Azotrex Caps	4- 2-69	445	3,158
Achrocidin Syrup	9-12-69	518	2,941
Ritonic Capsules	9-12-69	552	2,919
Mysteclin F Syrup	12-24-68	557	2,206
Signemycin Caps "375"	4- 2-69	144	1,426
Declostatin Caps	4- 2-69	204	1,369
Esidrix K Tablets	9- 5-69	360	1,286
Terrastatin Caps	4- 2-69	145	1,260
Tetrex APC w/Bristamin	9-12-69	232	1,171
Rautrax Tablets	9- 5-69	177	1,130
Rutorbin Tablets	1-27-68	165	1,110
CVP w/Vitamin K	1-23-68	182	842
Tetrex AP Syrup	9-12-69	188	806
Frenquel Tabs 100 mg.	4- 2-69	65	801
Hydrodiuril KA Tabs	9- 5-69	211	701
Duo CVP w/Vitamin K	1-23-68	82	526
Ruhexatal w/Reserpine	7-10-68	78	467
Achrostatin V Caps	4- 2-69	98	454
Frenquel Tabs 20 mg.	4- 2-69	62	411
Tetracydin Caps	9-12-69	93	359
Mesulfin Tablets	9-27-69	41	289
Rautrax N Modified Tablets	9- 5-69	70	287
TAO - AC Capsules	9-12-69	52	275
Pentid Sulfas "400" for Syrup	4- 2-69	65	219
Panalba Half STG Caps	12-24-68	41	177
Ilosone Sulfa Tabs	4- 2-69	35	152
Paredrine - SulfaThizole	9- 9-69	90	152
Lutrexin Tabs	5-24-68	16	131
Piptal Ped w/Phenobarb	9-27-69	49	103
Wycillin Sm Inj 600	4- 2-69	15	95
V-cillin K Sulfa Tabs	4- 2-69	22	84
V-Kor	9-12-69	34	84
Neopenzine 150 Tabs	4- 2-69	18	67
Mysteclin F	12-24-68	34	64
Comycin Capsules	4- 2-69	8	62
Total		26,268	$138,032

[1]Purchases of $50.00 or more.

APPENDIX II

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-146857

AUG 11 1971

Dear Mr. Chairman:

During testimony before your Subcommittee on January 19, 1971, concerning competitive problems in the drug industry and specifically the present status of competition in the pharmaceutical industry, you requested that we obtain information on the number of personnel and cost of purchasing drugs at the Veterans Administration and at the Defense Supply Agency.

By letters dated January 26 and 29, 1971, we asked the Administrator of Veterans Affairs and the Director of Defense Supply agency to furnish estimates of manpower requirements and administrative costs involved in the operation of their procurement systems for drugs. The information furnished is summarized below.

Veterans Administration
Drug Procurement Activities
Costs and Personnel
Fiscal Year 1970

Activity	Operations Included in Activity	Average Number of Personnel	Annual Cost
Marketing Center	Contracting (including Federal Supply Schedule), procurement, and control of stock.	13	$160,716
Depot Operations	Warehousing, distribution, accounting, and cataloging	61	579,380
Miscellaneous	Transportation, testing, inspection, etc.	13	574,421
	Total	87	$1,307,017

APPENDIX II

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Defense Supply Agency
Costs and Manpower for Providing
Drug Support
Fiscal Year 1971

Activity	Operations Included in Activity	Personnel Equivalents	Cost
Defense Personnel Support Center	Procurement (excluding contract administration)	50	$ 619,000
	Materiel management (item supply studies and accountability procurement requests, requirements determinations, and requisition processing)	32	368,000
	Technical support (cataloging, specification development and revision, quality assurance, laboratory analyses, and coordination with other Government agencies and professional activities)	44	640,000
Defense Contract Administration Services	Preaward surveys, postaward planning, contract administration, quality control and product inspection	32	438,000
Storage	Warehousing and distribution	479	3,689,000
	Total	637	$5,754,000

Neither agency separately identifies and accumulates costs related to all elements of their drug procurement systems. Accordingly, certain assumptions were made by each agency for the purpose of allocating costs to the above operations. The agencies' replies specify their assumptions and allocation methods used. It should be noted also that the estimated

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costs shown do not include costs incurred at the user activity level. Copies of the agencies' responses are enclosed.

We trust this information will serve the purpose of your request.

Sincerely yours,

(SIGNED) ELMER B. STAATS

Comptroller General
of the United States

Enclosures

The Honorable Gaylord Nelson
Chairman, Subcommittee on Monopoly
Select Committee on Small Business
United States Senate

APPENDIX III

Comparison of Selected Pharmaceutical Prices - 1971[1]
(Bottles of 100)

Product	USA	Australia	New Zealand	India
Analgesic:				
Propoxyphene HCL (65mg.)	$ 7.02 Darvon Lilly	$ 3.24 Doloxene Lilly	$ 2.50[11] Official Price	$ 4.75 Doloxene Lilly
Antibiotics:				
Ampicillin (250 mg.)	22.75 AWP Polycillin Bristol	12.29 Penbritin Beechan	10.06[12] Official Price	26.81[23] Ampicillin CIPLA
Demethylchlortetr-cycline HCL (150mg.)	19.79 AWP Declomycin Lederle	9.53 Ledermycin Lederle	4.16 Official Price	12.32 Demethychlor-tetrcycline Tablets PVT LTD
Erythromycin (250mg.)	26.12 AWP Erythrocin Abbott	11.83[3] Erythrocin Abbott	13.60 Official Price	15.80 Erythrocin Abbott
Oxytetracycline HCL (250mg.)	20.48 AWP Terramycin Pfizer	6.99[4] Terramycin Pfizer	3.76 Official Price	7.82 Terramycin Pfizer
Potassium phenoxy-methyl pencillin (250mg.)	8.95 V. Cillin K Lilly	6.13[5] Pencillin VK Knoll	3.18 Official Price	3.08 Pencillin V Tablets PVT LTD
Tetracycline HCL (250mg.)	5.27 Achromycin-V Lederle	6.99[6] Achromycin-V Lederle	4.16 Official Price	7.56 Achromycin-V Lederle
Antidepressant:				
Amitriptyline HCL (25mg.)	8.55 Elavil Merck	2.95 Tryptanol Merck	2.82[13] Official Price	——— ——— ———
Antidiabetic:				
Tolbutamide (500mg)	8.70 AWP[2] Orinase Upjohn	3.26 Rastinon Hoechst	3.19 Official Price	1.93 Rastinon Hoechst
Antihistamine:				
Diphenhydramine (50 mg.)	2.92 AWP Benadryl Park-Davis	1.72[7] Benadryl Park-Davis	1.55[15] Official Price	1.80[25] Benadryl Park-Davis
Ataraxics:				
Chlordiazepoxide HCL	7.02 AWP Librium Roche	4.01 Librium Roche	2.06[16] Official Price	1.99[26] Librium Roche

/ Prepared by the Office of Research and Statistics, Social Security Administration, Department of Health, Education, and Welfare.

APPENDIX III

Comparison of Selected Pharmaceutical Prices - 1971 Contd.

Product	USA	Australia	New Zealand	India
Chlorpromazine HCL (50mg.)	$ 4.40 Thorazine SKF	$ 2.38 Largactil May & Baker	$ 2.03[17]/ Official Price	$ 1.78[27]/ Largactil May & Baker
Diazepam (5mg.)	7.90 Valium Roche	3.45 Valium Roche	2.51[18]/ Official Price	2.20 Calmpose Ranbaxy
Meprobamate (400mg.)	7.06 Equanil Wyeth	4.47 Equanil Wyeth	2.21 Official Price	2.37[28]/ Equanil Wyeth
Prochlorperazine maleate (10mg.)	7.86 Compazine SKF	4.76[8]/ Stemetil May & Baker	2.87[19]/ Official Price	2.10[29]/ Stemetil May & Baker
Trifluoperazine HCL (5mg.)	9.75 Stelazine SKF	4.54 Stelazine SKF	3.99[20]/ Official Price	3.72 Eskazine SKF
Cardiovascular: Digoxin (.25mg.)	1.03 Lanoxin B-W	.74 Lanoxin B-W	.56[21]/ Official Price	.98 Lanoxin B-W
Oral Contraceptive: Ethynodial diacetate with mestranol (1mg. 6x21)	8.10 Ovulen 21 Searle	4.53[9]/ Ovulen 21 Searle	3.97[22]/ Official Price	4.32[30]/ Ovulen 21 Searle
Sedative: Glutethimide (250mg.)	3.00 Doriden Ciba	2.26 Doriden Ciba	1.40 Official Price	2.68 Doriden Ciba
Sulfonamide: Sulfisoxazole (500mg.)	2.94 Gantrisin Roche	3.00[10]/ Gantrisin Roche	———	1.22[31] Gantrisin Roche

See Attached sheet for footnotes

APPENDIX III

Footnotes:

1/ Calculated from the direct sale price March 15, 1971.

2/ Converted from price of 4.35 per 50 tablets.

3/ Converted from wholesale price of 14.89 per 150, 250 mg. tablets.

4/ Converted from wholesale price of 8.81 per 150, 250 mg. tablets.

5/ Converted from wholesale price of 7.72 per 150, 250 mg. tablets.

6/ Converted from wholesale price of 8.81 per 150, 250 mg. tablets.

7/ Converted from wholesale price of .72 per 50, 50 mg.

8/ Converted from wholesale price of .50 per 25, 5 mg.

9/ Converted from wholesale price of 1.90 per 3x21.

10/ Converted from wholesale price of .90 per 40, 500 mg.

11/ Converted from official price of 10.44 per 500.

12/ Converted from official price of 42.11 per 500.

13/ Converted from official price of 11.80 per 500.

14/ Converted from official price of 13.35 per 500.

15/ Converted from official price of .65 per 50.

16/ Converted from official price of 8.61 per 500.

17/ Converted from official price of .85 per 50.

18/ Converted from official price of 10.54 per 500.

19/ Converted from official price of 3.00 per 250, 5 mg.

20/ Converted from official price of 1.67 per 50.

21/ Converted from official price of 4.65 per 1000.

22/ Converted from official price of 1.66 per 3x21

23/ Converted from official price of 27.75 per 16.

Footnotes: contd.

24/ Converted from official price of 2.16 per 4.

25/ Converted from official price of 6.43 per 50.

26/ Converted from official price of 1.41 per 10.

27/ Converted from official price of 1.27 per 10.

28/ Converted from official price of 42.25 per 250.

29/ Converted from official price of .75 per 10, 5mg.

30/ Converted from official price of 5.14 for 1 cycle.

31/ Converted from official price of 3.74 per 20.

Sources:

USA--Drug Topics Readbook, 1971, Topics Publishing Co., Inc., New York.

Australia--Suggested Prices of Prescription Proprietaries for Dispensing, Issued by the Federal Council of the Pharmacy Guild of Australia, August 16, 1971.

New Zealand--New Zealand Department of Health, Prescription Pricing Schedule, August 1, 1971.

India--Indian Pharmaceutical Guide, 1971.

APPENDIX IV

PROCUREMENTS BY DPSC AND THE VA

FROM FOREIGN FIRMS FOR CALENDAR YEARS

1968 THROUGH 1971

Calendar year	DPSC	VA	Total amount spent (rounded)
1968	Tetracycline Hydrochloride Tab. Meprobamate Tab. Nitrofurantoin Tab. (two sizes) Tetracycline Syrup	Meprobamate Tab.	$3,002,000
1969	Tetracycline Hydrochloride Tab. Meprobamate Tab. Nitrofurantoin Tab.	Meprobamate	1,263,000
1970	Tetracycline Hydrochloride Tab.	None	633,000
1971	Tetracycline Hydrochloride Tab. Meprobamate Tab.	None	854,000

APPENDIX III

[From the New England Journal of Medicine, April 13, 1972, pages 813–815]

A COMPARATIVE EVALUATION OF MARKETED ANALGESIC DRUGS

(By C. G. Moertel, M.D., D. L. Ahmann, M.D., W. F. Taylor, Ph. D., and Neal Schwartau, B.S.†)

Abstract in a double-blind crossover study of marketed drugs given by the oral route to relieve pain, aspirin (650 mg) was superior to all agents tested. Mefenamic acid (250 mg), pentazocine (50 mg), acetaminophen (650 mg), phenacetin (650 mg), acetaminophen (650 mg), phenacetin (650 mg) and codeine (65 mg) also showed a significant advantage over a placebo. Propoxyphene (65 mg), ethoheptazine (75 mg) and promazine (25 mg) gave no significant evidence of therapeutic activity; and each of these agents was significantly inferior to aspirin in analgesic effect. Pentazocine (50 mg) produced sufficient gastrointestinal and central-nervous-system side effects to make this agent of dubious value for ambulatory patients. All other drugs tested in this single dose study did not produce significantly greater side effects than a placebo.

One of the most vital services rendered by the physician is that of relieving pain. Under the usual clinical circumstances, he attempts to provide this analgesia by medication administered orally, choosing from the multitude of prescription and over-the-counter preparations that line the pharmacists' shelves. Although promotional material abounds, scientific evidence of effectiveness for many marketed analgesics is scarce and frequently equivocal. Controlled comparisons of their effectiveness have been conspicuously rare. The purpose of this communication is to report a study comparing in a randomized, double-blind manner the therapeutic effectiveness of marketed analgesics given in pure form by the oral route of administration in the dosages usually prescribed.

METHOD

All 57 patients chosen for study had definite pain problems resulting from unresectable cancer. All were ambulatory, and all could reliably tolerate oral medication. They did not have appreciable systemic symptoms related to their tumors, and they were not receiving any antitumor treatment (e.g., chemotherapy or radiation therapy) that could confuse observation of analgesic side effects. The pain that the patients experienced was assumed to be related to intra-abdominal, retroperitoneal, pelvic or osseous malignant tumors. The pain was considered clinically to be mild or moderate in degree. Patients were not accepted for the study if they had previously been on a schedule of narcotic drugs that was judged capable of producing any degree of physiologic dependence. Particularly, subjects were chosen who in our opinion were intelligent, dependable observers. They were informed that they were participating in a randomized type of study. Patients were not allowed any other analgesics, narcotics, sedatives, stimulants, antiemetics, antidepressants or tranquilizers during the study.

All doses of analgesics and placebo were prepared in identical opaque blue gelatin capsules dispensed in sealed plastic cups identified only by code number. USP lactose was employed as placebo and also as a filler for all study drugs. Each patient was given a single dose of each of the study drugs and placebo in

† From the Division of Gastroenterology and Internal Medicine, the Division of Clinical Oncology and Internal Medicine, the Department of Medical Statistics Epidemiology and Population Genetics, Mayo Clinic and Mayo Foundation, and the Division of Pharmacy and Central Supply, Rochester Methodist Hospital (address reprint requests to Dr. Moertel at the Division of Gastroenterology and Internal Medicine, Mayo Clinic, Rochester, Minn. 55901). Supported in part by a grant (3 PO1 CA10731–01S1), from the National Institutes of Health.

randomized sequences according to the latin-square method. One drug was directly followed by another, and there was not a planned-placebo or no-treatment interval between active drugs. Each patient received only one test sequence of each of the study drugs. The oral form of pentazocine was not available to us when our investigation was initiated; this was added to the study after the initial 27 patients (three latin square) had been entered.

Patients were instructed to take the planned single dose whenever definite pain was present but no more often than every six hours. The intervals between doses were therefore variable, depending on the requirement of the patient for analgesia, but none were shorter than six hours. There was a corresponding variability in the total period required for each patient study. With each dose, patients were asked to record the time of administration, the time when the onset of definite relief of pain was noted, and the time when pain returned; they were also asked to record the estimated maximum degree of pain relief on a percentage basis. Specific inquiry was made regarding the following side effects: stomach upset, nausea, vomiting, sleepiness, dizziness, impaired thinking and excitement. Patients were also asked to volunteer any additional side effects that they experienced. This information was recorded on a separate form for each drug dose.

It should be emphasized that these observations were recorded by the patient and not by medical observers. It should also be emphasized that this was a study only of single-dose administration and not of chronic administration.

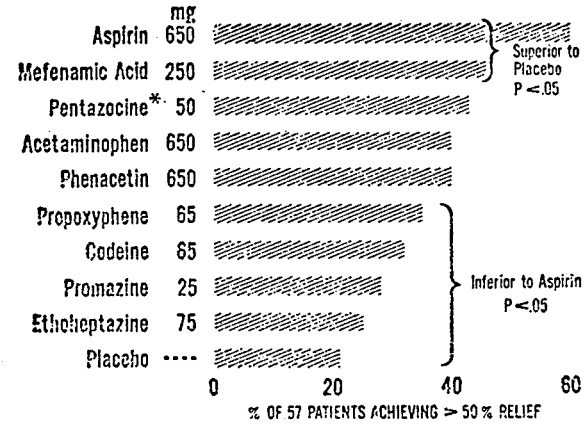
RESULTS

To avoid any possible statistical distortion and to make full use of data, analgesic effects were evaluated by three methods of analysis.

The first method used the proportion of patients treated with each analgesic agent and placebo who claimed greater than 50 per cent relief of pain at any time during six hours after drug administration. This approach seemed to be the best in selection of patients who obtained a truly useful therapeutic effect. The results (Fig. 1) showed that 650 mg of aspirin quite clearly led the pack. Both aspirin and mefenamic acid showed a significant advantage over placebo. In addition, aspirin was significantly superior (p less than 0.05) to ethoheptazine, promazine, codeine and propoxyphene. None of the other drug differences were at statistically significant levels.

The second means of analysis (Table 1) employed the mean percentage of analgesia claimed by patients with each study drug and placebo. This method allows a relative crediting of all degrees of analgesic effect from very minor to complete relief of pain. Again, aspirin leads, but pentazocine, acetaminophen, phenacetin, mefenamic acid, and codeine all show a significant advantage over the placebo. Propoxyphene, ethoheptazine and promazine remain significantly inferior to aspirin.

The third method of analysis (Table 2), perhaps most important from a comparative standpoint, employed the relative ranking method of analgesic effect assigned by each patient to each of the test drugs—i.e., the drug to which an individual patient attributed the greatest percentage relief of pain was given the rank of one, and that with the lowest percentage a rank of 10. The figures recorded in Table 2 are the sums of ranks accorded to each drug by the 57 patients. Still, aspirin is the leader, showing a highly significant superiority over the placebo as well as over propoxyphene, ethoheptazine and promazine.



Results for pentazocine in 30 patients.

FIGURE 1.—Relative Therapeutic Effect of Oral Analgesics According to Percentage of Patients Achieving Significant (More than 50 per Cent) Relief of Pain (Analysis by Student-Newman-Keuls Method (2)).

TABLE 1.—RELATIVE THERAPEUTIC EFFECT OF ORAL ANALGESICS ACCORDING TO MEAN PERCENTAGE OF RELIEF OF PAIN ACHIEVED IN 57 PATIENTS

Analgesic agent	Dose (mg.)	Relief of pain (percent)	
Aspirin	650	62	
Pentazocine*	50	54	
Acetaminophen	650	50	Significantly superior to placebo ($p<0.05$).†
Phenacetin	650	48	
Mefenamic acid	250	47	
Codeine	65	46	
Propoxyphene	65	43	
Ethoheptazine	75	38	Significantly inferior to aspirin ($p<0.05$).†
Promazine	25	37	
Placebo		32	

*Results for pentazocine in 30 patients (statistical significance calculated on basis of patients receiving pentazocine with use of Dunnett's procedure (1) for multiple comparisons with control).
†Student—Newman—Keufs method (2).

TABLE 2.—RELATIVE THERAPEUTIC EFFECT OF ORAL ANALGESICS ACCORDING TO SUM OF RANKS ACCORDED BY EACH PATIENT

Analgesic agent*	Dose (mg.)	Rank sum	
Aspirin	650	223.0	
Mefenamic acid	250	271.5	
Phenacetin	650	275.0	Significantly superior to placebo ($p<0.01$).†
Acetaminophen	650	280.5	
Codeine	65	284.5	
Propoxyphene	65	315.0	
Ethoheptazine	75	335.0	Significantly inferior to aspirin ($p<0.01$).†
Promazine	25	352.5	
Placebo		374.0	

*In 30 patients pentazocine, 50 mg., was in 5th position and significantly superior to placebo ($p<0.01$).
†Analysis by t-test.

For none of the three methods of analysis did the order in which the drugs were given have a detectable influence on the grade and therapeutic effectiveness accorded any single drug.

Many patients had difficulty adequately timing the onset and duration of relief of pain, especially if relief was incomplete. The median time from drug ingestion to the onset of definite relief ranged between 0.5 and one hour for all study drugs except propoxyphene, which had the longer time to onset of

relief—1.2 hours. The median duration of analgesia ranged between four and six hours except for the more ineffective placebo, ethoheptazine and propoxyphene, which had median durations of analgesia of three to 3.5 hours.

At the dosages employed, most agents studied produced no more side effects than placebo. Pentazocine, however, resulted in a greater frequency of gastrointestinal and central-nervous-system side effects than all other agents tested, and one patient suffered a severe mental aberration with hallucinations after treatment with this drug.

Of special interest was the response of these patients with cancer pain to placebo: 21 per cent claimed greater than 50 per cent relief of pain with a dummy medication (Fig. 1). Placebo therapeutic and side effects seemed to be characteristic responses of particular patients, extending to their response to active drugs. The overall analgesic effect of active agents in the patients who responded to the placebo was a mean relief of 54 per cent as compared to only 39 per cent in those who did not respond (p less than 0.01). Similarly, patients who experienced side effects to placebo had more than twice the frequency of side effects to active agents (56 vs. 22 per cent). Patients who experienced a placebo analgesic effect were also more characteristically those who would experience placebo side effects.

DISCUSSION

In this study, simple aspirin at a dosage of 650 mg (10 gr) was the superior agent for relief of cancer pain among the tested marketed analgesics. Indeed, among all analgesics and narcotics available for oral use, none have been demonstrated to show a consistent advantage over aspirin for the relief of any type of pain. Beaver (3) has collected 36 controlled studies from the literature also showing aspirin to have a significant advantage over placebo for relief of pain from a variety of etiologies. Although gastrointestinal bleeding and allergic reactions undoubtedly occur as side effects of aspirin ingestion, the rate of these complications in clinically important form must be very low in view of the many tons of aspirin consumed collectively each year by nearly every adult and child in this country. These advantages, coupled with minimum price (usually less than $1 for 100 doses of 650 mg), should make the aspirin the drug of preference for any pain problem requiring an oral analgesic. It has been our own experience that if aspirin is recommended with the strong endorsement of the physician, it is acceptable to even the most sophisticated patient.

The para-aminophenol derivatives, acetaminophen and phenacetin, also showed superiority to placebo in this study; although they ranked lower than aspirin by all means of analysis, this difference was not statistically significant. Side effects of these agents are primarily problems of drug abuse and not of usual therapeutic doses. When they are prescribed generically, their price is only moderately higher than that of aspirin (in the range of $2 to $3 per 100 doses of 650 mg), and they seem to be a reasonable alternative of therapy in cases of aspirin intolerance.

Mefenamic acid (Ponstel), pentazocine (Talwin) and codeine all gave evidence of real analgesic effect. Both mefenamic acid and codeine, however, may produce troublesome gastrointestinal side effects with chronic use, and pentazocine may induce sedation, dizziness, impaired thinking or even hallucinations, so that the patient should be warned not to engage in any activity in which his impaired performance could result in danger to himself or others. Particularly troublesome are the price tags on these agents; mefenamic acid, $9.72 per 100 doses of 250 mg; pentazocine, $9.88 per 100 doses of 50 mg; and codeine, $12.08 per 100 doses of 650 mg.*

The therapeutic credentials of both propoxyphene (Darvon, $9.50 per 100 doses of 65 mg)* and ethoheptazine (Zactane, $7.40 per 100 doses of 75 mg)* must be classified as very equivocal. In this study, neither showed a significant advantage over placebo, and both were significantly inferior to aspirin. The dubious record of propoxyphene in controlled clinical trials has recently been reviewed by Miller et al. (4) This is the eighth published study in which propoxyphene has not shown any significant superiority over placebo. The qualifications of ethoheptazine seem even more questionable. Of five controlled studies now published, (5–8) only one (5) showed ethoheptazine to have any indication of analgesic activity.

Promazine was chosen for this study because it was one of the few phenothiazines to show analgesic activity in the study of Dundee and Moore (9) published

*Average price at a hospital pharmacy, a medical-center pharmacy, a chain-store pharmacy and a privately owned neighborhood pharmacy, Rochester, Minn., January 1, 1971.

under the apt title, "The Myth of Phenothiazine Potentiation." We could not confirm this activity under the conditions of our investigation.

Although the results of this study indicate a general conformity to others in the literature, it must be emphasized that they can be interpreted only in terms of the patient population and methodology that we employed. Specifically, they cannot be applied to chronic use of analgesic agents, nor do they have any direct application to the commonly prescribed analgesic-drug combinations.

REFERENCES

1. Dunnett CW: New tables for multiple comparisons with a control. Biometrics 20:482–491, 1964
2. Bancroft TA: Topics in intermediate Statistical Methods, Iowa State University Press, Ames, Iowa, 1968
3. Beaver WT: Mild analgesics: a review of their clinical pharmacology. Am J Med Sci 250:577–604, 1965
4. Miller RR, Feingold A, Paxinos J: Propoxyphene hydrochloride: a critical review, JAMA 213:996–1006, 1970
5. Cass LJ, Frederik WS, Bartholomay AF: Methods in evaluating ethoheptazine and ethoheptazine combined with aspirin. JAMA 166:1829–1833, 1958
6. Brenman HS: Oral analgesics: preoperative vs postoperative use. J Am Dent Assoc 67:23–27, 1963
7. Bruni JR, Holt RE: Controlled double-blind evaluation of three analgesic medications for postpartum discomfort. Obstet Gynecol 25:76–81, 1965
8. DeKornfeld T, Lasagna L: Clinical trial of two analgesics: Win 14,098 and ethoheptazine. Fed Proc 18:382, 1959
9. Dundee JW, Moore J: The myth of phenothiazine potentiation. Anaesthesia 16:95–96, 1961

ELI LILLY AND CO.,
Indianapolis, Ind., April 17, 1972.

DEAR DOCTOR: In a recent issue of the *New England Journal of Medicine*, C. G. Moertel *et al.* published an article entitled "A Comparative Evaluation of Marketed Analgesic Drugs."

The authors administered in a randomized, double-blind manner nine oral analgesic drugs and a placebo. They concluded that aspirin (650 mg.) was superior to the other drugs tested. They also concluded that "the therapeutic credentials of . . . propoxylene . . . must be classified as very equivocal."

We are providing you with our comments so that the authors' work will not be ministerpreted with respect to continued administration of Darvon® (propoxyphene hydrochloride, Lilly) and the value of Darvon combination products.

There is no question that aspirin is an effective oral analgesic. It is sufficient for the pain relief needed in many situations.

At the same time, it is well established that Darvon is an effective analgesic. This is substantiated by recent studies conducted in connection with the introduction of Darvon–N™ (propoxyphene napsylate, Lilly) and Darvon–N™ with A.S.A.® (propoxyphene napsylate with aspirin, Lilly) as well as by many studies conducted at the time of the introduction of propoxyphene hydrochloride. The recent studies, reported in the July, 1971, issue of *Toxicology and Applied Pharmacology*, again affirmed the effectiveness of Darvon.

There is also expert opinion concerning the efficacy of Darvon. The NAS/NRC expert panel which reviewed Darvon for the Drug Efficacy Study of the Food and Drug Administration concluded that Darvon is an effective drug.

The physician in practice often finds himself with the patient who has not been sufficiently relieved by aspirin and needs something more. Prior to Darvon this was frequently codeine. a drug most clinicians would concede is a potent analgesic.

(Incidentally, in one method Dr. Moertel used to analyze his results, 65 mg. of propoxyphene ranked higher than 65 mg. of codeine.)

The advantage of Darvon® (propoxyphene hydrochloride, Lilly) over codeine is its lower incidence of untoward reactions. In a comparative study of these two compounds, Darvon had a side-effect incidence of 0.8 percent as compared with 3.4 percent for codeine.[1]

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[1] Borda, I. T., Slone, D., and Jick, H.: Assessment of Adverse Reactions Within a Drug Surveillance Program, *J.A.M.A.*, *205*: 645, 1968.

Investigators who work in the field of analgesia recognize the great difficulty of obtaining accurate assessment of pain relief. In many studies, even known potent analgesic agents have failed to show significant effects. To make a study valid, careful attention must be given to the experimental design.

Another very important point that this study admittedly did not consider is the value of combinations of two or more drugs that provide analgesia. Not all compounds produce their analgesic effect by the same mechanism. For example, aspirin has a significant peripheral activity for pain relief as well as an anti-inflammatory action, whereas the action of propoxyphene is primarily central. The combination, quite obviously then, attacks pain by two mechanisms. For these reasons, we have combined these analgesics in Pulvules® Darvon® Compound (propoxyphene hydrochloride, aspirin, phenacetin, and caffeine, Lilly) and Darvon® with A.S.A.® (propoxyphene hydrochloride and aspirin, Lilly). The NAS/NRC panel commented that "the combination of Darvon with an anti-pyretic-analgesic of the aspirin type results in analgesia superior to that achieved by either drug administered alone."

In fifteen years, Darvon products have won remarkable acceptance by many thousands of physicians and millions of patients. This success has been well deserved. It is based on satisfactory relief of mild to moderate pain and on a high degree of safety.

Sincerely,

ELI LILLY AND CO.

[From the Medical Tribune, April 5, 1972]

AMERICAN SCIENTISTS CHARGE U.S. MEDICINE LAGS, URGE MAJOR CHANGE IN REGUATORY POLICIES—ASK A REVIEW OF IMPACT ON MEDICINE, RESEARCH

(Medical Tribune Report)

WASHINGTON.—Leading scientists and university administrators warned here that American medical science is "falling behind" as a result of the procedures by which drugs are evaluated and approved in this country.

They called on Congress to conduct a "full-scale review" of the impact of the Food and Drug Administration's policies on American research and medical practice.

In a statement to the House Subcommittee on Public Health and Environment, the experts declared that the FDA policies since 1962 have brought about a "stifling" of scientific creativity, escalation of research costs, and a "continuing decline in the number of new drugs entering the market in this country."

The scientific group, including a Nobelist and five Lasker Award winners, cautioned that drug regulatory policies may be "depriving the practicing physician of agents beneficial to patient care." American medicine, they asserted, currently faces a "paradox" in which the drug industry's research capacity is getting better, the FDA is working harder, but there is "decreasing productivity."

Chairman of the group is Dr. Robert D. Dripps, vice-president for medical affairs, University of Pennsylvania. Among the other signers are Drs. Michael E. DeBakey, president, Baylor College of Medicine; Dickinson W. Richards, Nobelist and Professor of Medicine, Emeritus, Columbia University; and Alfred Gilman, Ph.D., chairman, Department of Pharmacology, Albert Einstein College of Medicine.

"We believe a change in the drug regulatory system is badly needed," the group declared in their call for a Congressional examination of FDA operations. "We believe this review should be undertaken as promptly as possible, since the welfare of patients may be at stake."

The scientists placed major responsibility for the FDA's problems on the Kefauver amendments of 1962, which vastly expanded the agency's authority and powers. The FDA was required to assure the safety and effectiveness of drugs and given new or expanded controls over research, manufacturing, promotion, and labeling of drugs.

In their statement, Dr. Dripps and his colleagues emphasized that they were directing their criticisms not at the FDA leadership or staff but at the difficult predicament in which the Kefauver mandate placed the agency in seeking to interpret and fulfill the laws.

"The system of drug regulation, which has evolved as a result of the 1962 drug act," the scientists said, "exposes the agency to a variety of pressures which make it difficult for rational decision making to take place."

Almost from the first year of the Kefauver amendments, the FDA found itself embroiled in disputes over the manner in which it was interpreting its widened regulatory functions under the new laws. For example, the issue of the drug package insert alone—how much, if any, legal weight it carries and how binding it is, or should be, on medical practice—has been a continuing source of contention between clinicians and pharmacologists on the one hand and the agency on the other.

CONCURRED WITH COMMISSIONER

Dr. Dripps and his colleagues said that they concurred with a recent statement by FDA Commissioner Dr. Charles C. Edwards, who had described the agency as being in a "particularly difficult environment because, in a sense, we are in the middle."

The Commissioner's statement continued: "We are, on the one hand, criticized for being 'soft' on industry and, on the other, called repressive, an enemy of free enterprise: on *every* major decision we are accused by some of acting too fast without sufficient evidence and by others of acting too slowly and too timidly to prevent unnecessary harm."

In their statement to the House Subcommittee, the Dripps group suggested that it was significant that the FDA has "long been the subject of study and investigation," with the Executive Branch alone conducting three studies of the agency in the past five years. But these appraisals, the scientists said, did not get to the heart of the problem because they focused primarily on the internal structure and workings of the FDA.

"As important as it is to improve the efficiency and scientific procedures and capabilities of the agency itself," the experts declared, "there still remains the crucial question as to the effect the agency's administration of the 1962 drug act has had in actual practice on drug research, innovation, and therapy."

They continued: "We believe a change in the drug regulatory system is badly needed. The system too often stifles creativity and escalates costs of research; perpetuates a continuing decline in the number of new drugs entering the market in this country; and may be depriving the practicing physician of agents benefical to patient care. The reasons for all this are not clear, are undoubtedly complex, and require thorough investigation and study."

SUBCOMMITTEE PROPER BODY

The group concluded: "Your subcommittee, it appears to us, would be the proper body to direct a full-scale review of the effect of the 1962 drug act and regulations on the practice of medicine and the conduct of academic and industrial drug research."

Chairman of the Subcommittee on Public Health and Environment is Rep. Paul G. Rogers (D.-Fla.). Two members are physicians, Rep. Tim Lee Carter (D.-Ky.) and Rep. William R. Roy (R.-Kans.).

OTHERS SIGNED STATEMENT

Other signers of the statement to the subcommittee were: Drs. Robert F. Bradley, *medical director, Joslin Clinic;* Eugene Braunwald, *Professor of Medicine and chairman of the department, University of California, La Jolla;* James E. Eckenhoff, *dean, Northwestern Medical School;* Edward D. Freis, *Professor of Medicine, Georgetown University and a Lasker Award winner;* Nathan S. Kline, *director of research, Rockland State Hospital, New York, and a Lasker recipient;* Louis Lasagna, *chairman, Department of Pharmacology and Toxicology, University of Rochester, N.Y.;* Walter Modell, *Professor of Pharmacology, Cornell University;* John A. Oates, *Professor of Medicine and Pharmacology, Vanderbilt University;* Irvine H. Page, *senior consultant, Research Division, Cleveland Clinic, and a Lasker recipient;* E. M. Papper, *vice-president for medical affairs and dean, University of Miami;* Burtrum C. Schiele, *Professor of Phychiatry and principal investigator, Clinical Psychopharmacology, University of Minnesota;* George W. Thorn, *physician-in-chief, Peter Bent Brigham Hospital;* Robert W. Wilkins, *chairman and director, Division of Medicine, Boston University, and a Lasker recipient;* William R. Wilson, *chairman, Department of Clinical Pharmacology, University of Iowa;* Robert I. Wise, *Magee Professor of Medicine, Jefferson Medical College;* and George D. Zuidema, *Professor of Surgery and department director, Johns Hopkins.*

[From the Medical Tribune, April 12, 1972]

BEHIND PROPOSAL TO HOUSE SUBCOMMITTEE—GROWING THERAPEUTIC GAP WORRIES AMERICAN SCIENTISTS

(Medical Tribune Report)

NEW YORK.—The developing therapeutic gap in American medicine was underscored here by scientific leaders as one of the major reasons behind their call for a Congressional "review" of American drug regulatory policies (MEDICAL TRIBUNE, April 5).

In exclusive interviews, several of the top medical scientists who took part in making the unprecedented proposal to a House health subcommittee noted that Europe has moved ahead of the United States in the number and usefulness of new drugs available to the clinician. They warned that the gap would widen unless there is a complete overhaul of Food and Drug Administration procedures.

"In England, a third of the drugs now in use have been introduced in the last five years. In this country, the corresponding figure is about 10 per cent," said Dr. Robert D. Dripps, Vice-President for Medical Affairs, University of Pennsylvania. "In the four-year period between 1966 to mid-1971, there were 70 products on the market in England not available to practicing physicians here. Many of these are not important therapeutic agents, but if there is only one vital agent available in England and not available here, it is one too many. Japan and Italy are also making great progress in drug research."

Dr. Dripps and others noted that, ironically, the decline in the number of new drugs introduced in the United States has occurred at a time when American drug research capacities are at an all-time high.

In their statement to the House Subcommittee on Public Health and Environment, the scientific group, which is headed by Dr. Dripps, asserted that FDA policies since 1962, when the Kefauver Amendments went into effect, have led to "stifling" of scientific creativity, escalation of research costs, and a "paradox" that finds the FDA working harder, U.S. research capacity greater, and productivity continually decreasing.

In wide-ranging interviews, several leaders of the group asserted that these results stemmed from protracted and, in their view, often unwarranted drug regulatory policies. They made these points:

- Fewer and simpler requirements abroad have given foreign medicine the benefit of more drugs with no loss of safety.
- Increasing costs of bringing a drug to market in the U.S., resulting in part from the need to comply with complex regulations, have brought about a slowdown in research.
- Limited manpower and dollars are being diverted to a large-scale review of old drugs at a time when the need is to develop promising new compounds.
- The Government's regulatory agency has gone beyond its mandate by actions that seek to dictate medical practice.

NO REVERSAL OF TREND SEEN

Dr. Dripps, commenting on the "steady decline in new products introduced in this country," noted that the FDA itself has acknowledged that "it sees no reversal of this trend in the near future."

He continued: "Whatever the reason is for this, we know that the time and cost of new product development has increased greatly and that money and personnel are being diverted from research and development into research required to clarify the status of old, already marketed ethical or proprietary medicines.

"Every dollar spent proving that Tums affects gastric acidity or that potent tranquilizers relieve neurotic anxiety represents dollars and man-hours not spent forging new weapons against disease."

Dr. Dripps stressed that the committee was not calling for "an immediate investigation [of FDA] by Congress," in the pejorative sense that term implies. "We are asking, however, the appropriate committee of the Congress to mandate an effort to develop a reliable body of information to provide a background for public policy decisions affecting new drugs," he declared.

Dr. Walter Modell, Professor of Pharmacology at Cornell University and editor of Clinical Pharmacology and Therapeutics, told MEDICAL TRIBUNE that

the call for a Congressional review of American drug regulatory policies was long overdue. "I have never questioned the FDA's good intentions or the honesty of its leadership. But the situation there is such that it cannot function properly."

Describing the FDA as a "stepchild in the superstructure" of the Department of Health, Education, and Welfare, Dr. Modell said: "The FDA staff is simply insecure inside the HEW. Too many people can interfere with their operations. It would be far better if the FDA were to be re-established as a separate agency—like the Federal Trade Commission, for example. Further, in my view, the agency's function should be confined to drug regulation, with the role of food regulation sent back to the Department of Agriculture. Too much highly specialized knowledge is required in both food and drugs to be handled effectively by a single agency."

"NEVER DEVELOPED SECURITY"

Dr. Modell pointed to what he saw as another cause of the agency's problems: "FDA's scientists have never developed security or scientific stature," he asserted. "They lack a sense of authority or security in their judgments. As a result, they do not act with assurance in making decisions. They proceed by delaying actions."

The pharmacologist disclosed that some major American drug firms are planning to build new research facilities abroad, as one way of coping with the problems they encounter in the U.S. "Reversing a trend," he said, "there is now a danger that we will experience a scientific brain drain."

[Editorials from the Medical Tribune, April 12, 1972]

FOR MODERATION . . .

Recently, many leading scientists as individuals and as members of ad hoc committees have begun to react to the whiplash effect of self-proclaimed crusaders on the public health and on health regulations. They protest the impingement by these new vested interests on the fundamental rights of researchers, practicing physicians, and patients. The most recent initiative on the part of scientists was a letter addressed to an outstanding legislative leader in the field of health, Representative Paul Rogers (D.–Fla.), chairman of the House Subcommittee on Public Health and Environment. It rightly pointed out that regulatory processes were deleteriously affecting medical progress and the best interest of patients. It called, in effect, for a full-scale review of FDA drug regulations and the drug law upon which they are based.

For several decades now, health has made headlines. As the "wonder drugs" were discovered by the lay press, headline mileage was generated first by euphoric stories and, after these had run their course, by declamatory exposés. Both have attracted the attention of the public and of political figures. A responsible press and public leaders have made and continue to make positive contributions in regard to health, but there are too many irresponsible individuals who seek and garner headlines without regard to whether they help or harm those for whom health is a life and death issue. The time is long overdue for moderation in our perspective, in the reportage of health issues, and in our approach to legislation and regulation.

Medical Tribune, as far back as 1960, warned of the potentially stultifying effects of the new food and drug law and, since its passage, of the dangerous regulatory extensions, whose proliferation has raised so many obstacles to both research and treatment. At this time, Medical Tribune believes we confront the need for moderation.

. . . AND A MORATORIUM

The most meticulous study and exploration by the practicing physicians of the effects of these regulations on their patients' interests is long overdue. The inhibitory effects on medical research must be carefully scrutinized. Both procedures must be carried through with the calm and considered judgment that such important subjects demand. What is not needed at this time is a new spate of legislative hearings on drugs and drug regulations. What is needed is a constructive approach to free both the practicing physician and the researcher from some of the ridiculous and unconscionable restraints placed on their rights to fulfill their professional responsibilities with true freedom of conscience.

We do not need a new "generation" of hysterical drug headlines. We do need a meeting of men and minds representing practicing physicians, researchers, and the public, on the one hand, and our key legislators and regulators, on the other—a meeting not held under the heat and glare of TV lights and cameras. We need an open and honest exchange of experiences and ideas—a presentation of constructive changes in regulations and alterations in procedures that will truly benefit our patients. This is a time for moderation—and for a moratorium on hearings, headline hunting, and health hysteria. A.M.S.

[From the Medical Tribune, April 19, 1972]

DR. FREIS, GILMAN, AND LASAGNA COMMENT—EXPERTS BLAME FDA FOR NEW DRUG 'STANDSTILL'

(Medical Tribune Report)

WASHINGTON.—New drug development has been brought to a "virtual standstill in the United States" because of the way drug regulatory policies are interpreted, one of the nation's top cardiovascular experts declared here.

Dr. Edward D. Freis, winner of the 1971 Lasker Award for his hypertension studies, asserted that the "working echelons" of the Food and Drug Administration are so fearful of making mistakes and so unclear in their demands as to what constitutes evidence of drug efficacy that "in my own area, that of cardiovascular medicine, no new antihypertensive compound has been introduced in this country in 10 years."

Two other authorities joined in expressing concern at the declining rate of new drug development. They were Alfred Gilman, Ph.D., author of the standard text, The Pharmocological Basis of Therapeutics, and Dr. Louis Lasagna, Professor of Pharmacology, University of Rochester.

The experts underscored regulatory problems as among their reasons for joining the group of university administrators and medical scientists who have called for a "full-scale review" of the procedures by which new drugs are approved for use in the U.S. (MEDICAL TRIBUNE, April 5).

"Some drugs have been under investigation in this country for a decade without satisfying the undefined requirements of the regulatory people at the working level," Dr. Freis commented. "There are excellent new antihypertensive agents available to clinicians in Europe but not in the United States," he asserted. "Bethanidine, for example, can be prescribed for patients in Great Britain and the Scandinavian countries but not here."

Like the other top scientists who have talked with MEDICAL TRIBUNE in this series, Dr. Freis, who is Professor of Medicine at Georgetown University, attributed the developing therapeutic gap between the U.S. and Europe largely to the way in which regulatory procedures are implemented in practice.

In their formal call for a review, the scientists told the House Subcommittee on Public Health and Environment that FDA policies since 1962, when the Kefauver Amendments went into effect, have led to a "stifling" of scientific activity, escalation of research costs, and a "paradox" that finds the FDA working harder, U.S. research capacity greater, and productivity continually decreasing.

Chairman of the scientific committee, which includes a Nobel Laureate and five Lasker Award winners, is Dr. Robert D. Dripps, Vice-President for Medical Affairs, University of Pennsylvania.

Dr. Freis asserted that the FDA's working procedures make it extremely difficult for a new drug to get approval for marketing. "At the working level, the FDA people are simply not making it clear to a drug company what kind of protocol will supply evidence that is satisfactory," he declared. "A drug company will bring in what it thinks is evidence, and the working echelons at the agency will then ask for more evidence. Often the demands are picayune. The whole objecitve behind these actions is to play it safe, not get itno trouble, not do anything that will invite criticism."

Dr. Freis said that one major American drug firm, after unsuccessfully trying for years to get approval of a new compound, "finally gave up and sold the drug to another company." The purchasing company, which then applied for approval of the drug, has been asked by the FDA, Dr. Freis said, to submit evidence from scratch.

SHIFT IN DECISION MAKING URGED

He suggested that one possible solution to the problem of drug review would be to take the decision-making power out of the FDA's hands and give it to a peer-review committee of outside experts.

"It would be comparable to the procedure followed by the British Dunlop Commission," Dr. Freis declared. "The consultants would draw up the protocol, define the kind of evidence required, and then let the FDA working echelons implement the policy. The decision as to whether the protocol has been satisfied would be left to the peer authorities."

Another fundamental criticism of FDA policy came from Dr. Lasagna, who voiced concern that the FDA is showing a "growing tendency to involve itself in details of medical practice."

"For example, the FDA is now making efficacy ratings of drugs, as well as offering the recommended sequence in which drugs should be given. Legally, there is no basis in the Kefauver Amendments of 1962 for accepting or rejecting drugs because of comparative efficacy. The point is that the ultimate application of a drug is part science and part art. It is simply not possible, at long distance, to define a unitary way of treating each patient. The FDA is doing what the Dunlop Commission [of Great Britain] consistently refused to do: getting involved in matters of professional judgment and application."

Like Dr. Freis and others, Dr. Lasagna called attention to the many new drugs available in Western Europe but not here. "The argument has been made that the FDA is protecting us from drugs like thalidomide and that we are being spared poor drugs. In the United Kingdom at least, one can't point to any large number of new drugs that are poor and one can find a number of new agents that are clearly useful."

He cited the availability of carbenoxalone, the drug of choice in gastric ulcer management in Great Britain. "In a recent poll of United Kingdom experts," Dr. Lasagna said, "this was rated as therapeutic maneuver number one. If that is so, it means that our patients are being deprived of an important drug."

"We have one beta blocker in the United States," he noted. "There are several in the United Kingdom. And even the one that we have is not approved for use in high blood pressure or angina, although the evidence suggests that it could be of benefit for those indications."

Dr. Lasagna deplored what he saw as a growing tendency on the FDA's part to violate governmental neutrality in scientific controversy. "There is nothing in the Kefauver Amendments to justify the FDA's acting as an umpire when medical experts disagree," he stated. "This is pharmacologic Lysenkoism—a Government line in science. Here, in an area where angels fear to tread, a Government agency has moved with alacrity!"

WORRIED BY DECLINING APPROVAL

In New York, Dr. Gilman, who is chairman of Albert Einstein's Department of Pharmacology, said that he, like his colleagues on the committee, is "concerned with the declining instance of approval of new drugs."

"That decline," he noted, "comes at a time when our research capacities are improving." He added that he has received "a lot of mail lately expressing a similar sense of concern."

Dr. Gilman commented on the delays experienced in getting a new drug into the hands of the clinician. "A New Drug Application at present takes two to three years. It is certainly one reason why the Europeans have more new drugs on the market than we do," he declared. "We must recognize, however, that the FDA has been given tremendous responsibilities without adequate manpower to meet those responsibilities."

He added that he was "encouraged" by recent evidence that the regulatory agency is eager to move more swiftly in approving new drugs. The FDA has hired an industrial research firm to review its methods of processing such applications, Dr. Gilman disclosed. And, he said, just one week before the interview with MEDICAL TRIBUNE, he had been an invited participant at a two-day meeting of pharmacologists, industry, and FDA leaders called to review methods for organizing a prospective follow-up of the development of an NDA or an Investigative New Drug.

"This concept was not unlike a suggestion that I made some years ago," Dr. Gilman said, "in which I urged prospective surveillance by outside experts so that an NDA could be corrected during the course of investigation."

Dr. Gilman voiced the hope that "by the time the new NDA procedures get rolling, much of the criticism by the academic community and by the drug industry will have been answered."

[Editorials from the Medical Tribune, April 19, 1972]

FOR MORE OUTSIDE CONSULTANTS . . .

The present FDA has been more vigorous, more hard-nosed, denied more New Drug Applications. and removed more medicinals from the market than any of its predecessors. The one man whom the drug executives have singled out, more than any other, as zealous to the point of therapeutic nihilism is the very director now attacked by consumerists on the use of outside consultants and also accused of having "arbitrarily reassigned important officers to modify the drug industry" (*New York Times*, April 3). To observe a consumer group attacking the Director of the Bureau of Drugs of the FDA recalls the spectacle of the French Revolution devouring its own leaders.

The irony goes further. Before the passage of the 1962 food and drug amendments, virtually every physician or scientist testifying pointed out the importance of the use of consultant committees and the resource of experts. MEDICAL TRIBUNE has for years advocated the use of advisory scientific committees and outside experts to assure both scientific input into and review of regulatory decision making. MEDICAL TRIBUNE has opposed extension of regulatory intrusion into research and the practice of medicine through utilization of such regulatory concepts as "comparative efficacy." MEDICAL TRIBUNE has opposed Government partisanship in scientific controversy as a manifestation of American Lysenkoism. In the last few months, a groundswell of rebellion has built up in the scientific community on these issues. It is of interest that among the recommendations put forth to correct such regulatory excesses has been the use of more outside clinicians, clinical pharmacologists, and other experts.

Today one can report the beginnings of a response to the demands of leaders in medicine and science. Of 26 current FDA advisory committees, 13 are advisory to the Bureau of Drugs. In 1972 there will be 60 meetings of these committees as compared to 12 in 1969. An FDA advisory group of one type or another will meet on the average of every two to three days. In addition, the FDA is beginning to use outside consultations in almost as great numbers as the members of the advisory committees.

As to FDA advisory committee members, in 1971, 62.5 per cent came from the academic community, 16 per cent from hospitals, clinics, medical institutes, and nonmedical foundations or institutions, 12.5 per cent were state and Government officials other than from the FDA, but only 2 per cent medical practitioners. In 1971, 7 per cent of the committees came from the drug industry; in 1972 it will be 10.5 per cent.

A general accusation of conflict of interest in the review of NDAs is difficult to assess. But the make-up of the FDA committees, the present FDA's regulatory history, and its "adversary type" relationship with the drug industry just do not seem to add up to charges that it is "mollifying" the industry.

. . . AND AFFIRMATIVE ACTION

"NO NEW ANTIHYPERTENSIVE COMPOUND HAS BEEN INTRODUCED IN THIS COUNTRY IN 10 YEARS"

(Dr. Edward D. Freis)

Dr. Freis won his 1971 Lasker Award for his studies of hypertension. He and many other clinicians and leaders in clinical pharmacology have been deeply disturbed by the developments that have brought important therapeutic research to a "virtual standstill in the Uuited States." Dr. Freis's comments were made prior to the accusation by consumerists that the Director of the Bureau of Drugs had transferred two medical officers of the FDA. As best we are able to

determine, both officers were associated most particularly with the clearance—or, rather, nonclearance—of cardiovascular agents.

The responsibility for the regulation of drugs cannot be solely a negative, censorial function but must also be a positive, affrmative, scientific action. A public health regulatory agency must recognize that its mandate to regulate is not a mandate to bring therapeutic medicinal developments to a "virtual standstill in the United States." Regulation does not simply imply rejection of dangerous new drugs but, equally important, the responsibility of promoting and making promptly available the benefits of new medicines. "To regulate" is not just to slow down; it can also be used to speed up.

In 1967 Maurice Visscher protested in *Science* (April 21) the FDA's refusal over a period of months to permit the testing for "*a new purpose a potentially lifesaving drug which had already been used, without evidence of toxicity, on half a million humans in other countries for a different purpose. . . . It happens that a million or more persons a year die of ventricular fibrillation, which this drug might prevent in many instances*" (our italics). He had previously warned that "many more lives may be lost by . . . delay than might be saved by excessive caution."

A.M.S.

[From the National Journal, Nov. 12, 1971, pages 2455–2457]

HUMAN RESOURCES—DRUG INDUSTRY LOBBY RIDING HIGH

(By Bruce E. Thorp)

Fresh from a victory with the Administration over the regulation of combination drugs, the prescription drug industry is ready for any new challenges the federal government may send its way.

The multi-billion-dollar industry, represented in Washington by the Pharmaceutical Manufacurers Association (PMA), has significantly strengthened its position with the Food and Drug Administration in the past year. The FDA backed away last summer from strict new requirements for combination drugs, after the industry protested vehemently and cultivated extensive support among doctors and Members of Congress.

PMA's relations with Congress may be better now than they have been at any time in the past 12 years. It was on Dec. 7, 1959, that the late Sen. (1949–1963) Estes Kefauver. D-Tenn., began hearings that led to the 1962 passage of the Kefauver-Harris Amendment (76 Stat. 780), a drug-regulation law that has aggravated the industry ever since.

But the PMA now is showing a confidence that indicates that the aggravation may have come to an end. Just last month. Sen. Gaylord Nelson, D-Wis., who picked up the Kefauver spirit and resumed hearings on the drug industry in 1967, introduced a comprehensive new bill (S. 2812) that would greatly increase government control over the manufacture and use of prescription drugs. The Nelson bill, which is the culmination of four years of investigation, has the PMA so unworried that Bruce J. Brennan, vice president and general counsel, says he has not even read it yet.

Combination drugs: The battle over combination drugs—those with more than one active ingredient—began in earnest last Feb. 18, when the FDA published proposed guidelines for deciding which combinations it would approve for marketing. (*For background on the drug controversy, see. No. 24, p. 1266.*)

The agency was using powers it had received from the 1962 drug amendment to review drug efficacy. Its proposed guidelines were strict, following the advice of those academic medical experts who believe that reliance on fixed-combination drugs is more dangerous than prescribing custom dosages of each drug to best suit a patient's needs.

But combination drugs are easier to prescribe, and they are very popular among doctors. The drug industry relied on this popularity in soliciting support from practicing doctors, who wrote letters of protest directly to the FDA and also to Members of Congress, who then sent inquiries to the agency.

Besieged by this opposition, the FDA modified its guidelines before publishing a final version Oct. 15. Four major changes were made in deference to opposition from medical and drug interests: Over-the-counter drugs were removed from the guidelines and handled separately; suggestions that combination drugs are less

desirable than individual dosages were eliminated; a requirement that the combination be effective for the duration of dosage was removed; and a requirement that the combination be advantageous for "most" patients was changed to require that combinations be "safe and effective for a significant patient population."

"We won the fight on combination drugs," said William C. Cray, PMA's vice president for public relations. "The final guidelines were quite reasonable."

New FDA lawyer: The drug industry's status with FDA also has been enhanced by the May 31, 1971, retirement of William W. Goodrich as the FDA's top lawyer. His exact title was assistant general counsel for food, drugs and environmental health in the Department of Health, Education and Welfare.

Goodrich, who had served in the government for 32 years, was not held in high esteem by the drug industry. Goodrich helped shape FDA policy against combination drugs, and it was Goodrich who defended the agency in court when the industry challenged—unsuccessfully—the removal from the market of the combination drug, Panalba. Panalba's manufacturer, the Upjohn Co., was joined by PMA in that fight.

"He was basically anti-industry," Cray said of Goodrich. "He tended to inject policy into the legal area, and he was influential in shaping that policy."

Brennan expressed relief that Goodrich is gone. "From where we sit, that can't hurt," he said.

Goodrich's successor is Peter Barton Hutt, who took over Sept. 1. Hutt was a partner in the prominent Washington law firm of Covington and Burling, where he specialized in representing food, drug and cosmetic firms in dealings with the government.

Hutt has a better perspective on government regulation, and he understands the industry point of view, Cray said. He and Brennan both said that Hutt is less interested in FDA policy, and they expect him to handle FDA court cases strictly from a legal standpoint, with much less regard for policy than Goodrich had.

But the PMA representatives said they respect Hutt as a top-notch lawyer who will be anything but a pushover. "Hutt is in there now, but let me tell you, he is not industry's man in that job," Brennan said. Cray said, "Hutt will be hard, but fair."

Hutt disagreed with the PMA's assessment that the drug industry is better off with Goodrich gone. "Let's wait five years and ask them again."

"My new client is the general public through the Food and Drug Administration, and I intend to represent that client as well as any lawyer can," he said. "I don't regard myself as a friend of anybody but the agency."

Hutt said he definitely is interested in policy and said he would consider policy and morality together with the law in carrying out his new responsibilities. "I've never been able to separate them," he said.

Congress: A year ago, the PMA was watching the progress of several bills in Congress. PMA President C. Joseph Stetler testified against four that were before the Senate Labor and Public Works Subcommittee on Health, including the bills (S 3096, S 3651 and S 3652) introduced by Sen. Nelson. The bills, which would have required new drug coding and labeling and more frequent plant inspection, all died in the 91st Congress and have not been introduced again.

Sen. Russell B. Long, D-La., chairman of the Senate Finance Committee, also had aroused PMA interest by reintroducing an amendment to the Social Security Act (49 Stat 622) to limit reimbursement under medicare and medicaid to those drugs approved by a government-sponsored committee and within an acceptable price range. Long's bill (Amendment 929 to HR 17550), was killed by his own committee and has not been introduced this year.

Nelson's new bill: In introducing his comprehensive new bill Nov. 4, Nelson told the Senate that its provisions were urgently needed to protect the public against dangerous and unnecessarily expensive drugs.

The bill would establish a national drug testing and evaluation center to clear new drugs before they are marketed; it would provide for publication of a compendium listing all drugs and their characteristics to help doctors in prescribing them; it would establish a committee to compile a formulary of recommended drugs (similar to the Long amendment); it would strengthen drug labeling and certification rules; and it would curtail certain types of drug promotion by manufacturers.

The bill, if it became law, would be the most far-reaching legislation aimed at the drug industry since the 1962 Kefauver-Harris Amendment.

The PMA clearly sees no threat in Nelson's proposal. Brennan joked about it: "I haven't seen Nelson's bill yet; he wouldn't give us a copy."

He then offered a serious analysis of its chances for passage and concluded that they are slim indeed. "It has an awful lot of controversial subjects in it," he said. "That would lessen its chances of getting anywhere as a package.

"Frankly, we just worry about bills that we think are going somewhere. We haven't done anything on this one and I don't even expect to take a look at it for a while yet."

The bill has been referred to the Senate Health Subcommittee, of which Nelson is a member. No hearings have been scheduled.

"We've done nothing with it," a spokesman said, explaining that the subcommittee is involved with too many other things at the moment.

Public relations: The biggest part of the PMA budget continues to go for public relations and advertising. Cray said the results in the past year have been encouraging.

The association last spring printed 97,000 copies of a new 118-page paperback book entitled, *Brands, Generics, Prices and Quality*. About 11,000 were sent to Members of Congress, medical and scientific personnel and libraries, with the rest bought by member companies for their own distribution, Cray said. Several thousand more copies were just printed, and a smaller version in booklet form is now being distributed to the general public, he said.

The association has budgeted $1,200,000 this year for advertising, with two-thirds of it going into consumer publications and one-third into medical journals.

When the consumer ads were first placed a year ago, hundreds of letters—80 per cent of them hostile—came in to the association, Cray said. That has stopped now. "We hardly get any anymore."

New challenges: The PMA is at least as strong as ever, and it is ready to fight any new battles that develop.

Health plans.—A major uncertainty among members of the drug industry is how they will come out under national health-insurance programs that are being proposed and discussed by Congress and the Administration.

The industry is particularly worried that the federal government might get into the business of telling the public what drugs they should buy and at what prices.

"The pharmaceutical industry has no objection to the extension of drug benefits in government health programs," Stetler told a meeting of the National Pharmaceutical Council in Washington Nov. 4.

"The industry's principal, immediate concern is that Congress and officials of the executive branch clearly understand that certain proposals advanced in the name of cost curtailment would pose grave problems regarding the quality of drug products and their availability," he said.

Stetler particularly objected to any proposal for a formula that would limit federal reimbursement for drug purchases to those drugs approved by a study committee.

Stetler warned that the committee would have "sweeping powers," and said, "It could require testing and the establishment of procedures to determine the inclusion or exclusion of any medicine in the formulary."

"Under this arrangement, a small, part-time government committee would be empowered, on the basis of highly questionable criteria, to decide the life or death of all drug products which are now lawfully on the markets," Stetler said.

Despite this concern, the drug industry can see benefits for itself and for the public in a health insurance plan for needed medicines.

"It is our fervent hope that whatever legislation passes will improve the delivery of medical care and bring costs within reasonable bounds," Stetler told the council.

FTC study.—A new government study of the prescription drug industry was announced Nov. 11 by H. Michael Mann, director of the Federal Trade Commission's Bureau of Economics.

Mann told the marketing committee of the National Association of Manufacturers that his bureau would try to determine whether the relatively high prices and high profits of the drug industry result from market concentration, or whether they are inevitable in this type of industry. "Can we have the benefits without such high prices and profits," he asked.

Cray said the PMA is not particularly concerned about the FTC study. "We will cooperate to the extent we can," he said.

But he said there was a serious danger that Mann and his staff would judge the drug industry, which requires large amounts of research to develop just a few new products, by the same standards as regular industries.

"He's taking industrial criteria to try to define the state of the art of medical treatment," Cray said.

The FTC study is just beginning, and no final report is expected for some time. But whatever the conclusions, the PMA will be ready with any necessary defenses.

[From the Federal Register, May 5, 1972, Vol. 37, No. 88, pages 9128-9138]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, FOOD AND DRUG ADMINISTRATION—[21 CFR PARTS 1, 2, 4, 8, 121, 130, 135, 146, 191]

PUBLIC INFORMATION—NOTICE OF PROPOSED RULEMAKING

The effect of Public Law 89-487, the Public Information section of the Administrative Procedure Act, more commonly known as the "Freedom of Information Act," has been to increase requests made of the Food and Drug Administration for release of documents contained in Food and Drug Administration files. In response, it has been the policy of the Department of Health, Education, and Welfare to provide disclosure consonant with statutory obligations of confidentiality and administrative necessities recognized by the act. Because of the vast amount of information in FDA files and the fact that FDA has never before attempted to set out in detail the rules applicable to public disclosure of this information, the Commissioner of Food and Drugs has concluded that it is in the public interest to reexamine the agency's practices on public disclosure of information and to adopt detailed regulations specifying the extent to which public disclosure is and is not permitted.

The Freedom of Information Act adopts a general rule that, except where specifically exempted, all documents in Government files shall be made available to the public. The Commissioner fully endorses this approach. Public disclosure should be the rule rather than the exception. Accordingly, all information in FDA files will be available for public disclosure unless they fall within one of the explicit exemptions contained in that act or other applicable statutes.

The Freedom of Information Act itself contains in 5 U.S.C. 552(b) nine exemptions from public disclosure in the following areas:

1. *National defense or foreign policy.*—This exemption has raised no difficulties with FDA.

2. *Internal procedure.*—FDA has recently reappraised the status of all of its internal operating manuals with the intent of separating all confidential material in orderd to make the remaining material publicly available. This review is now complete, and the manuals will shortly be made available through the office of the Assistant Commissioner for Public Affairs.

3. *Information specifically exempted from disclosure by statute.*—This exemption incorporates by reference the general and specific confidentiality provisions contained in other statutes. The Attorney General's Memorandum on the Public Information Section of the Administrative Procedure Act (1967) mentions 18 U.S.C. 1905, which is quoted below, as one of the specific confidentiality statutes not intended to be changed. Similarly, the specific confidentiality provisions in the various statutes administered by FDA, which are also quoted below, are incorporated by reference under this provision.

4. *Trade secrets and commercial or financial information obtained from any person and privileged or confidential.*—The Senate Report explained this exemption as follows:

This exception is necessary to portect the confidentiality of information which is obtained by the Government through questionnaires or other inquiries, but which would customarily not be released to the public by the person from whom it was obtained.

The House Report similarly stated that:

It exempts such material if it would not customarily be made public by the person from whom it was obtained by the Government. The exemption would include business sales statistics, inventories, customer lists, scientific or manufacturing processes or developments * * *.

The House Report also emphasized that:

It would also include information which is given to an agency in confidence, since a citizen must be able to confide in his Government. Moreover, where the Government has obligated itself in good faith not to disclose documents or information which it receives, it should be able to honor such obligations.

The Attorney General's memorandum has interpreted this exemption as follows:

An important consideration should be noted as to formulae, designs, drawings, research data, etc., which, although set forth on pieces of paper, are significant not as records but as items of valuable property. These may have been developed by or for the Government at great expense. There is no indication anywhere in the consideration of this legislation that the Congress intended by subsection (c), to give away such property to every citizen or alien who is willing to pay the price of making a copy. Where similar property in private hands would be held in confidence, such property in the hands of the United States should be covered under exemption (e)(4).

Comment b to section 757 of the Restatement of Torts defines a "trade secret" as follows:

A trade secret may consist of any formula pattern, device, or compilation of information which is used in one's business, and which gives him an opportunity to obtain an advantage over competitors who do not know or use it.

This exemption is the one most frequently in issue with respect to data and information in FDA files for which disclosure is sought. Much of it has been submitted to FDA in petitions and applications or on a voluntary basis with the understanding that it would be retained as confidential, and some of it is still highly valuable in that it gives the company having it a competitive advantage over others who are required by law to obtain it in order to receive FDA approval of a product or ingredient prior to marketing.

5. *Interagency or intra-agency memorandums or letters which would not be available by law to a private party in litigation with the agency.* The House Report explained this exemption as follows:

Agency witnesses argued that a full and frank exchange of opinions would be impossible if all internal communications were made public. They contended, and with merit, that advice from staff assistants and the exchange of ideas among agency personnel would not be completely frank if they were forced to "operate in a fishbowl." Moreover, a Government agency cannot always operate effectively if it is required to disclose documents or information which it has received or generated before it completes the process of awarding a contract or issuing an order, decision or regulation. This clause is intended to exempt from disclosure this and other information and records wherever necessary without, at the same time, permitting indiscriminate administrative secrecy * * *.

The Attorney General's memorandum further discussed it:

Conversely, internal communications which would not routinely be available to a party to litigation with the agency, such as internal drafts, memoranda between officials or agencies, opinions and interpretations prepared by agency staff personnel or consultants for the use of the agency, and records of the deliberations of the agency or staff groups, remain exempt so that free exchange of ideas will not be inhibited. As the President stated upon signing the new law, "officials within Government must be able to communicate with one another fully and frankly without publicity."

6. *Personnel and medical files.* This exemption has raised no difficulties with FDA.

7. *Investigatory files compiled for law enforcement purposes except to the extent available by law to a private party.* The House Report stated that this exemption includes enforcement of "all kinds of laws, labor and securities laws as well as criminal laws," and thus includes investigatory files compiled for enforcement of all the laws administered by FDA. It does not include, however, the enforcement action taken as the result of the investigation, whether it be formal or informal.

8. *Information concerning financial institutions.* This exemption does not appear to be relevant to FDA.

9. *Information concerning wells.* This exemption also does not appear to be relevant to FDA.

In addition to these specific exemptions under the Freedom of Information Act, other Federal laws also limit the availability to the public of information con-

tained in FDA files. The general Federal confidentiality statute, section 1905, title 18 U.S.C., Crimes and Criminal Procedure (18 U.S.C. 1905), provides that:

"Whoever, being an officer or employee of the United States or of any department or agency thereof, publishes, divulges, discloses, or makes known in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association; or permits any income return or copy thereof or any book containing any abstract or particulars thereof to be seen or examined by any person except as provided by law; shall be fined not more than $1,000, or imprisoned not more than 1 year, or both; and shall be removed from office or employment.

Section 301(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 331(j), prohibits:

The using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act, any information acquired under authority of section 404, 409, 505, 506, 507, 512, 704, or 706 concerning any method or process which as a trade secret is entitled to protection.

Section 4(h) of the Federal Hazardous Substances Act, 15 U.S.C. 1263(h), similarly prohibits:

The use by any person to his own advantage, or revealing other than to the secretary or offices or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act, of any information acquired under authority of section 11 concerning any method or process which as a trade secret is entitled to protection.

Section 359(d) of the Public Health Service Act, 42 U.S.C. 263g(d), as added by the Radiation Control for Health and Safety Act of 1968 provides that:

Every manufacturer of electronic products shall furnish to the Secretary a true or representative copy of all notices, bulletins, and other communications to the dealers or distributors of such manufacturer or to purchasers (or subsequent transferees) of electronic products of such manufacturer regarding any such defect in such product or any such failure to comply with a standard applicable to such product. The Secretary shall disclose to the public so much of the information contained in such notice or other information obtained under section 360A as he deems will assist in carrying out the purposes of this subpart, but he shall not disclose any information which contains or relates to a trade secret or other matter referred to in section 1905 of title 18 of the United States Code unless he determines that it is necessary to carry out the purposes of this subpart.

With respect to information obtained through inspection and reports on electronic products, section 360A(e) of the Public Health Service Act, 42 U.S.C. 263i, also provides that:

The Secretary or his representative shall not disclose any information reported to or otherwise obtained by him, pursuant to subsection (a) or (b) of this section, which concerns any information which contains or relates to a trade secret or other matter referred to in section 1905 of title 18 of the United States Code, except that such information may be disclosed to other officers or employees of the Department and of other agencies concerned with carrying out this subpart or when relevant in any proceeding under this subpart. Nothing in this section shall authorize the withholding of information by the Secretary, or by any officers or employees under his control, from the duly authorized committees of the Congress.

FDA has no authority either to grant public access to information prohibited from disclosure or to deny public access to information not exempt from disclosure. FDA has on many occasions urged a congressional review of the statutory provisions denying public access to information contained in its files, but no such review has been undertaken. Accordingly, this notice can serve only to interpret and clarify the application of existing statutory provisions. The Commissioner therefore proposes to amend the FDA regulations to reflect the following policy:

1. Section 305 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 335, and section 7 of the Federal Hazardous Substances Act, 15 U.S.C. 1266, provide for a hearing by FDA prior to recommendation of criminal prosecution. The documents relating to this proceeding constitute an investigatory file for law enforcement purposes and consist in large part of intra-agency memoranda. After the file is closed (either because FDA concludes not to take action or because the action has been taken and terminated) or the statute of limitations has run, the information contained in the file will be made available for public disclosure except that opinions, policy recommendations, intra-agency and interagency memoranda, statements of witnesses obtained through promises of confidentiality, names of individuals, trade secrets, and other confidential information will be deleted. Where no prosecution is brought against individuals, the names of individuals will not be disclosed, since to do so would unfairly stigmatize them without an opportunity for public defense in violation of due process of law, Wisconsin v. Constantineau, 400 U.S. 433 (1971).

2. Section 306 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 336, and section 360C of the Public Health Service Act, 42 U.S.C. 263k, provide for informal enforcement action in lieu of formal enforcement action, and section 701 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 371, and section 10 of the Federal Hazardous Substances Act, 15 U.S.C. 1269, authorize the promulgation of regulations for the efficient enforcement of these laws. Records of all informal enforcement action taken by FDA in the nature of communications to and resposes from companies following factory inspection, recall or detention requests, communications to companies requesting other corrective action or other informal action are made available for public disclosure. Confidential or trade secret information will be deleted.

3. Investigatory files compiled for law enforcement purposes, including information obtained from factory inspections, will not be made available for public disclosure until after a decision has been made not to institute informal or formal enforcement action or until such enforcement action is completed or until the statute of limitations runs, whichever occurs first. At such time the factual portions of the file will be made available for public disclosure with all trade secret or confidential information, opinions and recommendations, names of individuals, and other similar information deleted.

4. FDA regularly undertakes testing and research in a wide variety of fields, either in its own laboratories or in outside laboratories under contract or grant. Such testing and research includes toxicological testing, compliance assays, methodology studies, product testing of any type, and all other kinds of testing and research. The results of such testing and research represent internal information that will be publicly disclosed when the final report is complete (unless it constitutes part of an investigatory file for law enforcement purposes, in which case it will be disclosed as provided for such files). If the results are disclosed in an authorized manner to any member of the public before the final report is available, they will then be available to every member of the public who so requests. A list of current nonregulatory research being conducted by or for FDA (together with any research contract) is always available for public disclosure.

5. Research data on the safety, functionality, and effectiveness of a wide variety of ingredients and products are submitted to FDA as part of various petitions and applications. Since 1938, FDA has taken the position that such data ordinarily represent valuable commercial property and trade secrets that must be retained as confidential and may not be disclosed to the public. The Attorney General's memorandum concluded that such research data are to be retained as confidential, and the House Report emphasized that, when the Government receives information such as this under a good faith pledge of confidentiality, the Government should keep its word. On the other hand, public policy favors expanded public disclosure of this information. The Commissioner proposes to adopt the Restatement of Torts definition of "trade secrets," which emphasizes that the information must provide an advantage over competitors to be regarded as confidential. Accordingly, as of the effective date of the final regulation in this matter the following policy will apply:

a. The safety, functionality, and effectiveness data and information contained in food additive and color additive petitions and antibiotic drug forms are available for public disclosure unless extraordinary circumstances are shown. Since a food additive regulation or color additive regulation or antibiotic drug monograph, when issued, permits all persons to manufacture and market the ingredient or product, such data do not provide a commercial advantage over competi-

tors and are not the type of valuable commercial information customarily regarded as privileged. For future petitions or forms, such justification shall be provided when the petition is submitted. An opportunity will be provided for appeal if the data or information are regarded by the FDA as not confidential. Nonconfidential information will be released at the time the food additive or color additive regulation or antibiotic drug monograph is promulgated. For petitions or forms already submitted, manufacturers will be given 180 days within which to submit in writing a justification for holding specified information in such petitions confidential.

b. The safety and effectiveness data contained in FDA files relating to new drugs and new animal drugs may or may not represent valuable trade secret and confidential information depending upon the legal status of the particular drug. Nonpublic safety and effectiveness data and information relating to drugs for which a new-drug application (NDA) or a new animal drug application (NADA) is required clearly represent highly valuable material, since the law provides that a competitor cannot market or use the drug without first submitting such data and information to FDA for approval. With respect to drugs that may be marketed on the basis of an abbreviated application or that are "old drugs" which do not require premarketing approval, no such competitive advantage attaches to the safety and effectiveness data and information, and it therefore no longer represents valuable commercial property for which confidentiality may be maintained unless extraordinary circumstances can be shown. Similarly, when an application has been filed and approval has been withdrawn, the safety and effectiveness data and information contained therein provide no competitive advantage and will not be maintained as confidential. (Disclosure or nondisclosure of such data must depend upon the legal status of the product or ingredient as determined by FDA and not as determined by a manufacturer or a competitor, since FDA is not bound by anyone else's determination of that legal status.)

Accordingly, for such data already contained in FDA files for which disclosure will otherwise be permitted, the applicants will be granted 180 days within which to designate in writing the specific data that they believe remain confidential. In special cases where requests for information are pending, FDA will ask for an immediate reply on this matter. Adequate justification for confidentiality must be given. In order to avoid unnecessary work, FDA may wait for a request for public disclosure of a particular document before ruling on a request for confidentiality of that document. Where confidentiality is not requested or the justification is inadequate, the data will be made available for public disclosure. All such data otherwise previously made available to the public will not be held as confidential.

For applications submitted to FDA in the future, all data and information regarded as confidential must be clearly marked. Until the ingredient or product is classified by FDA as a human drug or animal drug that is no longer a new drug or new animal drug or that may be the subject of an abbreviated application, all such data will be retained as confidential. Thereafter, it will become publicly available unless extraordinary circumstances can be shown. Since the data and information in a new NDA are confidential and thus cannot be disclosed, in lieu thereof every future application or supplement will be required to contain a comprehensive summary of all safety and effectiveness data. When the application and the summary are approved by FDA, the summary will become publicly available. This summary will not constitute the full reports required by the statute for a competitor to obtain approval of an identical product.

The safety and effectiveness data in an investigational new drug plan (IND) or an investigational new animal drug plan (INAD) which has been terminated or discontinued and in an NDA or NADA for which FDA has withdrawn approval for any reason pursuant to section 505(e) or section 512(e) of the Federal Food, Drug, and Cosmetic Act will be available for public disclosure unless extraordinary circumstances are shown.

6. Studies, tests, and other research often include the names of patients or research subjects. Such names or other identifying characteristics in data or information disclosed to the public will be deleted to avoid invasion of personal privacy.

7. Quantitative or semiquantitative product formulae contained in applications and petitions are valuable commercial property that provide an advantage over competitors and therefore will not be made publicly available unless they have otherwise previously been disclosed (e.g., in a patient or scientific article) by the manufacturer. A list of all ingredients in a product, or a list of all products containing a particular ingredient, or similar lists will be available for public disclosure unless a particular ingredient is shown to be a trade secret.

8. Assay methods contained in applications and petitions are methods or processes which are trade secrets and valuable commercial property that provide an advantage over competitors and therefore will not be publicly disclosed unless other, more specific, statutory provisions so require. The food additive, color additive, new drug, and new animal drug provisions of the law require FDA to determine safe conditions of use. An assay method may or may not be required as part of that determination. When public disclosure of an assay method is required to assure safety (which will usually be the situation with food additives, color additives, old human and animal drugs, and human and animal drugs that may be the subject of abbreviated applications), the confidentiality of the method will not be retained.

9. Manufacturing processes are methods or processes which are trade secrets and valuable commercial property that provide an advantage over competitors and therefore will not be made publicly available unless they have otherwise previously been disclosed by the manufacturer.

10. Protocols (methods and procedures) for tests or studies will be made available to the public except upon a showing that they constitute trade secrets or confidential information because they are unique, have not previously been disclosed to any member of the public (other than a paid consultant), have been developed at significant cost, and provide a competitive advantage.

11. The existence of pending new drug applications will be made known by a list of such pending matters. Each applicant will, however, be given an opportunity to persuade FDA that particular circumstances justify excluding his application from the list.

12. The Food and Drug Administration has in the past received, and will continue to receive, a wide variety of information that is voluntarily submitted to the agency by members of the public, physicians, the regulated industries, and professional organizations and that is not a part of any application or petition or otherwise required to be submitted. All such information submitted in the future will be publicly disclosed unless it is marked confidential and adequate justification for its confidentiality is stated. In the event that the Food and Drug Administration concludes that adequate justification for confidentiality is not shown, the person submitting the information will be given the opportunity either to withdraw the information or to submit it without a request for confidentiality. Since submission of this data and information could not be compelled and the Food and Drug Administration is thus dependent upon the goodwill of individuals and companies to receive this information, a somewhat more narrow disclosure policy will be followed than is the case with data and information required to be submitted. For example, adverse reaction and complaint data for new drugs, which are required to be submitted to FDA, will be available for public disclosure with only the names of patients and physicians deleted; but adverse reaction and complaint data for foods, devices, cosmetics, and hazardous substances voluntarily disclosed by companies, which are not required to be submitted to FDA, will be available for public disclosure only in a way that does not reveal the manufacturer or brand name if the manufacturer will otherwise not disclose the information to FDA. The fact that information is voluntarily submitted, however, will not in any way inhibit the Food and Drug Administration from taking whatever regulatory action may be warranted under the circumstances. Information of this type submitted in the past will routinely be disclosed to the public upon request unless it contains confidential information or has been received pursuant to a pledge of confidentiality or unless the person submitting it sends to the Food and Drug Administration within 180 days from the effective date of the regulation in this matter a statement justifying why the information should be retained as confidential.

13. All correspondence or summaries of discussions with members of the public, members of Congress, company officials, or other persons who are not Government employees or special Government employees shall be publicly available unless it contains confidential information or constitutes part of an investigatory file for law enforcement purposes.

14. Data and information otherwise not available for public disclosure may be disclosed to Food and Drug Administration consultants, advisory committees, and other persons who are special Government employees. Such persons are thereafter subject to the same laws and regulations with respect to disclosure of such data and information as any other FDA employee.

FDA has at times received broad requests for information which would require deployment of many man-hours to conduct the necessary search, to delete exempt information, to copy the information, and otherwise to process the request.

Fees paid to FDA for searching and copying may not be used by FDA to employ persons to conduct the agency's public information program, because they are paid to the U.S. Treasury. The Freedom of Information Act was not intended by Congress to require FDA to divert a major portion of its scarce manpower for conducting such searches and processing rather than in enforcing the important consumer safety laws within its jurisdiction. Accordingly, broad or general requests for information (without at least a minimal description of the documents desired) or for large numbers of documents will be processed taking into account the man-hours required, the tasks from which these resources must be diverted, the impact that this diversion will have upon the Agency's consumer protection activities, and the public policy reasons justifying the request.

Requests are also frequently received to waive the payment of fees. FDA will honor such requests when there is an adequate showing of indigence and when the request has a strong public interest justification. Except under these circumstances, FDA will not discriminate in favor of any person who requests a document by granting an exemption from the payment of costs.

The purpose of this notice is to propose comprehensive rules designed to provide, so far as possible, clear and unambiguous guidelines with respect to the voluminous documents contained in FDA files that are and are not available for public disclosure. Although it is not possible to state with particularity the status of every type of document, it is hoped that the regulations will provide both those who submit information to the Food and Drug Administration and those who seek information from the Food and Drug Administration sufficient guidance to understand what documents will and will not be kept confidential. Specific comment is therefore requested as to whether additional categories of documents should be explicitly covered in the regulations or whether clarification of any of the proposed regulations set out below is advisable.

Paragraphs 8 and 11 of Appendix A to 45 CFR Part 5 contain examples of kinds of FDA records not available for public disclosure. These paragraphs will be revised to reflect the new policy when a final regulation is promulgated in this matter.

Accordingly, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 201 et seq., 52 Stat. 1040 et seq. as amended; 21 U.S.C. 321 et seq.), the Federal Hazardous Substances Act (sec. 1 et seq., 74 Stat. 372 et seq. as amended; 15 U.S.C. 1261 et seq.), the Public Health Service Act (sec. 1, et seq., 58 Stat. 682 et seq. as amended; 42 U.S.C. 201 et seq.), and the Public Information Act (Public Law 89–487 as codified by Public Law 90–23, 81 Stat. 54; 5 U.S.C. 552) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Parts 1, 2, 4, 8, 121, 130, 135, 146, and 191 be amended:

PART 1—REGULATIONS FOR THE ENFORCEMENT OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND THE FAIR PACKAGING AND LABELING ACT

1. In Part 1, by adding a new paragraph (c) to § 1.6, as follows:

§ 1.6 Presentation of views under section 305 of the act.

* * * * * * *

(c) The documents relating to this proceeding constitute an investigatory file for law enforcement purposes and may include interagency and intra-agency memoranda. No data or information contained in this file are available for public disclosure prior to the file's being closed or the statute of limitations' running, whichever occurs first. After the file is closed or the statute of limitations runs, the factual information contained in the file will be made available for public disclosure except that opinions, policy recommendations, interagency and intra-agency memoranda, statements of witnesses obtained through promises of confidentiality, names of individuals, trade secrets, and other confidential information will be deleted.

PART 2—ADMINISTRATIVE FUNCTIONS, PRACTICES, AND PROCEDURES

Subpart G—Public Information

2. In Part 2, by deleting Subpart G—Public Information containing § 2.115 *Fee schedule for searching, supplying, and certifying records.* Concurrently, the information in this subpart is being recodified into Part 4 as § 4.20.

PART 4—OFFICIAL RECORDS AND INFORMATION

3. In Part 4, by adding the following new sections.

§ 4.20 Fee schedule for searching, supplying, and certifying records.

(a) Certain routine information is provided to the general public at no charge; however, special informational services involving more than routine search and allocation of staff time are subject to fees as necessary to recover costs to the Government.

(b) Charges for special services regarding Food and Drug Administration records are as follows:

(1) Search for records and deletion of nondisclosable data and information: $4 per hour. Where a substantial amount of time is spent by higher salaried professional, managerial, or program personnel in searching for or producing requested documents or in deleting nondisclosable data and information, special rates not to exceed the cost to the agency of such services will be determined and charged. (In determining these rates, the man-hours spent by such personnel, will be taken into account.)

(2) Reproduction, duplication, or copying of records: 25 cents for the first page and 10 cents for each subsequent page.

(3) Reproduction, duplication, or copying of microfilm: 50 cents per microfilm frame and 50 cents per microfiche.

(4) Certification or authentication of records: $5 per certification.

(5) Forwarding material to destination: Postage, insurance, and special fees will be charged on an actual cost basis.

(c) This schedule does not apply to official records and information provided under § 4.1.

(d) The payment of fees may be waived by the Assistant Commissioner for Public Affairs on an adequate showing that the person making the request is indigent and that disclosure has a strong public interest justification.

(e) The Food and Drug Administration may furnish the requested documents to a private contractor for copying. Under these circumstances, the Food and Drug Administration will charge for the costs of searching for the documents and arranging for copying. The private contractor will charge directly for the cost of copying.

§ 4.21 Informal enforcement action.

Records of all informal enforcement action, such as letters to and responses from companies following factory inspection, recall or detention requests, letters to companies requesting other corrective measures, or other similar action, are made available for public disclosure.

§ 4.22 Agency testing and research.

(a) A list of nonregulatory testing and research being conducted by or with funds provided by the Food and Drug Administration (together with any research contract) is available for public disclosure.

(b) The results of testing or research conducted by or with funds provided by the Food and Drug Administration such as Toxicological testing, compliance assays, methodology studies, and product testing, are available for public disclosure when the final report is complete. If such results are disclosed in an authorized manner to any member of the public before the final report is available, they will be available for public disclosure to every member of the public who so requests.

§ 4.23 Agency correspondence.

All correspondence to or from members of the public, members of Congress, organization or company officials, or other persons who are not Government employees or special Government employees is available for public disclosure.

§ 4.24 Summaries of telephone calls and meetings.

(a) A summary of a telephone call or meeting involving only Government employees or special Government employees, including discussions by or with advisory committees or consultants, is an intra-agency or interagency memorandum that is not available for public disclosure except to the extent of nonconfidential factual information.

(b) A summary of a telephone call or meeting involving any person who is not a Government employee or a special Government employee is available for public disclosure.

§ 4.25 Trade secrets and confidential data or information.

(a) Data and information which are submitted to the Food and Drug Administration or contained in any records of the Food and Drug Administration and which constitute trade secrets or which are confidential are not available for public disclosure. Such data and information will be deleted from any documents that are otherwise available for public disclosure before they are furnished to the public.

(b) A trade secret may consist of any formula, pattern, device, or compilation of information which is used in one's business and which gives them an opportunity to obtain an advantage over competitors who do not know or use it.

(c) Confidential data or information includes trade secrets and other valuable data or information of a type customarily held in strict confidence or regarded as privileged and not disclosed to the public by the person to whom it belongs.

§ 4.26 Data and information submitted voluntarily.

(a) Data and information submitted voluntarily to the Food and Drug Administration and not as a part of any petition, application, or other required submission or request for action are not available for public disclosure if clearly marked as confidential, good cause is shown to justify confidentiality, and the Food and Drug Administration accepts it on this basis. Whenever data or information are submitted voluntarily to the Food and Drug Administration and are marked confidential, a decision will be made prior to acceptance concerning whether it will be accepted on this basis. Applying the guidelines in this section and in Subpart B of Part 4, the director of the bureau to which the data or information is submitted will make the initial determination on whether good cause has been shown to justify confidentiality of the material. If the director concludes that good cause has not been shown, the person submitting the material will be so informed and may appeal this decision to the Assistant Commissioner for Public Affairs whose decision on the matter will be final. If the final decision is that the data or information is not confidential and thus is available for public disclosure, the person will have the opportunity either not to make the submission or to submit it as not confidential.

(b) Safety, effectiveness, and functionality data and information for a developmental or marketed product are available for public disclosure unless the person submitting the data or information refuses to submit it except on a confidential basis.

(c) A protocol for a test or study is available for public disclosure unless it is adequately shown to constitute a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or a paid consultant, has been developed at significant cost, and provides a competitive advantage.

(d) Manufacturing methods or processes, including quality control procedures, are not available for public disclosure except to the extent previously disclosed to the public.

(e) Production and sales data and information are not available for public disclosure except to the extent previously disclosed to the public.

(f) Adverse reaction and complaint data and information and product experience reports with the names of individuals deleted (including the name of the person using the product and the person reporting the information) are available for public disclosure unless the person submitting the data or information information, and reports which are received on a confidential basis will be available for public disclosure with the names of individuals deleted (including the person using the product and the person reporting the information). The names of manufacturers or product brand names will not be deleted prior to public disclosure unless the person submitting the data or information refuses to submit it except on that condition.

(g) Quantitative or semiquantitative formulae are not available for public disclosure except to the extent previously disclosed to the public. A list of all ingredients contained in a product or a list of all products containing a specified ingredient or a list of all products known to possess a particular characteristic or any similar list is available for public disclosure. A particular ingredient (or product containing that ingredient) may be excluded from any such list upon a showing that the ingredient is a trade secret in that it is unique, is important to the product, and is not known to competitors.

(h) Every person who has voluntarily submitted data or information to the Food and Drug Administration prior to the effective date of this section may

submit in writing, within 180 days after such effective date, a request that specified data and information which are contained in the submission(s) and which will otherwise be available for public disclosure in accordance with the principles established in this section shall be retained as confidential and exempt from public disclosure. This request must be accompanied by a statement justifying confidentiality. Any such data and information for which confidentiality is not requested or which the Food and Drug Administration concludes (in accordance with paragraph (a) of this section) are not exempt from public disclosure will be available for public disclosure at the end of this 180-day period. The Food and Drug Administration may defer ruling upon such a request for confidentiality of specified data or information until a request for public disclosure of that data or information is received. In special cases where requests for public disclosure of documents are pending, the Food and Drug Administration may ask for an expedited submission on this matter.

(i) Data and information that may be required to be submitted to the Food and Drug Administration but that are submitted voluntarily instead are not subject to the provisions of this section and will be handled as if they had been required to be submitted.

§ 4.27 Intra-agency and interagency memoranda.

(a) Intra-agency and interagency memoranda which would not be available by law to a private party in litigation with the agency are not available for public disclosure.

(b) Factual information contained in intra-agency or interagency memoranda that are otherwise exempt from public disclosure are available for public disclosure.

§ 4.28 Data and information previously made available to the public.

All data and information contained in Food and Drug Administration files that have in any way previously been furnished to anyone other than an employee or paid consultant in an authorized manner by any person will not be retained by the Food and Drug Administration as confidential unless extraordinary circumstances are shown. Any data or information submitted to the Food and Drug Administration that is requested to be retained as confidential must be accompanied by a statement that the information has not previously been published or furnished to anyone other than an employee or paid consultant. Any such statement is subject to the False Report to the Government Act, 18 U.S.C. 1001.

§ 4.29 Disclosure in administrative or court proceedings.

Data and information otherwise exempt from public disclosure may be revealed in Food and Drug Administration administrative or court proceedings where the data or information are relevant. The Food and Drug Administration will request that the data or information be held in camera and that any other appropriate measures be taken to reduce public disclosure to the minimum necessary under the circumstances.

§ 4.30 Disclosure to consultants and advisory committees.

Data and information otherwise exempt from public disclosure may be disclosed to Food and Drug Administration consultants, advisory committees, and other special Government employees. Such persons are thereafter subject to the same restrictions with respect to the disclosure of such data and information as any other Food and Drug Administration employee.

§ 4.31 Disclosure of identity of individuals.

(a) The names of individuals submitting data or information to the Food and Drug Administration (including the names of consumers who write the Food and Drug Administration) are available for public disclosure unless a request for confidentiality is included or clearly implied. Any such request for confidentiality with respect to the name, address, or other identifying characteristic of an individual will be honored, but requests for confidentiality of corporate names will not be honored unless extraordinary circumstances are shown.

(b) The names or other identifying characteristics of individuals participating as patients or research subjects in any test, study, or other research project will be deleted before the data or information with respect to such test or study are disclosed to the public. Such names or other identifying characteristics should be replaced by a coded means of identification prior to making any such

submission (e.g., as part of an IND or NDA) to the Food and Drug Administration. Should the Food and Drug Administration need the actual names of such individuals for followup purposes, a separate request will be made.

§ 4.32 Investigatory files compiled for law enforcement purposes.

No data or information contained in investigatory files compiled for law enforcement purposes (including correspondence, memoranda, test results, and information obtained from factory inspections) will be made available for public disclosure until after a decision has been made not to institute informal or formal enforcement action or until such action is completed or until the statute of limitations runs, whichever occurs first. At such time the factual information contained in the file will be made available for public disclosure except that opinions, policy recommendations, intra-agency and interagency memoranda, statements of witnesses obtained through promises of confidentiality, names of individuals, trade secrets, and other confidential information will be deleted.

§ 4.33 Situations for which confidentiality is uncertain.

In situations where the confidentiality of data or information is uncertain and there is a request for its public disclosure, the Food and Drug Administration will consult the person who has submitted the data or information before concluding whether it is available for public disclosure.

§ 4.34 Use of data or information for formal or informal actions.

Nothing in this part or this title shall prevent the Food and Drug Administration from using any data or information, whether obtained voluntarily or involuntarily and whether or not it is confidential, as the basis for taking any formal or informal action within its jurisdiction.

§ 4.35 Nonspecific and overly burdensome requests.

The Food and Drug Administration will make every reasonable effort to comply fully with all requests for disclosure of nonexempt records. Nonspecific requests or requests for a large number of documents that require the deployment of a substantial amount of agency man-hours to search and compile will be processed taking into account the man-hours required, the tasks from which these resources must be diverted, the impact that this diversion will have upon the agency's consumer protection activities, and the public policy reasons justifying the requests. A decision on the procesisng of such a request for information shall be made after balancing the public benefit to be gained by the disclosure against the public loss that will result from diverting agency personnel from their other responsibilities. In any situation in which a request for information cannot fully be complied with under these circumstances, the person making the request will be asked to be more specific or to narrow the request, and an attempt will be made to provide as much of the type of data or information sought as is feasible under the circumstances.

§ 4.36 Availability of documents.

(a) In any situation where a document is available for public disclosure, but a portion of the data or information contained in the document is not available for such disclosure (e.g., it contains a trade secret or confidential information or names or individuals or law enforcement information), the portion that is not available for disclosure will be deleted before the document is disclosed to the public.

(b) A document that is ordinarily available for public disclosure (e.g., a letter within § 4.23 or a memorandum within § 4.24(b)) will not be available for such disclosure if it falls within an exemption (e.g., it is part of a law enforcement file within § 4.32 or is confidential within § 4.25).

PART 8—COLOR ADDITIVES

4. In Part 8, by revising § 8.9 to read as follows:

§ 8.9 Confidentiality of petition.

(a) All data and information submitted with or incorporated by reference in a petition shall be clearly marked confidential if the petitioner considers it to be confidential and exempt from public disclosure. Adequate grounds must be given

to justify the confidentiality of each item so marked. All data and information previously made public in any authorized manner will not be retained by the Food and Drug Administration as confidential unless extraordinary circumstances are shown. Any such request shall state that the data or information so specified has not previously been made available to any person who is not an employee or paid consultant or shall explain why the data or information should remain confidential in spite of such prior disclosure. Applying the guidelines in this section and in Subpart B of Part 4, the Director of the Bureau of Foods will make the initial determination on whether information marked confidential will be available for public disclosure. If the Director concludes that an item so marked is not exempt from public disclosure, the petitioner or master file holder will be so informed and will be given an opportunity to appeal that decision to the Assistant Commissioner for Public Affairs, whose decision on the matter will be final.

(b) All safety and functionality data and information submitted with or incorporated by reference in a petition are available for public disclosure after the regulation is promulgated unless extraordinary circumstances are shown.

(c) A protocol for a test or study is available for public disclosure unless an adequate showing is made that it constitutes a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or a paid consultant, has been developed at significant cost, and provides a competitive advantage.

(d) Manufacturing methods or processes, including quality control procedures, are not available for public disclosure except to the extent previously disclosed to the public by the petitioner or master file holder.

(e) An assay method is not available for public disclosure except to the extent previously disclosed to the public by the petitioner or master file holder unless it must be available to permit manufacturers to comply with limits established for the additive. The availability of an assay method will be included in the regulation.

(f) Every person who has filed a petition prior to the effective date of this section may submit in writing to the Food and Drug Administration, within 180 days after such effective date, a request that specified safety, functionality, protocol, or assay data and information which are contained in the petition and which will otherwise be available for public disclosure in accordance with the principles established in this section shall be retained as confidential and exempt from public disclosure. This request must be accompanied by a statement justifying confidentiality. Any such data and information for which confidentiality is not requested or which the Food and Drug Administration concludes (in accordance with paragraph (a) of this section) are not exempt from public disclosure will be made available to the public at the end of this 180-day period. The Food and Drug Administration may defer ruling upon such a request for confidentiality of specified data or information until a request for public disclosure of that data or information is received. In cases where requests for public disclosure of documents are pending, the Food and Drug Administration may ask for an expedited submission on this matter.

PART 121—FOOD ADDITIVES

5. In part 121, by revising paragraph (h) in § 121.51 to read as follows:

§ 121.51 Petitions proposing regulations for food additives.

* * * * * * *

(h) (1) All data and information submitted with or incorporated by reference in a petition shall be clearly marked confidential if the petitioner considers it to be confidential and exempt from public disclosure. Adequate grounds must be given to justify the confidentiality of each item so marked. All data and information previously made public in any authorized manner will not be retained by the Food and Drug Administration as confidential unless extraordinary circumstances are shown. Any such request shall state that the data or information so specified has not previously been made available to any person who is not an employee or paid consultant or shall explain why the rata or information should remain confidential in spite of such prior disclosure. Applying the guidelines in subparagraphs (2) through (5) of this paragraph and Subpart B of Part 4, the

Director of the Bureau of Foods will make the initial decision on whether information marked confidential will be available for public disclosure. If the Director concludes that an item so marked is not exempt from public disclosure, the petitioner or master file holder will be so informed and will be given an opportunity to appeal that decision to the Assistant Commissioner for Public Affairs, whose decision on the matter will be final.

(2) All safety and functionality data and information submitted with or incorporated by reference in a petition are available for public disclosure after the regulation is promulgated unless extraordinary circumstances are shown.

(3) A protocol for a test or study is available for public disclosure unless an adequate showing is made that it constitutes a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or a paid consultant, has been developed at significant cost, and provides a competitive advantage.

(4) Manufacturing methods or processes, including quality control procedures, are not available for public disclosure except to the extent previously disclosed to the public by the petitioner or master file holder.

(5) An assay method is not available for public disclosure except to the extent previously disclosed to the public by the petitioner or master file holder unless it must be available to permit manufacturers to comply with limits established for the additive. The availability of an assay method will be included in the regulation.

(6) Every person who has filed a petition prior to the effective date of this section may submit in writing to the Food and Drug Administration, within 180 days after such effective date, a request that specified safety, functionality, protocol, or assay data and information which are contained in the petition and which will otherwise be available for public disclosure in accordance with the principles established in this section shall be retained as confidential and exempt from public disclosure. This request must be accompanied by a statement justifying confidentiality. Any such data and information for which confidentiality is not requested or which the Food and Drug Administration concludes (in accordance with subparagraph (1) of this paragraph) are not exempt from public disclosure will be made available to the public at the end of this 180-day period. The Food and Drug Administration may defer ruling upon such a request for confidentiality of specified data or information until a request for public disclosure of that data or information is received. In cases where requests for public disclosure of documents are pending, the Food and Drug Administration may ask for an expedited submission on this matter.

* * * * * * *

PART 130—NEW DRUGS

6. In Part 130:

a. By adding a new item 14 to the form in paragraph (c)(2) of § 130.4, as follows:

§ 130.4 Applications.

* * * * * * *

(c) * * *

(2) * * *

14. A summary of all the safety and effectiveness data and information submitted with or incorporated by reference in the applicttion (including an IND, supplemental NDA, § 130.13 report, master file, or other similar submission). The summary will be reviewed and, where appropriate, revised by the Food and Drug Administration and will be available for public disclosure when the application is approved. A current summary will be submitted by the applicant and will be reviewed and revised for each submission made subsequent to approval of the application. The summary does not constitute the full reports of investigations required under section 505(b)(1) of the act on which the safety or efficacy of the drug may be approved.

* * * * * * *

b. By revising § 130.32 to read as follows:

§ 130.32 Confidentiality of data and information.

(a) The existence of an IND is confidential and will not be publicly disclosed unless it has previously been acknowledged by the sponsor. The Assistant Commissioner for Public Affairs will maintain a list available for public inspection of pending NDA's. The list will disclose the name of the drug and the name of the applicant. An applicant may submit to the Food and Drug Administration a request to exclude his NDA from the list for good cause. The Director of the Bureau of Drugs will make the initial determination on whether good cause has been shown. If the Director concludes that good cause has not been shown, the sponsor or applicant may appeal this decision to the Assistant Commissioner for Public Affairs whose decision on the matter will be final.

(b) Prior to the termination or discontinuation of an IND or the approval of an NDA, all data and information submitted or incorporated by reference in the IND file are confidential and not available for public disclosure except to the extent previously made public in an authorized manner by the sponsor or master file holder.

(c) All data and information submitted or incorporated by reference in an NDA file (including an IND, supplemental NDA, § 130.13 report, master file, or other similar submission) shall be clearly marked confidential if the applicant considers it to be confidential and exempt from public disclosure. Adequate grounds must be given to justify the confidentiality of each item so marked. All data and information previously made public in any authorized manner will not be retained by the Food and Drug Administration as confidential unless extraordinary circumstances are shown. Any request for confidentiality shall state that the data or information so marked has not previously been made available to any person who is not an employee or paid consultant or shall explain why the data or information should remain confidential in spite of such prior disclosure. Applying the guidelines in this section and in Subpart B of Part 4, the Director of the Bureau of Drugs will make the initial decision on whether information marked confidential will be available for public disclosure. If the Director concludes that an item so marked is not exempt from public disclosure, the applicant or master file holder will be so informed and will be given an opportunity to appeal that decision to the Assistant Commissioner for Public Affairs, whose decision on the matter will be final.

(d) Unless otherwise publicly disclosed, no safety and effectiveness data and information submitted with or incorporated by reference in an NDA file are available for public disclosure until the Food and Drug Administration withdraws approval of the NDA or determines that the drug is not a new drug or may be marketed pursuant to an abbreviated NDA. All such data and information are available for public disclosure when the Food and Drug Administration withdraws approval of the NDA or determines that the drug is not a new drug or may be marketed pursuant to an abbreviated NDA unless extraordinary circumstances are shown.

(e) A protocol for a test or study is available for public disclosure unless an adequate showing is made that it constitutes a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or a paid consultant, has been developed at significant cost, and provides a competitive advantage.

(f) Manufacturing methods or processes, including quality control procedures, are not available for public disclosure except to the extent previously disclosed to the public by the sponsor or applicant or master file holder.

(g) An assay method is not available for public disclosure except to the extent previously disclosed to the public by the sponsor or applicant or master file holder unless it must be available to permit other manufacturers to comply with limits established for the drug under an old drug monograph or an abbreviated NDA. The availability of an assay method will be included in the regulation.

(h) All safety and effectiveness data and information contained in an IND file which has been discontinued or terminated are available for public disclosure unless extraordinary circumstances are shown.

(i) Adverse reaction data and information are available for public disclosure with the names and other identifying information of individuals deleted (including the person using the product and the person reporting the information).

(j) Production and sales data and information are not available for public disclosure except to the extent previously disclosed to the public.

(k) Quantitative or semiquantitative formulae are not available for public disclosure except to the extent previously disclosed to the public. A list of all ingredients contained in a product or a list of all products containing a specified ingredient or a list of all products known to possess a particular characteristic or any similar list is available for public disclosure. A particular ingredient (or product containing that ingredient) may be excluded from any such list upon a showing that the ingredient is a trade secret in that it is unique, is important to the product, and is not known to competitors.

(l) Every person who has submitted an IND or NDA file prior to the effective date of this section may submit in writing to the Food and Drug Administration, within 180 days after such effective date, a request that specified data and information which are contained in the submission(s) and which will otherwise be available for public disclosure in accordance with the principles established in this section shall be retained as confidential and exempt from public disclosure. This request must be accompanied by a statement justifying confidentiality. Any such data and information for which confidentiality is not requested or which the Food and Drug Administration concludes (in accordance with paragraph (c) of this section) are not exempt from public disclosure will be made available to the public at the end of this 180-day period. An extension in the 180-day time period will be granted upon a showing that the volume of prior submissions precludes completion of this job within that time and will be conditioned upon prompt filing of all requests for confidentiality as they are completed. The Food and Drug Administration may defer ruling upon such a request for confidentiality of specified data or information until a request for public disclosure of that data or information is received. In cases where requests for public disclosure of documents are pending, the Food and Drug Administration may ask for an expedited decision on this matter. A summary of all safety and effectiveness data and information as required by § 130.4(c)(2)(14) must accompany a request for confidentiality. If the request for confidentiality is granted, the summary and all nonconfidential information will be made available for public disclosure.

PART 135—NEW ANIMAL DRUGS

7. In Part 135:

a. In § 135.4a(b), by redesignating subparagraph (13) *Assembling and binding the application* as subparagraph (15) and adding a new subparagraph (13) as follows (a new subparagraph (14) will be proposed in the near future):

§ 135.4a New animal drug applications.

* * * * * * *

(b) * * *

(13) *Summary of safety and effectiveness data and information.* A summary shall be given of all the safety and effectiveness data and information submitted with or incorporated by reference in the application (including an INAD, supplemental NADA, § 135.14a or § 135.14b report, master file, or other similar submission). The summary will be reviewed and, where appropriate, revised by the Food and Drug Administration and will be available for public disclosure when the application is approved. A current summary will be submitted by the applicant and will be reviewed and revised for each submission made subsequent to approval of the application. The summary does not constitute the full reports of investigations required under section 512(b)(1) of the act on which the safety or efficacy of the drug may be approved.

* * * * * * *

b. By revising § 135.33 to read as follows:

§ 135.33 Confidentiality of data and information.

(a) The existence of an IND is confidential and will not be publicly disclosed unless it has previously been acknowledged by the sponsor. The Assistant Commissioner for Public Affairs will maintain a list available for public inspection of pending NADA petitions. The list will disclose the name of the drug and the name of the applicant. An applicant may submit to the Food and Drug Administration a request to exclude his NADA from the list for good cause. The Director

of the Bureau of Veterinary Medicine will make the initial determination on whether good cause has been shown. If the Director concludes that good cause has not been shown, the applicant may appeal this decision to the Assistant Commissioner for Public Affairs, whose decision on the matter will be final.

(b) Prior to the termination or discontinuation of an INAD or the approval of an NADA, all data and information submitted or incorporated by reference in the INAD file are confidential and not available for public disclosure except to the extent previously made public in an authorized manner by the sponsor or master file holder.

(c) All data and information submitted or incorporated by reference in an NADA file (including an INAD, supplemental NADA, § 135.14a or § 135.14b report, master file, or other similar submission) shall be clearly marked confidential if the sponsor or applicant considers it to be confidential and exempt from public disclosure. Adequate grounds must be given to justify the confidentiality of each item so marked. All data and information previously made public in any authorized manner will not be retained by the Food and Drug Administration as confidential unless extraordinary circumstances are shown. Any request for confidentiality shall state that the data or information so marked has not previously been made available to any person who is not an employee or paid consultant or shall explain why the data or information should remain confidential in spite of such prior disclosure. Applying the guidelines in this section and in Subpart B of Part 5, the Director of the Bureau of Veterinary Medicine will make the initial decision on whether information marked confidential will be available for public disclosure. If the Director concludes that an item so marked is not exempt from public disclosure, the applicant or master file holder will be so informed and will be given an opportunity to appeal that decision to the Assistant Commissioner for Public Affairs, whose decision on the matter will be final.

(d) Unless otherwise publicly disclosed, no safety and effectiveness data and information submitted with or incorporated by reference in an NADA file are available for public disclosure until the Food and Drug Administration withdraws approval of the NADA or determines that the drug is not a new animal drug or may be marketed pursuant to an abbreviated NADA. All such data and information are available for public disclosure when the Food and Drug Administration withdraws approval of the NADA or determines that the drug is not a new animal drug or may be marketed pursuant to an abbreviated NADA, unless extraordinary circumstances are shown.

(e) A protocol for a test or study is available for public disclosure unless an adequate showing is made that it constitutes a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or a paid consultant, has been developed at significant cost and provides a competitive advantage.

(f) Manufacturing methods or processes, including quality control procedures, are not available for public disclosure except to the extent previously disclosed to the public by the sponsor or applicant or master file holder.

(g) An assay method is not available for public disclosure except to the extent previously disclosed to the public by the sponsor or applicant or master file holder except pursuant to section 512(i) of the act or unless it must be available to permit other manufacturers to comply with limits established for the drug under an old animal drug monograph or an abbreviated NADA. The availability of an assay method will be included in the regulation.

(h) All safety and effectiveness data and information contained in an INAD file which has been discontinued or terminated are available for public disclosure unless extraordinary circumstances are shown.

(i) Adverse reaction data and information are available for public disclosure with the names of individuals deleted.

(j) Production and sales data and information are not available for public disclosure except to the extent previously disclosed to the public.

(k) Quantitative or semiquantitative formulae are not available for public disclosure except to the extent previously disclosed to the public. A list of all ingredients contained in a product or a list of all products containing a specified ingredient or a list of all products known to possess a particular characteristic or any similar list is available for public disclosure. A particular ingredient (or product containing that ingredient) may be excluded from any such list upon a showing that the ingredient is a trade secret in that it is unique, is important to the product, and is not known to competitors.

(l) Every person who has submited an INAD or NADA file prior to the effective date of this section may submit in writing to the Food and Drug Administration, within 180 days after such effective date, a request that specified data and infor-

mation which are contained in the submission(s) and which will otherwise be available for public disclosure in accordance with the principles established in this section shall be retained as confidential and exempt from public disclosure. This request must be accompanied by a statement justifying confidentiality. Any such data and information for which confidentiality is not requested or which the Food and Drug Administration concludes (in accordance with paragraph (c) of this section) are not exempt from public disclosure will be made available to the public at the end of this 180-day period. An extension in the 180-day time period will be granted upon a showing that the volume of prior submissions precludes completion of this job within that time and will be conditioned upon prompt filing of all requests for confidentiality as they are completed. The Food and Drug Administration may defer ruling upon such a request for confidentiality of specified data or information until a request for public disclosure of that data or information is received. In cases where requests for public disclosure of documents are pending the Food and Drug Administration may ask for an expedited submission on this matter. A summary of safety and functionality data and information as required by § 135.4a(b)(13) must accompany a request for confidentiality. If the request for confidentiality is granted, the summary and all nonconfidential information will be made available for public disclosure.

PART 146—ANTIBIOTIC DRUGS; PROCEDURAL AND INTERPRETATIVE REGULATIONS

8. In part 146, by adding the following new section:

§ 146.16 Confidentiality of data and information.

(a) The existence of an IND is confidential and will not be publicly disclosed unless it has been previously acknowledged by the sponsor. The Assistant Commissioner for Public Affairs will maintain a list available for public inspection of pending Forms 5. The list will disclose the name of the drug and the name of the applicant. An applicant may submit to the Food and Drug Administration a request to exclude his Form 5 from the list for good cause. The Director of the Bureau of Drugs will make the initial determination on whether good cause has been shown. If the Director concludes that good cause has not been shown, the sponsor or applicant may appeal this decision to the Assistant Commissioner for Public Affairs, whose decision on the matter will be final.

(b) Prior to the termination or discontinuation of an IND or the approval of an NDA, all data and information submitted or incorporated by reference in an IND file are confidential and not available for public disclosure except to the extent previously made public in an authorized manner by the sponsor or master file holder. All data and information submitted or incorporated by reference in any form submitted pursuant to § 146.13 or § 146.14 shall be clearly marked confidential if the sponsor or applicant considers it to be confidential and exempt from public disclosure. Adequate grounds must be given to justify the confidentiality of each item so marked. All data and information previously made public in any authorized manner will not be retained by the Food and Drug Administration as confidential unless extraordinary circumstances are shown. Any such request shall state that the data or information so specified has not previously been made available to any person who is not an employee or paid consultant or shall explain why the data or information should remain confidential in spite of such prior disclosure. Applying the guidelines in this section and in Subpart B of Part 4, the Director of the Bureau of Drugs will make the initial decision on whether information marked confidential will be available for public disclosure. If the Director concludes that an item so marked is not exempt from public disclosure, the applicant or master file holder will be so informed and will be given an opportunity to appeal that decision to the Assistant Commissioner for Public Affairs, whose decision on the matter will be final.

(d) All safety and effectiveness data and information submitted with or incorporated by reference in any form submitted pursuant to § 146.13 or § 146.14 are available for public disclosure after approval of the drug unless extraordinary circumstances are shown.

(e) A protocol for a test or study is available for public disclosure unless an adequate showing is made that it constitutes a trade secret or confidential information because it is unique, has not previously been disclosed in an authorized manner to anyone other than a company employee or a paid consultant, has been developed at significant cost, and provides a competitive advantage.

(f) Manufacturing methods or processes, including quality control procedures, are not available for public disclosure except to the extent previously disclosed to the public by the applicant or master file holder.

(g) All safety and effectiveness data and information contained in an IND file which has been discontinued or terminated or contained in a Form 5 file for which the Food and Drug Administration has withdrawn approval for any reason will be available for public disclosure unless extraordinary circumstances are shown.

(h) Adverse reaction data and information are available for public disclosure with the names and other identifying information of individuals deleted (including the person using the product and the person reporting the information).

(i) Production and sales data and information are not available for public disclosure except to the extent previously disclosed to the public.

(j) Quantitative or semiquantitative formulae are not available for public disclosure except to the extent previously disclosed to the public. A list of all ingredients contained in a product or a list of all products containing a specified ingredient or a list of all products known to possess a particular characteristic or any similar list is available for public disclosure. A particular ingredient (or product containing that ingredient) may be excluded from any such list upon a showing that the ingredient is a trade secret in that it is unique, is important to the product, and is not known to competitors.

(k) Every person who has filed an IND or any form pursuant to §146.13 or § 146.14 prior to the effective date of this section may submit in writing to the Food and Drug Administration, within 180 days after such effective date, a request that specified safety, effectiveness, protocol, or assay data and information which are contained in the submission(s) and which will otherwise be available for public disclosure in accordance with the principles established in this section shall be retained as confidential and exempt from public disclosure. This request shall be accompanied by a statement justifying confidentiality. Any such data and information for which confidentiality is not requested or which the Food and Drug Administration concludes (in accordance with paragraph (c) of this section) are not exempt from public disclosure, will be made available to the public at the end of this 180-day period. An extension of the 180-day period will be granted upon a showing that the volume of prior submissions precludes completion of this job within that time and will be conditioned upon prompt filing of all requests for confidentiality as they are completed. The Food and Drug Administration may defer ruling upon such a request for confidentiality of specified data or information until a request for public disclosure of that data or information is received. In cases where public requests for information are pending, the Food and Drug Administration may ask for an expedited submission on this matter.

PART 191—HAZARDOUS SUBSTANCES: DEFINITIONS AND PROCEDURAL AND INTERPRETATIVE REGULATIONS

9. In Part 191, by adding a new paragraph (d) to § 191.213, as follows:

§ 191.213 Presentation of views under section 7 of the act.

* * * * * * *

(d) The documents relating to this proceeding constitute an investigatory file for law enforcement purposes and may include interagency and intra-agency memoranda. No data or information contained in this file are available for public disclosure prior to the file's being closed or the statute of limitations' running, whichever occurs first. After the file is closed or the statute of limitations runs, the factual information contained in the file will be made available for public disclosure except that opinions, policy recommendations, interagency and intra-agency memoranda, statements of witnesses obtained through promises of confidentiality, names of individuals, trade secrets, and other confidential information will be deleted.

Interested persons may, within 60 days after publication hereof in the Federal Register, file with the Hearing Clerk, department of Health, Education, and Welfare, Room 6–88, 5600 Fishers Lane, Rockville, Maryland 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: May 1, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc. 72–6864 Filed 5–4–72; 8:47 a.m.]

[From The Medical Letter, May 26, 1972, Vol. 14, No. 11, pages 37–38]

DARVON AND DARVON–N

Propoxyphene, a mild analgesic, is now available as one of two salts in nine different formulations. The napsylate (Darvon–N—Lilly) was recently introduced and is more stable than the hydrochloride (Darvon—Lilly); it is available as a liquid or in tablets. Because of differences in molecular weight, a dose of 100 mg of the napsylate is needed to provide an amount of propoxyphene equivalent to that in 65 mg of the hydrochloride. Both preparations cost several times as much as aspirin. Since the pharmacologic effects are similar, the following discussion applies to both salts.

Efficacy.—Proxyphene was the most frequently prescribed drug in the Los Angeles County-University of Southern California Medical Center (R.F. Maronde et al., Med. Care, 9:383, 1971); Darvon preparations probably have been prescribed more often than any other drug for the last five years in the United States. Nevertheless, reservations about the efficacy of propoxyphene continue to be expressed. Several reviews have questioned its place in therapeutics. Two of these, by W. T. Beaver (Am. J. Med. Sci., 251:576, 1966) and the Drug Efficacy Study of the National Academy of Sciences-National Research Council, were discussed in the last Medical Letter review of propoxyphene (Vol. 12, p. 5, 1970). Since then, R. R. Miller et al. (JAMA, 213:996, 1970) have reviewed all available double-blind studies of propoxyphene and concluded that it ". . . is no more effective than aspirin or codeine and may even be inferior to these analgesics." It is generally agreed that a 32-mg. dose provides little more than a placebo effect in most patients. In a recently published double-blind study of single doses of propoxyphene, aspirin, and other oral analgesics in patients with cancer, C. G. Moertel et al. (N. Engl. J. Med., 286:813, April 13, 1972) were unable to demonstrate that even 65 mg of propoxyphene was significantly superior to placebo. In this study, aspirin was the most effective analgesic tested.

Adverse effects.—One Medical Letter consultant reports that the adverse reaction rate for propoxyphene administered to over 2,000 hospitalized medical patients was about 0.5 per cent and the reactions were mostly minor (nausea, vomiting, drowsiness, rash, vertigo). One case of hallucinations and disorientation was observed. The drug also may cause encephalopathy in patients with diminished liver function. The frequency of adverse effects varies with dosage; there is no evidence that truly analgesic doses of propoxyphene are less harmful than equianalgesic doses of other drugs.

Overdosage.—An increasing number of cases of ingestion of lethal and near-lethal doses of propoxyphene is being reported. In general, the symptoms of overdosage are similar to those seen with narcotic drugs. Various degrees of respiratory, central-nervous-system, and circulatory depression are usually present. Convulsions (seldom seen with narcotics other than meperidine) and coma have been observed. Analeptic agents are dangerous in patients with propoxyphene poisoning because they increase the risk of convulsions. Death usually results from hypoxia, with pulmonary edema and vascular congestion. Propoxyphene toxicity can be treated with narcotic antagonists such as naloxone (The Medical Letter, Vol. 14, p. 2, Panuary 7, 1972).

Dependence.—Dependence on propoxyphene is well documented; it is usually psychological and substantially less intense than that seen with morphine or heroin. Physical dependence has been observed with high doses. Some Medical Letter consultants suggest that dependence would be more frequent if this drug were given in doses high enough to provide effective analgesia.

Abuse.—Orally-administered propoxyphene is reported to be widely abused by adolescents. Since propoxyphene preparations have been reformulated to eliminate the pellet of propoxyphene in capsules, abuse by intravenous injection no longer appears to be a problem.

Aspirin vs. Darvon.—Propoxyphene has been used as an alternative to aspirin. While adverse reactions to aspirin are observed in about five percent of hospitalized patients, only a small fraction are serious (e.g., severe gastrointestinal bleeding, interference with normal clotting processes). Inasmuch as propoxyphene is largely prescribed as Darvon Compound–65, which includes aspirin, the potential toxicity of aspirin is not avoided. Since the analgesic efficacy of aspirin has been established beyond doubt and since it is inexpensive, aspirin is recommended as the drug of first choice in treating mild to moderate pain except when it is contraindicated in such conditions as peptic ulcer. The cost to the pharma-

cist of the usual daily dose of aspirin is as little as two cents; the cost to the pharmacist of the usual daily dose of Darvon Compound–65 is 29 cents.

Conclusion.—While some controlled studies have shown that propoxyphene in doses of 65 mg is a more more effective analgesic than a placebo, other controlled trials have not. In patients who cannot take aspirin, acetaminophen is an acceptable and much less expensive alternative. (A list of commonly used mild analgesics, their usual dosages and their comparative costs appeared in The Medical Letter. Vol. 14, p. 32, April 28, 1972.)

USE OF DRUGS UNDER THE MISSISSIPPI MEDICAID PROGRAM

(By Alton B. Cobb, M.D., M.P.H., Donnie P. Wilson and John M. Abide) *

The Mississippi Medicaid Commission began payments on July 1, 1970, for legend drugs, insulin and a limited number of over-the-counter drug products when prescribed by a physician or dentist. Any legend drug prescribed by a physician or dentist, except those containing amphetamines or vitamins, was covered under reimbursement to over 700 participating pharmacies and 13 dispensing physicians. Among the legend drugs, 27 were covered only as generics. The purpose of this report is to review actual utilization patterns, costs, etc. of drugs under a relatively unrestricted program for a rather well defined population sub-group.

The Mississippi Medicaid Program has a contract with Mississippi Hospital & Medical Service (Blue Cross-Blue Shield) for claim payments, computer informational storage, retrieval, and reporting systems to satisfy Federal and State requirements. This includes program reports necessary for planning and administration of the Medicaid Program.

Near the end of the Program's first year of operation, a series of special program reports were prepared for program review, evaluation and planning of possible program changes. These reports covered the period from July 1, 1970. through February 19, 1971.

The first part of this paper summarizes information gathered from these special reports and includes: 1. Recipient usage of drugs by eligibility classification; 2. Frequency of individual drug usage by overall ranks; and 3. A breakdown of drug utilization by race and sex.

Individuals eligible for benefits under the program by public assistance categories, percent eligible by category, and payments for drugs during the period July 1, 1970, through February 19, 1971, are shown in Table I.

It is apparent from Table I that the aged and disabled represent the largest users of drugs. Each of these categories used almost twice the percentage of drugs as their proportionate share of the total eligible pool.

TABLE I.—NUMBER OF PERSONS ELIGIBLE FOR MEDICAID AND EXPENDITURES FOR DRUGS WITH PERCENTAGE DISTRIBUTION BY PROGRAM CATEGORY, JULY 1, 1970 TO FEB. 19, 1971

Program	Eligibles		Expenditures	
	Number	Percent	Amount	Percent
Total	199,050	100.0	$4,477,162.43	100.0
Old age assistance	74,943	37.6	2,977,498.94	66.5
Aid to the blind	2,126	1.1	62,782.36	1.4
Aid to permanently and totally disabled	22,030	11.1	1,119,810.70	25.0
Aid to dependent children	99,951	50.2	317,070.43	7.1

All drugs used under the program are classified into 38 groups or therapeutic classes. In addition, all non-coded legend and all coded injectables represent a drug group. In Table II, the 10 most popular classes of drugs are shown for each category of eligibles.

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*Alton B. Cobb, M.D., M.P.H. is Director of the Mississippi Medicaid Commission. Donnie P. Wilson and John M. Abide are students at the University of Mississippi School of Medicine. Mrs. Louise Wallace, Program Analyst of the Mississippi Medicaid Commission, provided statistical consultation.

Usage within each class by eligibility categories generally followed expected patterns; i.e., children used most of the anthelminthics (94%) and the disabled and aged used all (100%) of the anticoagulents.

Analgesics were the first or second most frequently used class of drugs by each group of adult recipients (Old Age Assistance, Aid to the Blind, and Aid to the Permanently and Totally Disabled). Only among the children did analgesics fall to third place, being replaced by antibacterials and the class that included over-the-counter drug products.

Among the disabled and the aged, the second leading class of drugs was the antihypertensive agents. This is undoubtedly due to the relatively high prevalence of hypertension among these groups.

Only for the children (Aid to Dependent Children) did the antibacterials represent the leading class; antibacterials ranked third, however, for the blind and disabled, but ranked only sixth for the aged.

TABLE II.—10 MOST FREQUENTLY PRESCRIBED DRUG CLASSIFICATIONS, NUMBER OF PRESCRIPTIONS AND AMOUNT OF EXPENDITURES BY PROGRAM CATEGORY, JULY 1, 1970–FEB. 19, 1971

Drug classification	Prescriptions	Expenditures
Old age assistance:		
Analgesics	83,393	$338,705.35
Antihypertensive agents	80,854	353,875.89
All noncoded legend and all coded injectables [1]	79,103	322,491.60
Gastrointestinal agents	64,232	199,662.93
Diuretics	56,572	188,908.75
Antibacterials	54,292	254,807.21
Cardiac agents	43,497	99,112.41
Sedative—hypnotics	42,600	92,959.43
Peripheral vasodilators	36,602	184,268.57
Hypoglycemics	35,642	168,642.85
Aid to the blind:		
All noncoded legend and all coded injectables [1]	2,164	8,408.24
Analgesics	1,767	6,030.77
Antibacterials	1,519	7,530.38
Gastrointestinal agents	1,360	4,086.12
Antihypertensive agents	1,223	4,626.60
Diuretics	1,118	4,241.00
Hypoglycemic agents	1,012	4,475.52
Antianxiety agents	924	4,810.78
Sedatives—Hypnotics	906	1,998.18
Cardiac agents	412	955.59
Aid to permanently and totally disabled:		
Analgesics	34,467	134,114.67
Antihypertensive agents	25,569	117,943.18
Antibaciterials	22,403	104,746.65
Gastrointestinal agents	20,064	63,038.71
Sedative—Hypnotics	17,469	37,945.77
Antianxiety agents	16,540	85,963.09
Diuretics	16,463	56,516.71
Hypoglycemic agents	16,093	77,367.72
Antipsychotic agents	12,653	81,448.40
Cardiac agents	11,247	26,031.36
Aid to dependent children:		
Antibacterials	35,566	141,519.95
All noncoded legend and all coded injectables [1]	14,437	49,489.86
Analgesics	6,416	14,450.25
Antihistaminics	5,178	12,872.50
Antitussives	4,476	10,141.35
Topicals	4,285	11,842.40
Antiemetics	4,185	10,714.09
Gastrointestinal agents	3,654	9,047.27
Anthelmintics	2,547	6,590.65
Nasal decongestants	1,925	4,864.41

[1] This group contains drugs from all therapeutic classes, and so has no comparative relationship to other classes in this table.

The top ranking drug by amount spent was Indocin 25mg Capsules. This drug ranked third in number of prescriptions. The top ranking drug by number of prescriptions was Darvon Compound–65 Capsules. Darvon Compound–65 Capsules ranked second in amount spent.

Table III shows the ranking of the top 50 drugs by amount and also shows the ranking of these 50 drugs by number of prescriptions.

The 50 drugs listed in Table III accounted for 38.7% of all drug payments from July 1, 1970, through February 19, 1971. This amounted to $1,736,894.59.

It is interesting to note that among the 10 leading drugs ranked by total amount paid, 5 drugs are specified as "not recommended" or as "irrational mixtures" by the "*AMA Drug Evaluations.*—1971." Also, one drug among the ten has been classified as "possibly ineffective" by the Food and Drug Administration. This indicates an overall negative relationship between popular usage of drugs and the evaluation of their efficiency and safety by the AMA Council on Drugs and the FDA. It is suggested that this represents a fertile area for professional education.

TABLE III.—RANK OF TOP 50 DRUGS BY AMOUNT PAID AND BY NUMBER OF PRESCRIPTIONS, JULY 1, 1970 TO FEB. 19, 1971—Continued

Drug name	Rank	
	Amount paid	Rx
Indocin 25 mg. capsules	1	3
Darvon Compound-65 capsules	2	11
Pavabid capsules	3	7
Orinase tablets 500 mg	4	6
DBI-TD capsules	5	12
Valium 5 mg. tablets	6	9
Aldoril 25 tablets [1]	7	16
Salutensin tablets [1]	8	5
Antivert [1 2]	9	4
Ser-ap-es tablets [1]	10	10
Indocin 50 mg. capsules	11	34
Lasix 40 mg. tablets	12	8
Al and hydroxide gel. susp	13	2
Meprobamate 400 mg. tablets	14	11
Diabinese 250 mg. tablets	15	19
Librium 10 mg. capsules	16	27
Hydropres 50 tablets	17	18
Cyclospasmol 200 mg. capsules	18	39
Aldomet 250 mg. tablets	19	31
Hydropres, 25 tablets	20	20
Dyazid capsules	21	15
Mellaril 25 mg. tablets	22	45
Tetracyclinic 250 mg. capsules	23	13
Cerespan capsules [1]	24	58
Aldoril, 15 capsules [1]	25	41
Regroton tablets	26	23
Hydergine sublingual tablets 0.5 mg	27	49
Arlidin 6 mg. tablets	28	51
Diupres, 500 tablets	29	43
Diuril 500 mg. tablets	30	22
Darvon 65 mg. capsules	31	29
Peritrate SA 80 mg. tablets	32	56
Ampicillin capsules 250 mg	33	69
Triavil 2-25 tablets	34	89
NegGram 500 mg. tablets	35	103
Pnenobarbital 30 mg. tablets	36	14
Donnatal tablets [1]	37	21
Equagesic tablets [1 2]	38	57
Trinsicon capsules	39	53
Butazolidin alka capsules	40	47
Dilantin 100 mg. capsules	41	28
Macrodantin 50 mg. capsules	42	65
Quinidine sulfate 200 mg. (caps or tabs)	43	50
Iletin Insulin NPH 80u/cc 10cc	44	44
Mellaril 50 mg. tablets	45	95
Vasodilan 10 mg tablets	46	71
Diupres, 250 tablets	47	42
HydroDiuril 50 mg. tablets	48	37
Theragran hematinic tablets	49	54
Tolinase 250 mg. tablets	50	97

[1] Drugs listed as "not recommended" or as "irrational mixtures" by AMA Drug Evaluations, 1971.
[2] Drugs listed as "possibly ineffective" by FDA as of N.v. 1, 1970.

The second part of this paper reviews overall use of drugs under the program between January 1, 1971, and May 31, 1971. In Table IV, actual number of eligibles using drugs is shown as "recipients". During this period, a little over 100,000 Medicaid eligibles obtained drugs under the program; this represents about 50% of the total eligibles. Among those receiving drugs, the average prescription per recipient as shown in Table IV reveal that white females had the highest use rate, followed by white males, non-white females and non-white males.

TABLE IV.—NUMBER OF RECIPIENTS OF PRESCRIBED DRUGS, NUMBER OF PRESCRIPTIONS AND AVERAGE PRESCRIPTIONS PER RECIPIENT BY RACE AND SEX, JANUARY–MAY 1971

Race and sex	Number of recipients	Number of prescriptions	Average prescription per recipient
Total	102,228	1,128,673	11.0
White males	13,533	208,311	15.4
White females	23,274	410,120	17.6
Nonwhite males	26,599	186,357	7.0
Nonwhite females	38,822	323,885	8.3

Differences in the number of prescriptions received per recipient varied considerably in the Program categories. Prescriptions per recipient for the Old Age Assistance recipients were more than four times those for the Aid to Dependent Children recipients. (Table V)

TABLE V.—NUMBER OF RECIPIENTS OF PRESCRIBED DRUGS, NUMBER OF PRESCRIPTIONS AND AVERAGE PRESCRIPTIONS PER RECIPIENT BY PROGRAM CATEGORY, JANUARY–MAY 1971

Program category	Number of recipients	Number of prescriptions	Average prescriptions per recipient
Total	102,228	1,128,673	11.0
Old age assistance	53,118	746,885	14.1
Aid to the blind	1,234	15,185	12.3
Aid to the permanently and totally disabled	17,577	269,938	15.4
Aid to dependent children	30,299	96,665	3.2

Utilization rates were much higher in whites of each category. (Table VI) During the Period January 1, 1971–May 31, 1971, 68.3% of total white eligibles used drug benefits and among all non-white eligibles, 41.3% used drug benefits. In each category of Program eligibility, utilization rate for drugs under Medicaid was highest among the whites. The smallest differences between the races for drug utilization were for the blind and dependent children.

TABLE VI.—NUMBER OF ELIGIBLES, NUMBER OF RECIPIENTS OF PRESCRIBED DRUGS AND UTILIZATION RATES FOR WHITES AND NONWHITES BY PROGRAM CATEGORY OF ELIGIBILITY, JANUARY–MAY, 1971

Program category	Eligibles[1]		Recipients		Utilization rate (percent)	
	Whites	Nonwhites	Whites	Nonwhites	Whites	Nonwhites
Total	53,858	158,494	36,807	65,421	68.3	41.3
OAA	32,042	46,110	25,393	27,725	79.2	60.1
AB	691	1,468	428	806	61.9	54.9
APTD	9,290	15,157	7,414	10,163	79.8	67.1
ADC	11,835	95,759	3,572	26,727	30.2	27.9

[1] Based on data from Mississippi Department of Public Welfare as of September 1969.

Evaluation of data on average number of prescriptions per eligible person during the period January 1, 1971–May 31, 1971, as shown on Table VII, reveals that whites averaged 11.5 prescriptions while nonwhites averaged 3.2 for the over 200,000 total eligibles. Again, in all categories, whites showed much higher drug usage.

TABLE VII.—NUMBER OF PRESCRIPTIONS, NUMBER OF ELIGIBLES AND AVERAGE PRESCRIPTIONS PER ELIGIBLE BY RACE AND PROGRAM CATEGORY, JANUARY–MAY 1971

Program	Prescriptions		Eligibles		Average per eligible	
	Whites	Nonwhites	Whites	Nonwhites	Whites	Nonwhites
Total	618,431	510,242	53,858	158,494	11.5	3.2
OAA	454,514	292,371	32,042	46,110	14.2	6.3
AB	6,631	8,554	691	1,468	9.6	5.8
APTD	142,824	127,114	9,290	15,157	15.4	8.4
ADC	14,462	82,203	11,835	95,759	1.2	.9

SUMMARY

Patterns and rates for prescribed drug usage under a relatively unrestricted Medicaid drug program are presented. Utilization rates are described for categories of Program eligibles and by a "top 50" drug usage listing. In addition, usage rates are detailed by race and sex groupings.

The relatively high usage of several drugs listed as "possibly ineffective" by the FDA or as "not recommended" or as "irrational mixtures" by AMA Drug Evaluations—1971 suggests a need for professional education on drug usage.

The higher usage rate for white eligibles is probably due to a number of factors, including long-standing differences in the accessibility and usage of health services between whites and blacks.

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Drug Prescribing and Use in an American Community

PAUL D. STOLLEY, M.D., M.P.H., MARSHALL H. BECKER, Ph.D., M.P.H., JOSEPH D. MCEVILLA, Ph.D., LOUIS LASAGNA, M.D., MARLANE GAINOR, M.A., and LOIS M. SLOANE, M.A., Baltimore, Maryland

The overall patterns of drug prescribing and use in an entire community were studied for a year. A substantial proportion of the drugs prescribed were psychotropic agents that either sedate or stimulate. These psychotropic drugs accounted for 17% of all prescriptions, with almost 13% of all patients receiving one of these agents through a doctor's prescription. The amphetamines were the eighth most frequently dispensed class of drugs, with almost 3% of all patients who received a prescription being given an amphetamine. The general impression that there is a high rate of psychotropic drug use in the United States was substantiated in this community study.

IN RECENT YEARS there has been a great deal of interest in patterns of drug prescribing and use in the United States. We have been called an "over-medicated" society by some, whereas others have claimed that the medical profession has been prescribing drugs with care and restraint.

In an article in this journal in 1969 Sir Derrick Dunlop reviewed the patterns of drug consumption in Britain over the past two decades (1). He pointed out that the removal of the financial barrier between the patient and drugs has led to increasing rates of prescribing, consumption, and amounts spent on drugs by the British National Health Service. He expressed particular concern with the increasing use of psychotropic medicines, which accounted for "some 15% of the total written."

In the United States most patients still pay "out-of-pocket" for their prescribed drugs, but examination of national marketing research data suggests patterns of prescribing and use similar to that of Britain. To help explain these trends this study describes patterns of drug prescribing and use in an entire community.

► From The Johns Hopkins School of Hygiene and Public Health, Department of Medical Care and Hospitals, Baltimore, Md., and The University of Pittsburgh, School of Pharmacy, Pittsburgh, Pa.

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Methods

A COMPUTERIZED PRESCRIPTION RECORDING SYSTEM

Since 1963 a computerized prescription recording system has been monitoring 85% of the prescriptions dispensed in a defined geographic area, hospital pharmacies being excluded from the study (2). The area, which is located in a United States mid-Atlantic state, has a population of 112 000, 97% of which is Caucasian, mainly of Italian and East European ancestry. There are three voluntary hospitals but no university

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Table 1. Prescriptions Dispensed by County* Pharmacies in a Mid-Atlantic State in 1968

Prescriptions, *no.*	111 982	(57%)
Refills, *no.*	84 873	(43%)
Total	196 855	
Total dosage units dispensed, *no.*	9 002 188	
Average number units per prescription (capsules, tablets, or liquid units)	46	
Total retail cost	$ 677 466	
Average cost per prescription	$ 3.44	

* Population 112 000.

medical center in the county and 91 practicing physicians, of whom 47 practice a specialty.

The population studied comprised those patients who received a prescription from a doctor and presented it to a community pharmacy to be filled. If they presented it to a hospital pharmacy, an out-of-county pharmacy, or did not fill it at all, our prescription recording system did not capture it. An estimated 15% of all outpatient prescriptions were thus unrecorded in this study.

The prescription recording system permits the storage and retrieval of the following information:

1. *Patient Drug Profile for Individual Patients:* This is a list of all prescriptions dispensed, by therapeutic category and specific name, that includes: refills, quantity prescribed, dosage form, expenditures, and code name of prescribing physician.

2. *Physician Prescribing Profile for Individual Physicians:* This is a list of all prescriptions presented to the community pharmacies, by therapeutic category and specific name, including refills, cost of the prescriptions issued, quantity and dosage forms prescribed, number of different drugs prescribed, and the most frequently prescribed drugs.

3. *Community Drug Consumption Profile for the Community:* This gives the total prescriptions issued, including refills, total expenditures for drugs, and selected characteristics of persons receiving the greatest number of drugs.

Results

OUTPATIENT DRUG USE IN THE COMMUNITY

All of the data presented have been tabulated and summarized for the calendar year 1968 (Table 1). During that year, nearly 200 000 prescriptions (including refills) issued by the 91 doctors practicing in the community were dispensed by local pharmacies. Forty-three percent of all prescriptions presented to pharmacies were refills, however, and therefore patient-initiated to some extent. The average prescription price was $3.44, a retail cost similar to that found in most marketing research surveys. The total community expenditure for outpatient prescriptions came to $678 000, and for this amount more than 9 million dosage units were dispensed (capsules, tablets, or liquid units).

THE MOST FREQUENTLY PRESCRIBED DRUGS

When the most frequently used drugs are tabulated by therapeutic class, it is seen that antibiotics were by far the most commonly dispensed, with tranquilizers in second place. The sympathomimetic anorexients (largely amphetamines) were the eighth most frequently dispensed class of drugs in 1968: the Food and Drug Administration has recently narrowed the permissible indications for these agents. If the psychotropic drugs are grouped together (tranquilizers, hypnotics and sedatives, and anorexients) they account for almost 17% of total prescriptions (Table 2 and Figure 1).

Librium® (chlordiazepoxide) and Valium® (diazepam) were the first and third most frequently prescribed drugs in the county and the average prescription prices were $4.64 and $5.52, respectively. Almost 4000 Librium and 3000 Valium prescriptions were filled in this county. The estimated community expenditure for these two drugs alone came to almost $35 000, or 5% of the total retail drug cost. Our figures on the use of these two drugs compare with national estimates for the same year, 1968, when an estimated 24 million Librium and 18 million Valium prescriptions were dispensed.

Darvon Compound® (propoxyphene, aspirin, phenacetin, and caffeine) was the second most frequently prescribed drug, and the estimated total cost to the community was more than $11 000. Chloromycetin® (chloramphenicol) was the 64th most frequently prescribed drug, with only three physicians accounting for one third of the prescriptions issued. General practitioners accounted for almost all of the Chloromycetin prescriptions.

In view of the current concern with drug costs it is of great interest that only 5½% of all prescriptions were written by the generic form. Penicillin, phenobarbital, thyroid, prednisone, tetracycline, and digitalis head the list of generically prescribed drugs. The average retail cost of the generic form is usually lower than the average cost of the equivalent proprietary-name counterparts, and some saving to the consumer is usually evident.

Table 2. Psychotropics Dispensed in a Mid-Atlantic State County* in 1968

		Percent of Total Prescriptions	Percent of Total Patients Receiving Drugs
Tranquilizers		7.7	5.4
Hypnotics and sedatives		3.6	2.9
Amphetamines		3.4	2.9
Psychomotor stimulants		2.1	1.6
Total		16.8	12.8
Total prescriptions, *no.*	33 273		
Total cost	$144 590		

* Population 112 000.

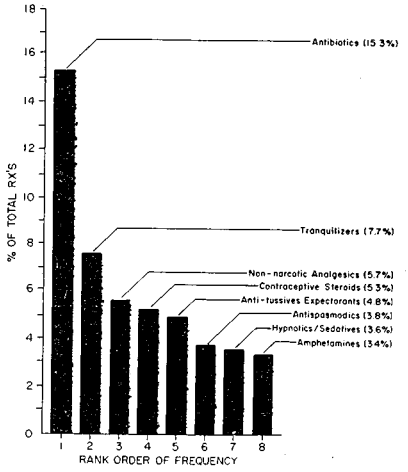

Figure 1. The eight most frequently dispensed classes of drugs in a mid-Atlantic state county (population, 112 000) in 1968.

OVERALL PHYSICIANS' PRESCRIBING PROFILE

The mean number of *different* drugs prescribed in 1968 by the primary care physicians (general practitioners and general internists) monitored was 270. Some doctors managed their practices with only about 100 different drugs, whereas others prescribed almost 500. These findings may be compared with the size of the New York Hospital Formulary (3), in which less than 500 different drugs are considered sufficient for a hospital practice (which includes inpatient and ambulatory care patients). The physicians in the area issued an average of more than 2000 prescriptions (including refills) during 1968, and some issued more than 5000 prescriptions that year: the practice size also varied greatly.

SELECTED PATIENT CHARACTERISTICS AND DRUG USE

The age of the patients receiving prescriptions was recorded in a special study, and it was found that the elderly (especially older *women*) accounted for a disproportionate amount of drug use. One woman patient's profile showed that she had consulted nine different physicians and received 181 prescriptions at a total cost of $586 during a 1-year period.

Patients who received free drugs under the State Public Assistance Program were usually issued prescriptions of larger quantities than private, paying patients; these quantities were often close to the maximum allowed under the program, illustrating the effect of payment mechanisms on prescription practices.

Summary and Conclusions

In 1968, the American public received more than one billion prescriptions, dispensed from some 54 000 community pharmacies, at a total consumer expenditure of more than $3.5 billion (4).

When this expenditure is analyzed for a single county, as was done in this study, the pattern of drug consumption, prescribing, and expenditure become more obvious and interpretable.

It is clear that a substantial proportion of the community drug expenditure was for psychotropic drugs that either sedate or stimulate. It is equally apparent that a large amount of drug prescribing and drug costs are for common, benign, and self-limiting illnesses (for example, the uncomplicated common cold). United States national marketing research data also indicate that most physicians (about 95%) will issue one or more prescriptions to a patient whom they diagnose as having the "common cold," and almost 60% of these prescriptions will be for antibiotics. Data are not available to determine what proportion represent bacterial complications of an illness that was originally viral (5).

The study of the most frequently prescribed drugs in the community shows the vast amount spent on currently popular drugs to treat conditions for which older drugs with similar actions are available (for example, Darvon Compound versus codeine, Librium versus phenobarbital). The insignificant amount of generic prescribing in this community points to the deeply ingrained practice of prescribing by proprietary name that has been encouraged successfully by the promotional activities of the drug industry. For this reason it is unlikely that drug costs will be controlled if the sole or central cost-control measure employed is an attempt to get physicians to switch to generic prescribing.

Although there are over 22 000 drugs and drug products marketed, most primary care physicians manage to practice medicine with only several hundred. But the confusing U.S. nomenclature, which allows multiple proprietary names for the same generic ingredient, results in a large number of drugs with identical modes of action being dispensed in any community.

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► Requests for reprints should be addressed to Paul D. Stolley, M.D., Department of Medical Care and Hospitals, The Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, Md. 21205.

References

1. DUNLOP D: Drug control and the British Health Service. *Ann Intern Med* 71:237-244, 1969
2. MCEVILLA JD: A computerized prescription recording system. *J Am Pharm Assoc* NS7:636-638, 1967
3. NEW YORK HOSPITAL: New York Hospital Formulary, 1970
4. BRODIE DC: *Drug Utilization and Drug Utilization Review and Control.* Rockville, Md., National Center for Health Services Research and Development, 1970, pp. 1-71
5. STOLLEY PD, LASAGNA L: Prescribing patterns of physicians. *J Chronic Dis* 22:395-405, 1969

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Attention is called to a variety of records which can be used for analysis of a medical care system. This is specifically illustrated by data on prescribing.

THE STUDY OF PRESCRIBING AS A TECHNIC OF EXAMINING A MEDICAL CARE SYSTEM

Charlotte F. Muller, Ph.D., F.A.P.H.A.

Drug Records as Sources of Information

DOCUMENTS relating to drugs, which are generated in the normal course of medical care activities within a country or a medical care system, are a useful and underutilized source of information on the structure, organization, and quality of medical services.

"Documents" is perhaps an unfamiliar term for prescriptions, records of purchase, patient charts containing orders for drugs, and other related materials. The term "prescription" in the narrow sense refers to the slip of paper filled out by the doctor identifying the patient and the drug—ideally, with dosage, strength, and instructions. In medical care settings with which the author is familiar, this form appears in ambulatory care and in home care services—the patient receives the paper and he or a family member presents himself at a pharmacy either in the residential neighborhood or in the hospital clinic area to receive the medication. For hospitalized patients prescription forms tend to be replaced by the doctor's chart entry, which is transcribed by the nurse to her daily medication sheet as a guide in the performance of her tasks, and also to order forms which are sent to the pharmacy, and to the accounting department as well if charges are to be posted to individual accounts. Thus "prescription" as the "act of prescribing" goes on for all patients but takes a variety of documentary forms. With automation, change in forms can be expected.

Another documentary source is the printed formulary or drug list and the associated list of rules in force within an institution or system. Still another data source for the social scientist is the published paper reporting clinical research on drugs.

In a sense the use of records for analytic study bears a resemblance to the work of the archaeologist reading the explicit and implicit messages in the residue of the past. But the social science investigator who studies prescribing has additional resources, such as direct observation, personal interview, and written questionnaire to amplify what is learned from prescribing records. Comparison of policy statements and actual prescriptions may reveal conflicts between announced policy and day-to-day practice which tell quite a bit about the locus of control, and even about communication and evaluation within the medical care system. Historical and descriptive sources suggest trends and give background for the design of studies.

Analysis of available drug records is

not only a clue to general processes and relationships, but also is a way of studying a specific aspect of medical care which is important in itself—how appropriate the drugs in use are, how much concern there is with economy of drug outlay, and so on. Drug therapy as such has become a significant modality placed daily at the disposal of society through prescribing physicians. Whether actual usefulness measures up to the potential is not to be prejudged but there are ways of studying it.

The decision to prescribe a certain medication is not only per se an important aspect of the medical job of the doctor but also reflects a number of broader characteristics of the medical care process. Several types of studies focusing on varying elements of the act of prescribing will be cited here. Such studies could be adapted to different national environments and international comparisons could be developed. Studies of prescribing would add to the understanding of the medical care process within a country, region, or city and would aid in policy formation.

Choice of Names

When the doctor writes a prescription, does he refer to the drug by its proprietary or generic name? His choices as shown in a sampling of his prescriptions reveal the strength of competing influences acting on the doctor's mind. In particular, the effectiveness of promotional efforts by private drug companies is indicated by the frequency of use of proprietary names, which are usually short, thus easily remembered and quickly written. The use of generic names results from a confluence of factors. The generic name is often used when the doctor is prescribing somewhat older drugs which antedated the therapeutic innovations of the last 20 years. When the generic name is used for a newer drug, this may show a sophisticated detachment from the promotional activities of the companies, an effort to keep down costs of drugs by in effect authorizing competitive shopping for a generic equivalent of a "name brand," and willingness to put more time into remembering and writing out the appropriate generic reference. (Behind these choices lie still other influences: public policy on the naming of new drugs, whether advertising must include the generic name, and so on.) One should note here that the penetration of private drug commerce into countries whose health services are predominantly lodged in the public sector makes doctors' loyalties to brand names a live issue in many different national environments, including developing countries which have substantial imports to meet their drug requirements.

Studies to be cited here have been done in England (Forsyth, 1961),[6] in Baltimore (Furstenberg, 1950-1951)[7] and in New York City (Muller, 1963).[13] An official committee in England (the Cohen Committee) recommended in 1954 that "the practitioner should normally prescribe standard preparations." Forsyth studied the prescriptions of 19 family doctors in a northern industrial town and found that 60 per cent of the prescriptions were for proprietary drugs, of which 90 per cent had a cheaper identical substitute (which showed that there really was a choice).*

Dr. Furstenberg studied a 1 per cent sample of over 100,000 prescriptions written by 159 physicians rendering care under the public welfare medical care program of Baltimore, Md. He found that 55 per cent were for proprietary preparations and identified the actions as pointless waste of the program's money since less expensive official preparations (listed in official sources) were quite suitable.

The New York City study conducted

* Other findings by Forsyth are mentioned in other contexts below.

by this author used data from a large center for ambulatory care and showed that certain drugs were habitually referred to by trade name, others by generic; that the selection correlated significantly with the length of the names (the proprietary being one-third shorter on the average); and that the generically specified drugs constituted a somewhat older group of drugs. The choice of vendors was considerably wider for the generic group; therefore the use of the generic name kept purchasing choices open for the institution. Vendor monopoly in many (over half) of the drugs in the proprietary group meant that the use of a generic name would not have widened the choices at the point of purchasing by the pharmacy. Name selection has to be considered in conjunction with institutional policy as to competitive bidding and with the actual degree of monopoly for specific drugs if one wishes to evaluate the influence of doctors' choices on the purchasing process.

Stability and Change in Doctors' Selection of Drugs

The outpouring of new drugs in the recent decades of innovation, especially in the United States before the effort to strengthen controls embodied in the 1962 Kefauver-Harris Law, raised questions concerning the stability of physicians' drug selection habits under conditions of rapid change in the drug market. Changes in habits over a period of years and in various places can be studied through existing data. An important source of data is total money values of drug production, trade, and consumption, which are or should be available at national levels. These figures permit comparison of specific products and classes of products in use in different years and in different countries. For example, in the United States data on production tell, or at least strongly suggest, which types of illnesses are self-medicated rather than seen by physicians (through figures on dollar values of "ethical" and "over-the-counter" drugs produced for domestic consumption) and which symptoms and illnesses account for the major share of financial resources devoted to medicaments at different times.[3]

Students of the medical care process may inquire: do doctors' choices have a "chronic" stability based on early habit formation and the medical necessities of a given patient load? If not, how rapidly and under what conditions do they change? Menzel, Katz, and Coleman used survey research methods to make a sociological study of the adoption of a new drug within a medical community.[4] They found the process associated with the interpersonal relations of the physicians, and with a number of their individual attributes, including attachment to medical institutions outside the community, and relative concern with recognition within their profession as compared with the respect of patients and the esteem of the community. Doctors who were more isolated from the local medical community introduced the new drugs later than those who were more socially integrated with their colleagues, and the former were more influenced by detail men and advertising than by doctor-doctor relationships.

The study was carried out among 125 general practitioners, internists, and pediatricians constituting 85 per cent of the practitioners in these fields in four cities in the midwestern United States. The social-professional context in which the study was performed was further elaborated in a later study which treated readiness to try the newer antibiotics of the day (circa 1959) as one of several "dimensions of being modern."[11] (Today widespread apprehension about toxic effects very probably would lead investigators to a different criterion of "modern" attitudes toward introducing new drugs.) These studies carried implica-

tions about methods which would be effective in influencing doctors to change habits.

In the New York City study mentioned above, stability in prescribing choices over time was studied in an institution where doctors were young, group relationships of medical practice were strong, and most doctors were qualified in a specialty.[13] The finding that 99 drugs accounted for about nine-tenths of the prescribing in two study periods one year apart, 1963 and 1964, may be considered indicative of considerable stability. In fact 13 drugs made up about half of the prescribing in each period studied. The biological variables —the incidence and prevalence of disease—appeared to influence doctors' choices strongly despite the pressure of advertising. One implication of high stability is that the institution's drug supply is more amenable to bulk purchase and standard specifications and handling if rapid turnover of prescribing style does not have to be accommodated. This subject might be studied as an aspect of cooperation toward institutional goals, or goals of the medical care system.

Forsyth also found an index of stability in the fact that only 13 per cent of the prescriptions studied were for drugs less than two years old (in 1960-1961).[6]

Variation in prescribing choices between institutions and areas must be approached with caution because of differences in the composition of patient diagnoses, in age, and other pertinent variables. A current study of utilization of drugs at four different types of hospitals (public and voluntary, teaching and nonteaching) attempts some comparisons. Fewer than 20 per cent of the drugs which turned up at least once were used at all four hospitals studied; 45 per cent of the drugs actually prescribed were used at a single institution. The hospital with the longest list of different prescribed drugs was the smallest hospital (a voluntary one) and did not take on the most complex medical problems.[5] A measure of interhospital consensus might be an interesting index of evolution toward a rational hospital and medical system (given the necessary scientific base). One must give weight to frequency of appearance of a drug as well as to its ever having appeared in order to avoid overemphasizing the occasional idiosyncrasy of a physician or the patient with a bizarre problem.

Therapeutic Probabilities of Drugs

Studies which identify the therapeutic probabilities attached to the various drugs prescribed by physicians illuminate another aspect of performance in the health services. The prescription or chart is the source of information on what was prescribed; interview or questionnaire methods are used to classify the therapeutic intent, although available listings of therapeutic classes of drugs could be drawn on up to a point. In the Forsyth study, the prescriber himself was asked about intent. A surprisingly low proportion of "specific" drugs, such as digitalis in heart disease, were prescribed. Use of drugs with low probability of success reflects a combination of doctor-patient situations where the need of the patient for reassurance, validation of the sick role and so on, is most easily met by prescribing drugs which had no strong likelihood of therapeutic effect and drugs which provide a placebo effect; types of disease where symptomatic treatment is all that can rationally be offered; inadequacy of diagnosis; and lack of knowledge on the part of the physician. Analysis of these diverse situations leads off into several directions in interpreting strong and weak areas in medical care—medical education, unsolved problems in medical research, social provision for diagnostic facilities, and supportive social and psychological services for the population. In

fact, the evaluation of drug therapy according to rationality is a very significant device for examining the whole medical service system. Adding the judgment of qualified independent observers to the therapeutic probabilities assigned by the prescriber is an interesting research effort, sometimes embodied in the general medical audit. A study concentrating on drug evaluation[14] showed that acquaintance with the full record was necessary for a considered judgment—and that qualified observers do not always agree. There is an area of consensus about therapy—and an area of lack of consensus—particularly when discussing the management of individual patients.

Despite difficulties, the classification of therapeutic expectations and probabilities of drugs is a significant and feasible tool for the understanding of the type of medical care rendered. But for fullest value the use of drugs should be appraised in the context of the type and sequence of diagnostic tests performed and of nondrug therapies (such as surgery, physical medicine, electroshock, and psychotherapy) applied. Thus we are back to elements of the complete medical audit.

Frequency and Cost of Prescribing

J. P. Martin in England attempted to track down the amount and causes of interarea variation in frequency and cost of prescriptions.[10] For cross-sectional analysis he chose the year 1951 and studied 67 medium-sized county boroughs, in ten regions, with a total population of 8.82 million. The causal variables included: characteristics of medical practice, such as size of patient list and the proportion of single-handed practices; patient age and sex distribution; measures of social class and regional prosperity; measures of morbidity and climatic parameters.

To summarize a few findings: regional variations in cost of prescribed drugs per patient were found, and were associated with frequency of prescribing, which in turn had a relation to climatic variation, morbidity indexes and the factor of "custom." This last summed up attitudes and expectations in the doctor-patient relation. The areas populated by working-class patients appeared to have lower-cost prescriptions for a variety of reasons.

Although not all of Mr. Martin's leads were rewarding, the systematic and inventive design indicated ways of studying prescribing as a resultant of various factors within the medical organization, in the general social structure, in regional economy, and in the geographic-biologic (hence, ecological) influences on need for care.

Other statistical analyses of prescribing are useful in the smaller settings of the health plan, hospital, or clinic.

The number of drugs prescribed for a patient on a single day is a revealing fact, or at least a suggestive one. The use of several drugs at once may imply uncertainty and an absence of adequate diagnosis. It may be less than rational in that no one drug is given a chance to work effectively, and in the worst case the drugs may cancel each other. Numbers alone are a screening device to identify cases for further study.

In certain outpatient clinics, one may find that the doctor spends little time with each patient and usually ends the visit with a prescription. The patient typically sees a different doctor at each visit even within the same clinic. These events are determined from ordinary records by computing the number of patients seen per doctor-hour, the proportion of visits resulting in a prescription, and the number of different doctors seen by patients with a given number of visits. Such figures point up areas of inadequacy in ambulatory care. If doctors were responsible for seeing fewer patients per hour, would they find other

ways of serving patient needs besides ordering drugs? If the patient will most probably see another doctor on his next visit, is the sketchy chart entry relative to medication enough of a link to assure coordinated medical care? If institutional authorities and professional persons are more or less aware of the tone of clinic care, what is blocking a community decision to pay for more doctor time in ambulatory care to avoid ill-justified expenditure on drugs? (The total outlay may be redistributed rather than increased.) Why is drug therapy in ambulatory care handled so differently from inpatient medication? The hospitalized patient, although sicker, is under much more vigilant monitoring by human and electronic observers with respect to his reaction and response to medication.

The Formulary: The Hospital as an Institution

The act of prescribing in an institutional setting is per se an act of complying with or deviating from a set of rules established by the staff—namely, the formulary. The rules identify which drugs may be selected by the doctor and the procedures which must be followed to secure exceptions under special circumstances.

For those concerned with innovation in the provision of medical care, comparison of formularies issued at different dates may yield some interesting information. The author has reviewed the formulary of Mount Sinai Hospital in New York for 1964 and its precursor of 1924.[5,12] The difference in content suggests how thoroughly the job of the physician with respect to therapy has had to be redrafted. Morphine, nitroglycerine, milk of magnesia, and acetylsalicylic acid have survived along with a few dozen other familiar drugs. The antiphlogistic mixtures have gone. Dermatology was the specialty still using the greatest number of drugs current 40 years earlier—but radiology, microbiology, urology, and allergy departments listed on their departmental formularies virtually no drugs contained in the 1924 volume.*

Anesthetics and diagnostic agents are among the categories in which change has occurred (as well as the better known antibiotics, tranquilizers, and antihistamines which are especially associated with the drug product revolution after World War II). The time span covered was great enough to encompass tremendous turnover, but study of formularies separated less widely in time is a possible way of exploring the gradual application of innovation in varying environmental settings.

The active use of a formulary is indicative of several characteristics of a hospital. It is correlated with size of hospital, type of sponsorship, and level of teaching activities. It requires a regular staff activity to keep the drug list up to date, and readiness to enforce the policy when the institution is confronted with deviations. The prescriber must justify his request on rational grounds to his chief, the pharmacy committee, or other designated authorities. The use of a selective formulary may be an index to the intellectual leadership within the hospital and to the sharing of responsibility for the quality of medical care of individual patients.[16]

Comparison of actual prescribing with formulary drugs which were therapeutically accepted by specified official agencies was carried out by Furstenberg in a public medical care program in Baltimore.[8] With greater supervision, the conformity was increased over time, to a point where 70 per cent of prescribing was identified as "formulary" and another 20 per cent as "in the spirit of

* Ammonium chloride and sodium bicarbonate, listed by the urology department, were the two drugs included in both 1924 and 1964.

the formulary." Initially, unacceptable prescribing was more often noted in offices of general practitioners than in the hospital setting. In retrospect, this experiment was the more remarkable in that it was conducted in the face of the influx of new drugs which occurred in the 1950's. Furstenberg, interested in policy, program money, and quality, showed researchers how prescription records could be used as an index of rationality of drug therapy when compared with official listings of acceptable drugs.

The presence, composition, and intent of formularies and their implications as to staff organization, sanctions, and communication can be studied by perusal and comparison of actual formularies in printed form. Interviews with important responsible parties are a useful supplement to review of the printed material, but the author's experience is that the intention to have a mandatory formulary, or a permissive one, and the quality of staff resources applied to the effort, are quickly evident in the document itself—in the statement of procedures, the attempt to assign drugs to therapeutic classes, and the care given to dosage schedules, available forms, and counter-indications.

Compliance with formularies within an institution can quickly be estimated by comparing purchase records with the list of approved drugs. At one teaching hospital about 95 per cent of purchases by dollar volume went to drugs approved by the medical staff committee on formulary.[15] The "deviant" purchases were for a scattering of items, many of which appeared on a single prescription during the year.

One hundred per cent compliance is not to be accepted at face value, whether estimated from purchase accounts, charts or prescriptions, because of the possibility that drugs previously taken are being brought in by the patient at hospitalization (or by his family afterward). Provision for exception shows thought in designing rules—if exceptions are not prepared for, a variety of pressures leads to a variety of evasions.

Dispensing: Communication, Standardization, Authority

Research into the dispensing of drugs, again using routine records as the source, helps illuminate certain conflict situations involving the changing role of the pharmacist within a hospital system which is also changing—with more formal institutional rules and evolving authority of the medical staff. An example of such situations is found in New York City hospitals where the pharmacy routine calls for indicating on the prescription any changes in quantity or strength of the medicine which has had to be made because the pharmacy did not have exactly what was ordered.[16] Review of frequency of such noted changes would permit appraisal of communication between medical staff and pharmacy. Effective communication means that the medical staff keeps the pharmacy well informed on its preferences and the pharmacy's standard inventory of package sizes and strengths is well known to the doctors. Labor time in the pharmacy is conserved when doctors and pharmacy make these connections. The same applies to review of prescriptions in which another drug has had to be substituted, and this occurrence can be used to study the relevant communication chain: whom did the pharmacist consult when confronted with an order for an out-of-stock drug; how much autonomy did the pharmacist have under hospital rules; did the selection of the original drug reflect inadequate linkage between medical staff and pharmacy; did the need for substitution arise from unavoidable intervals between deliveries, or from purchase practices ill coordinated with hospital needs? One could compare the man-

agement of these events in the retail or neighborhood pharmacy as well as between institutions, for insight into differences in communication and coordination.

An interesting area for exploration is the evolving role of the pharmacist within the hospital as the hospital itself becomes a more formal institutional structure and as the manual skills of compounding have vanished. The pharmacist usually has more control over the intake (purchase) of drugs than over the internal flow of drugs within the hospital where the doctor wields far more power. The pharmacist may "catch" the mistakes of doctors but ultimately must refer them to designated foci of authority within the medical staff. The lack of strong institutional support for the pharmacist's authority (especially in large hospitals abounding in pharmacologists and other medical specialists) tends to make him turn to informal means of extending his influence or building up a reserve of influence—such as taking care of staff drug needs, and being a good team member in hospital activities not related to the pharmacy.

There are some sources of conflict in this situation in that patient welfare depends critically on the pharmacist's judgment. In contrast to nursing, where this is also true but only a few patients are so dependent on a single nurse, the population of the entire hospital depends on a few pharmacists in this critical way.

Sources of Drug Information Used by Doctors

In the sequence of events which leads to a decision to prescribe, the receipt of information by doctors is an important stage. Something can be learned from analyzing subscription lists of specific medical journals, government bulletins, and independent bulletins such as the "Medical Letter" even though some journals are less read and less heeded than others.

Efforts have been made in the United Kingdom and in the United States to determine sources of information on drugs used by practitioners.[1,2,4] Analysis could also be made of the informational components and attitudes conveyed by drug advertising—particularly of change over time. In the United States, some advertisers shifted perceptibly after 1959 from pride in innovation to appeal to the "tried and true" qualities of drugs. Establishing a trend in advertising content would take systematic study.

Clinical Trials as a Social Process

Going back even further, one meets the whole process of building a record of successful clinical trials reported in the medical literature as a prerequisite of government approval for marketing a new drug. For those interested in the level of intellectual activity involved in reported clinical research, the review by Laties and Weiss[9] of a number of papers on the use of meprobamate (a tranquilizer) in treatment of anxiety is most illuminating. The review shows great unevenness as to the experimenters' provision for dealing with bias, the technics of measuring response to the drug, and the interpretation of results.

For those concerned with interrelations between conduct of research and the provision of care, published papers on clinical trials show to what extent they are centered at teaching hospitals and thus whether new drugs are introduced into patient care under conditions of approval by medical peers, monitoring for side effects, and sophisticated evaluation of results. Papers on drug research also show how often the trials involve the very sick as against the mildly ill patient (and by implication what decisions about total care have

to be made), and how dependent the researchers are on the availability of more or less "captive" populations, ranging from prisons and orphanages to hospital wards and schools.

International comparisons show differences in statistical sophistication, customs of reporting clinical detail and, predictably, types of illness to which clinical research is applied. In Britain the reporting by several organized groups of researchers such as the Council for Investigation of Fertility Control and the General Practitioner Research Group is of interest. Informal groups are implied by the long lists of authors on some North American studies. It is hard to infer from these (and indeed from the British group papers) the extent of group rules and criteria and their influence on the research without more intimate knowledge. In at least some cases, the character of the research reported appears to be mediocre. Exploration of clinical trials is more applicable to the countries engaging in much research, but of course it affects all the countries in which the drugs are eventually marketed, and countries with developing pharmaceutical industries may have a particular interest in knowing which experiences of their predecessors can and should be avoided. There is certainly every reason to use such knowledge to develop social and scientific standards for clinical research through existing international organizations.

The study of important human activities from routinely available records poses many challenges to the inquisitive and offers rewards for persistence and ingenuity. With sampling tools and preparatory observation, this method is relatively economical and lends itself to a variety of research purposes, some more closely connected than others with administrative and policy implications. Perhaps the types of studies touched on here will suggest inquiries which are applicable and of interest in a variety of social and political environments—in all of which a prescribing process is part of a medical care system.

Summary

This paper has attempted to call to the attention of health workers, including social scientists, a variety of records which offer many opportunities for analytic research on the medical care system. Prescribing data tell about the attitudes and range of choices of the doctor ministering to patient needs and the relation of care decisions to socioeconomic context. The use of formularies as a standard of drug selection shows levels and paths of coordination within a hospital or system. The characteristics of research papers on new drugs cast light on the connections linking science, commerce, and care.

The frame for a drug research study can be a single institution or a small geographical area—or as large as a nation, and international comparison is one of the most interesting possibilities. It is hoped that this review of methods, selected findings, and insights will invite the reader to action.

REFERENCES

1. Peterson, O. L., et al. An Analytical Study of North Carolina General Practice 1953-1954. J. M. Educ. 31,12 (Dec.), 1956, Part 2.
2. Research Project on Prescribing. Cited in Barber, B. Drugs and Society. Russell Sage, 1964, pp. 90–93.
3. US Bureau of the Census. Current Industrial Reports, Ser. M28G(63)-1, Pharmaceutical Preparations, Except Biologicals, 1963 (Oct. 28), 1964.
4. Coleman, J.; Katz, E.; and Menzel, H. The Diffusion of an Innovation Among Physicians. Reprinted from Sociometry, Vol. XX (Dec.), 1957.
5. Departmental Sheets for Mount Sinai Hospital Formulary, 1964.
6. Forsyth, Gordon. An Enquiry into the Drug Bill. M. Care 1,1 (Jan.-Mar.), 1963.
7. Furstenberg, F. F., et al. Prescribing, an Index to Quality of Medical Care: A Study of the Baltimore City Medical Care Program. A.J.P.H. 43,10:1299 (Oct.), 1953.
8. Furstenberg, F. F., and Cline, R. The Effect of a Drug Formulary on Costs and Quality of Medical Care in a Public Medical Program. (Unpublished, 1960.)
9. Laties, V., and Weiss, B. A Critical Review of the Efficacy of Meprobamate (Miltown, Equanil) in the Treatment of Anxiety. J. Chronic Dis. 7,6, 1958.
10. Martin, J. P. Social Aspects of Prescribing. London: William Heinemann, 1957.
11. Menzel, H.; Coleman, J.; and Katz, E. Dimensions

of Being "Modern" in Medical Practice. J. Chronic Dis. 9.1 (Jan.), 1959.
12. Mount Sinai Hospital Formulary (5th edition) 1924.
13. Muller, C. Institutional Drug Purchasing: Factors Influencing Drug Choices by Pharmacists and Physicians. Hospitals Vol. 39 (June 16), 1965.
14. ————. Medical Review of Prescribing. J. Chronic Dis. 18:689–696, 1965.
15. ————. Unpublished data.
16. Muller, C., and Westheimer, R. Formularies and Drug Standards in Metropolitan Hospitals. Hospitals (Jan. 16), 1966.

Dr. Muller is affiliated with the Center for Social Research, City University of New York (33 West 42nd St.), New York, N. Y.

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APPENDIX IV

EXHIBITS PROVIDED BY THE DEPARTMENT OF DEFENSE

DEPARTMENT OF THE ARMY
VALLEY FORGE GENERAL HOSPITAL
PHOENIXVILLE, PA. 19460

MEDFV-W 18 January 1972

SUBJECT: Minutes of the Therapeutic Agents Board Meeting and Adverse Drug Reaction Report

Commanding Officer
Valley Forge General Hospital
Phoenixville, Pennsylvania 19460

1. In compliance with Hospital Regulations 40-2-126 and 40-2-126A, the Therapeutic Agents Board met at 1330 hours, on 17 January 1972, in Conference Room 108, Headquarters Building. The following members were present:

COL Frank J. Shannon, Jr., MC	C, Professional Svcs (Chairman)
COL Clare W. Sauser, DC	C, Dept of Dentistry
COL Ekrem S. Turan, MC	Asst C, Dept of Surgery
COL Casimir A. Gorczyca, MC	C, Dept of Medicine
COL George L. Mitchell, MC	C, Dept of Psychiatry
COL Archibald W. McFadden, MC	C, Dept of Clinics & CHCS
COL Joseph E. Kmiecik, MC	C, Pulmonary Disease Svc
LTC Donald F. Maeder, MSC	Acting C, Logistics Div
MAJ Joel S. Carr, MC	C, Anes & Operative Svc
MAJ Charles E. Thomas, MSC	C, Pharmacy Svc (Recorder)

Also present:

MAJ Alan F. Wolf, MC	Ophthalmology Svc
1LT William A. Klein, MSC	Asst C, Pharmacy Svc

2. The minutes of the last meeting held on 15 November 1971 were reviewed and approved.

3. Old Business: None.

4. New Business:

a. In conformance with instructions in Circular 40-76, "Drug Abuse Prevention and Control," DF's were presented from Chief,

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Logistics Division for the month of November and Chief, Pharmacy Service for the months of November and December stating compliance with the Circular.

b. Discussion of proposed new Hospital Formulary and Drug List - It was decided to include in the new Formulary the cost of each drug and to have it printed in pocket size rather than the present larger size edition.

c. Discussion of list of "slow moving" controlled drugs stocked by the Pharmacy - Because of little or no usage over a period of time, it was decided to delete the following:

(1) Schedule II Drugs -

Ambar Tablets
Dexamyl Capsules #1
Dexamyl Capsules #2
Eskatrol Capsules
Levodromoran Injection
Opium Powder
*Codeine Phos (30mg medi-vial)
*Meperidine (50mg medi-vial)
*Meperidine (100mg medi-vial)

*NOTE: Company has ceased manufacture of medi-vials; replaced by Wyeth tubex system.

(2) Schedule III & IV Drugs -

Alurate Tablets
Amobarbital Capsules, 200mg
Butabarbital Tablets, 50mg
Butabarbital Tablets, 100mg
Mephobarbital Tablets, 32mg
Mephobarbital Tablets, 100mg
Nalline Injection, 5mg/cc
Nalline Injection, 0.2mg/cc
Pentobarbital Elixir
Paraldehyde Injection, 10cc - (Paraldehyde 5cc is being used)
Pentothal Injection, 500mg amp - (Pentothal 5 Gm and 12.5 Gm are being used)

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Also discussed under Schedule II drugs was Preludin Tablets. It was decided to retain this drug as it is being used; usage will be observed in the next quarter to determine whether or not to delete at a later date.

d. Discussion on possible reduction of number of parenteral solutions presently stocked in hospital - LTC Maeder, Acting Chief, Logistics Division brought out the fact that these solutions have been stocked in every possible combination and size and are available through Pharmacy Service, Central Issue Section and Central Materiel Section. For example, Dextrose alone is stocked in combination with as many as 40 items. LTC Maeder was granted permission to draw up a listing of all standard and non-standard items, including all combinations, and usage from each source of supply. Complete nomenclature and cost for each unit to be included. This listing will be distributed to each Department Chief to determine usage in each Department or Service and TAB members will report results at next meeting for possible deletion of some of these solutions. The Chairman stated he would like the Board to discuss at the next meeting the possibility of consolidating the issue of all IV's from Pharmacy Service, instead of three separate locations as under the present system.

e. The following were submitted as new drug requests and it is recommended that they be added to the Formulary, with restrictions cited:

(1) Sodium Sulfacetamide, Phenylephrine Ophth Sol (Vasosulf) --

(Physician felt the presently stocked 15% Sulfacetamide was too strong a solution and preferred the 10% as in Vasosulf.)

(2) Diagnex Blue Kit --

(Usage infrequent. Used as screening test to rule out pernicious anemia in selected patients with peripheral neuropathies.)

(3) Bayer Long-Acting Aspirin --

(This item is advantageous particularly to arthritic patients who have pain during the night because of its long-acting

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features - to be used only in specific cases, but not restricted to any particular department.)

(4) Chlorobutanol (Dentalone) --

(Not a prescribed drug - used as an analgesic. Applied locally by opening route canal and floating material into it as an anodyne or anesthetic to make patient comfortable until next visit.)

(5) Tetracaine HCl Powder, 10mg (Pontocaine) --

(Is used to make a solution along with Xylocaine and gives longer lasting results - usage rare.)

(6) Cetacaine Topical Spray --

(Recommend purchase as required - only used by Pulmonary and EENT Clinic.)

(7) Sulfasuxidine Tablets, 500mg --

(This item was deleted at last meeting under "Possibly Effective" category, but was requested by Dept of Surgery to be restored for use as a bowel prep.)

(8) Chlorophyll Derivative Water Soluble (Chloresium) --

(Promotes tissue repair and deodorization - physician has noted results. Recommend purchase as required.)

(9) Haloperidol Tablets, 5mg (Haldol) --

(Presently stock 0.5mg, 1mg and 2mg. The 5mg tablet was requested to cut down on volume of tablets given to each patient, and is also cheaper than combinations of presently stocked items.)

(10) Acne-Dome Lotion, pH 5.0 --

(At present have only one similar lotion and physician felt an alternate lotion was needed.)

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(11) Fluorescein, Proparacaine Solution (Fluress) --

(Needed in procedures where Fluoristrip cannot be used.)

(12) Trypin Chymetrypsin, Neomycin Palmitate, HC, Acetate Ointment (Biozyme & Biozyme HC Oint) --

(Only similar item available is Elase Oint. Podiatrist has been getting better results with these preparations.)

(13) Griseofulvin Tablets, 500mg (Fulvisin Ultrafine) --

We are now buying only ultrafine.

(This was a one-time purchase for a particular patient who could not tolerate stocked item.)

(14) Fluocinolone Acetonide Sol (Synalar) --

FSN item is synalar

(Recommend ~~purchase~~ as required.)

f. The Board recommended disapproval of the following new drug requests presented:

(1) Prednisolone Sodium Phosphate Sol 1/8% (Inflamase) --

(Presently stock Prednedrin which is satisfactory.)

(2) Prednisolone Sodium Phosphate Sol 1% (Inflamase Forte) --

(Presently stock Prednefrin Forte which is satisfactory.)

(3) Prednisolone 21 Phosphate Sodium with Phenylephrine and Sulfacetamide Ophth Sol (Vasocidin) --

(Presently stock Blephamide Solution which is satisfactory.)

(4) Naphazoline HCl, Antazoline Phosphate Ophth Sol (Vasocon-A) --

(Presently stock Prefrin-A which is satisfactory)

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(5) Quinine Sulf 260mg; Aminophylline 195mg (Quinamm) --

(Disapproved because of high cost. Physicians favorably impressed and good patient acceptance for diabetics with leg cramps, but felt present lower cost item, Quinine Sulfate, was satisfactory.)

(6) Perphenazine Tablets, 8mg (Trilafon) --

(Presently stock 2 and 4mg, but 8mg would provide a much smaller volume of medication; however, since 8mg is non-standard, cost is prohibitive. It was decided to request DPSC to make the Trilafon 8mg a standard item so cost would be lower. If made standard, this request will be considered later.)

g. The following item was deleted by the Board - Sodium Sulfacetamide Ophthalmic Sol, 15% (Sulamyd). This will be replaced by Sod Sulfacetamide 10%, Phenylephrine Ophth Sol (Vasosulf).

h. Discussion of Darvon Compound-65 (Deleted by depot as a standard item) - This is one of the biggest volume items in Pharmacy. Plain Darvon, 65mg, does not have the same acceptance with either physician or patient - preference is approximately 10 - 1 in favor of D.C.-65. It was unanimously agreed by Board members to continue stockage of this item as a non-standard item. Through Department Chiefs, a physician/patient education program will be initiated with the aim of reducing requests for this item.

5. The Adverse Drug Reaction Committee, which meets as a sub-committee of the Therapeutic Agents Board, presented completed Drug Experience Report on Keflin Injection from Dept of Medicine to be submitted to the FDA. No additional adverse drug reactions have been submitted since the last meeting.

6. The Board adjourned at 1445 hours.

William A. Klein 1LT, MSC
for CHARLES E. THOMAS
MAJ, MSC
Recorder

FRANK J. SHANNON, JR.
COL, MC
Chairman

PHARMACY NEWSLETTER

MARTIN ARMY HOSPITAL FT. BENNING, GEORGIA

Volume XII *January 1972* *Number 1*

This newsletter is prepared by Pharmacy Service to disseminate information to the hospital staff on additions and deletions to the MAH-Formulary, current drug usage, drug legislation, adverse drug reactions, and drug interactions.

PROFILES OF DRUG UTILIZATION WITHIN MEDDAC ACTIVITIES

At a time when the total expenditures for health care have reached alarming proportions, it is essential that individual components be under continual study and evaluation. One of the elements that must be evaluated is the utilization of drugs not only as it pertains to their therapeutic value but also as to its impact on budget considerations.

It is the intent of this column to bring to the attention of the staff subjects that have a bearing on proper drug utilization. It is our expectation that a greater concern by all personnel develops as a result of disseminating this information. Our ultimate goal is better utilization of drugs and a reduction of funds presently channeled toward the procurement of drugs.

Contributions, suggestions, and constructive criticism are welcome and will be published in forthcoming issues of this newsletter.

From The Department of Clinics

The Department of Clinics is engaged in a program of reducing the number and amounts prescribed of drugs subject to abuse or addiction. Statistics generated out of this program reveals aspects of drug utilization which should be of interest to all personnel.

During the year ending in October 1971 a review of utilization of 10 commonly prescribed drugs disclosed the following:

Drug	Number of Units	Total $ Value
Amytal	4,500	$24.30
Seconal	41,300	$209.06
Placidyl	9,800	$270.48
Ritalin	17,800	$338.06
Meprobamate	8,500	$448.80
Phenobarbital	318,400	$540.72
Chloral Hydrate	46,400	$672.80
Fiorinal	287,000	$2,631.79
Librium	419,000	$12,057.30
Valium	727,000	$28,203.00

It should be noted that the bulk of funds expended on these type of drugs is attributable to only three drugs:

FIORINAL, LIBRIUM, & VALIUM

These three drugs accounted for a total of 1,433,000 units at a cost of $42,892.09

The significance of these figures can better be evaluated when comparison is made to the other drugs stocked and used in MEDDAC. A total of 1100 drug products are authorized for use in our activities. The cost per line on a monthly basis of these 1100 lines is $59.00 while for each one of the aforementioned three drugs is $1,194.00.

While no attempt was made to determine proper utilization of these drugs, physicians and dentists who have studied these figures have raised the following question:

How many of those patients started on Valium or Librium for its tranquilizing

Continuation: Profiles of Drug Utilization

properties could have benefited from the use of Phenobarbital, a much less expensive product and effective tranquilizer..

How many of the patients that were treated with FIORINAL as a pain reliever could have obtained the same relief from Aspirin, APC, or Codeine - all much less expensive and effective pain killers...

Rx Rx Rx Rx Rx Rx Rx Rx Rx Rx

A NEW NARCOTIC ANTAGONIST

Naloxone HCl (NARCAN-Endo) is a narcotic antagonist which is indicated for complete or partial reversal of narcotic and pentazocine-induced depression. Eli Lilly suggests that naloxone may also be useful in the treatment of propoxyphene overdosage. It can be used as a diagnostic-therapeutic tool in respiratory and CNS depression of undetermined but suspected opiate etiology because it has no agonistic properties and will not produce further depression. Naloxone does not possess above potential thus is not considered a Controlled Substance.

Dosage: I.V., I.M., or S.Q. - Adults, 0.4 mg.

If the desired improvement in respiratory function is not obtained immediately, the dose may be repeated at 2 to 3 minutes intervals up to 3 times.

The duration of action of some narcotics may exceed that of naloxone and repeated doses may be necessary.

Safe and effective use of naloxone in children, neonates, and pregnancy has not been established. Nalline injectable (Pediatric)is still available and should be used when treating pediatric cases.

Available:
For Injection: 0.4mg per ml, 10 ml Vial
Stocked: Emergency Room and Inpatient Pharmacy

ADDITIONS TO THE FORMULARY

The following drugs recently approved by the Therapeutic Agents Board have been received and are on hand at both Pharmacies

ALDOMET Injectable
ANUSOL-HC Suppositories
ARISTOPAN Injectable
GAVISCON Foamtabs (Gastroenterology)
LEVODOPA Tablets (Neurology)
NARCAN Injectable
TINACTIN Powder
TRANSACT
CLEOCIN Syrup
COGENTIN Tablets, 0.5 mg

Rx Rx Rx Rx Rx Rx Rx Rx Rx Rx Rx

UNOFFICIAL ABBREVIATIONS

We remind prescribers that the abbreviations "Q.D." and "O.D." are not official abbreviations and should not be used when writing prescriptions. These two abbreviations are subject to misinterpretation and have been the cause of some medications being mislabeled. It is strongly suggested that "Once Daily", "One a day", or "Daily" be used.

Rx Rx Rx Rx Rx Rx Rx Rx Rx Rx

OUTPATIENT DISPENSING POLICIES

The Therapeutic Agents Board is continuously revising and updating the outpatient dispensing policies to conform with Federal Laws, DoD instructions, and also with suggestions submitted by the medical staff which are considered to be in the best interest of the patient's health. Several changes to these policies have been made since the last edition of the Formulary (1971) was published. As a convenience to the staff a summary of all current policies is included as an inclossure to this newsletter. We urge all prescribers to become familiar with these policies and to abide by them. Cooperation in this area of prescribing will reduce the number of inconveniences to our patients created when prescriptions are not in accordance with policies.

LUIS L. PLA
LTC, MSC
Chief, Pharmacy Service

WILFORD HALL USAF MEDICAL CENTER

FORMULARY

LACKLAND AIR FORCE BASE, TEXAS
AEROSPACE MEDICAL DIVISION (AFSC)

THE PHARMACY AND THERAPEUTICS COMMITTEE

Colonel Ray F. Fitch, Chairman, Department of Medicine

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Colonel John J. Halki, Member, Department of Obstetrics/Gynecology

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Lieutenant Colonel James A. Reinarz, Member, Infectious Disease Service

Col. Ralph H. GALATI.
~~Major Richard A. Lund,~~ Member Medical Material Division

Captain Ronald D. Trusty, Recorder

THE PHARMACY AND THERAPEUTICS COMMITTEE

The existence of a Pharmacy and Therapeutics Committee at Wilford Hall USAF Medical Center is provided for in Air Force Manual 168-4 and Medical Center Regulation 160-38. It is a committee of doctors from various medical specialities, the Chief of the Material Division and the Chairman, Pharmacy Department serving as Recorder. One of the committee's major responsibilities is the selection of drugs for the development of a Formulary of Accepted Drugs for use in Wilford Hall USAF Medical Center.

THE FORMULARY SYSTEM

The Formulary System is an accepted method whereby the medical staff of the hospital, working through the Pharmacy and Therapeutics Committee, evaluates, appraises and selects from among the numerous medicinal agents available, those that are considered most useful in patient care, together with dosage forms in which they may be administered most effectively.

Under the Formulary System, each member of the medical staff agrees that in each instance in which he prescribes a drug by brand name he authorizes the hospital pharmacist to dispense, and the nurse to administer, the same drug under its generic name; irrespective of whether it is or is not the same brand referred to in the prescription or drug order.

THE FORMULARY OF ACCEPTED DRUGS

All drugs approved for use in Wilford Hall USAF Medical Center are listed in the Formulary of Accepted Drugs. The drugs are listed alphabetically by generic name. Trade names of single entity drugs are cross-indexed to the generic name. Brand names of combination drugs are cross-indexed to the generic name of the major therapeutic ingredient. For your convenience, a drug classification index has been included in the Formulary of Accepted Drugs as an Appendix.

The Formulary can be used as a convenient source of information on drugs stocked in the Pharmacy. Brand names, generic names, dosage forms and product strengths can be rapidly obtained by using the formulary.

REQUEST FOR ADDITIONS TO THE FORMULARY OF ACCEPTED DRUGS

Requests for additions to the Formulary of Accepted Drugs will be directed in writing to the Recorder, Pharmacy and Therapeutics Committee using a form letter that is available from the Pharmacy Department. The requesting physician is responsible for filling out page 1 of the request.

REQUEST FOR EMERGENCY PROCUREMENT OF DRUGS

The Pharmacy Department cannot purchase a nonformulary drug unless an emergency exists and the request is validated by the Director of Hospital Services. A form letter is available from the Pharmacy Department that can be used to request an emergency drug procurement.

DRUG SAMPLES ISSUED BY PRESCRIPTION

In a military hospital, the uncontrolled use of samples often causes patient inconvenience and detracts from rational drug therapy. The Pharmacy is authorized to store and dispense new drug samples providing the physician understands the conditions imposed by Air Force Regulations and Medical Center Policies. These conditions are:

a. Refills are not authorized. This restriction is necessary since the Pharmacy cannot guarantee that a supply of samples will still be available when the patient returns.

b. The Pharmacy Department cannot purchase a drug to augment samples. Drugs can only be purchased when:

(1) An emergency exists and the request is validated by the Director of Hospital Services.

(2) They have been approved for use by the Pharmacy and Therapeutics Committee.

PAUL W. MYERS
Colonel, USAF, MC
Commander

1 July 197

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FORMULARY
OF
ACCEPTED DRUGS

A

A & D OINTMENT
30 Gram Jar

ACETAMINOPHEN NF (Tempra) (Tylenol)
325 mg Tablets 100/$0.30
120 mg per 5 ml Elixir 120 ml/$0.26
60 mg per 0.6 ml Pediatric Drops 15 ml/$0.23

ACETAZOLAMIDE USP (Diamox)
250 mg Tablets 100/$5.89

Acetest - See ACETONE TEST TABLETS

ACETIC ACID
0.25% Sterile Solution in Irrigating Bottle 1000 ml/$0.99

ACETIC ACID, GLACIAL USP
99% 30 ml

ACETIC ACID EAR DROPS
3% Acetic Acid in Alcohol USP 15 ml Bottle

ACETOHEXAMIDE (Dymelor)
500 mg Tablets 100/$2.93

ACETONE TEST TABLETS (Acetest)
Bottle of 100/$1.85

ACETYLCHOLINE CHLORIDE INTRAOCULAR (Miochol)
20 mg per 2 ml 2 ml/$4.05

ACETYLCYSTEINE SOLUTION (Mucomyst)
20% Solution 30 ml/$3.93

ACETYL SULFISOXAZOLE ORAL SUSPENSION (Gantrisin)
50 mg per 5 ml 120 ml/$0.55

Achromycin - See TETRACYCLINE HCL

Acidulin - See GLUTAMIC ACID CAPSULES

ACNE LOTION
Contains: 120 ml

Calamine.....6.0%	
Zinc Oxide..... 8.0%	
Talc..... 8.0%	No. 1 (Light)
Glycerin..... 6.4%	
Resorcinol..... 2.8%	No. 2 (Medium)
Sulfur..... 4.7%	
Demineralized Water.....32.0%	No. 3 (Dark)
Alcohol USP.....39.2%	

ACTH - See CORTICOTROPIN INJECTION USP

Acthar Gel - See CORTICOTROPIN INJECTION, REPOSITORY

Actifed - See TRIPROLIDINE HCL AND PSEUDOEPHEDRINE HCL

Adrenalin - See EPINEPHRINE INJECTION

Adroyd - See OXYMETHOLONE

Aerolate - See THEOPHYLLINE

Aerosporin - See POLYMYXIN B SULFATE

Afrin - See OXYMETAZOLINE HCL

Airkem - See DETERGENT NON-IONIC

ALBUMIN, NORMAL HUMAN SERUM USP

5% Solution	500 ml/$34.00
25% Solution (Salt Poor)	100 ml/$24.70

ALCOHOL USP (Ethanol)

ALCOHOL ABSOLUTE

2 ml Ampuls	2 ml/$0.28

ALCOHYDE SOLUTION
Contains: 10,000 ml
Formaldehyde Solution 37%..... 2.5%

Merthiolate Tincture..... 0.4%
Sodium Nitrite..... 0.1%
Isopropyl Alcohol.....67.9%
Demineralized Water.....29.1%

Alcopara - See BEPHENIUM HYDROXYNAPHTHOATE

Aldactone - See SPIRONOLACTONE

Aldomet - See METHYLDOPA

Alkeran - See MEPHALAN

ALLOPURINOL (Zyloprim)
100 mg Tablet 100/$5.15

ALPHA-CHYMOTRYPSIN (Zolyse)
750 NF Units with 10 ml Dilvent 10 ml/$6.48

Alpha-Keri - See MINERAL OIL, LANOLATED, WATER-DISPERSIBLE

ALPHAPRODINE HCL (Nisentil)
60 mg per ml 10 ml/$1.92

ALPHA TOCOPHERYL ACETATE (Vitamin E)
25 mg Tablet 100/$0.47

ALUMINUM ACETATE OTIC SOLUTION (Burow's Ear Drops)
1:100 Solution 15 ml

ALUMINUM ACETATE SOLUTION TABLETS EFFERVESCENT (Burow's Solution Tablets)
100/$2.44

ALUMINUM ASPIRIN TABLETS (Baby Aspirin)
75 mg Chewable Tablets 25/$0.08

ALUMINUM HYDROXIDE GEL (Ampojel)
324 mg Tablet 100/$0.41
4% Flavored 473 ml/$0.43

ALUMINUM HYDROXIDE GEL, MAGNESIUM HYDROXIDE, AND MAGNESIUM

TRISILICATE SUSPENSION (Gelusil M)
Each 5 ml Contains: 177 ml/$0.08
Aluminum Hydroxide.....250 mg
Magnesium Hydroxide.....200 mg
Magnesium Trisilicate.....500 mg

ALUMINUM HYDROXIDE GEL AND MAGNESIUM TRISILACATE (Gelusil) (A.M.T.)
Each Tablet Contains: 100/$0.74
Aluminum Hydroxide Gel Dried.....250 mg
Calcium Phosphate, Tribasic..... 2.5 mg
Magnesium Trisilicate.....500 mg
Each 4 ml Contains: 473 ml/$0.56
Aluminum Hydroxide.....160 mg
Magnesium Trisilicate.....500 mg

ALUMINUM HYDROXIDE GEL WITH MAGNESIUM HYDROXIDE (Maalox)
Each ml Contains: 177 ml/$0.11
Aluminum Hydroxide Gel.....22 mg
Magnesium Hydroxide.....39 mg

ALUMINUM PASTE

AMANTADINE HCL (Symmetrol)
100 mg Capsules 100/$9.60
50 mg per 5 ml Syrup 120 ml/$1.65

Ambar - See METHAMPHETAMINE AND PHENOBARBITAL

Amicar - See AMINOCAPROIC ACID

AMINOBENZOATE AND TETRACAINE (Cetacaine)
Spray Bottle 50 ml/$2.95

AMINOCAPROIC ACID (Amicar)
250 mg per ml 20 ml/$2.30

AMINOPHYLLINE USP
200 mg Tablets 100/$0.77
25 mg per ml Injection 10 ml/$0.13
500 mg Rectal Suppository 12/$0.96

AMINOSALICYLIC ACID RESIN (Rezipas)
453.6 Gram/$7.30