The meeting was called to order by Chairman Robinson at 3:30 P.M.

MEMBERS PRESENT: Mr. Benkovich
Mr. Demers
Mr. Getto
Mr. Harmon
Mr. Hickey
Mr. Moody
Mr. Schofield
Mr. Wittenberg
Mr. Chairman

MEMBERS ABSENT: None

SPEAKING GUESTS: Assemblyman Coulter
Barbara Silberling, Nevada Consumers League
Joe Lawler, Consumers Affairs Division
James Edmundson, representing Food Commissioner
George Bennett, State Board of Pharmacy
Minor Kelso, Title XIX
Janice Goodhue, citizen
Wally Roanhaus, Division for Aging
John Kimball, Commission on Aging
Elliot King, pharmacist
Robert C. Rodgers, The Upjohn Company
Joe Foley, Southern Nevada Chapter of the American Institute of Architects
Clinton Wooster, Nevada Association of Architects
Jack McCulloch, Nevada State Board of Architecture
Jim Joyce, Nevada Association of Building Designers
I. R. Ashleman, Nevada Association of Building Designers

The purpose of this meeting was to hear testimony on the following bills:

AB 436
AB 583
SB 283

Also discussed were:

AB 455
SB 84
SB 89
SB 213

The first bill to be heard was AB 436 which:

> Allows prescriptions for drugs designated by trade or brand name to be filled with less expensive drugs selected by generic name, unless otherwise specified.

Assemblyman Coulter spoke on behalf of this bill saying what the bill says is that when a doctor prescribes a drug by brand name, the pharmacist may make a substitution of an equivalent, lower priced drug. He said there is a provision in the bill that if the doctor objects to any substitutions, all he has to do is indicate on the prescription that he does not want any substitutions made and none will be made. He said the California Assembly passed a similar measure in that State on April 4 of this year by a 61-13 vote and at the same time a court suit has been filed which would seek to overturn the anti-substitution law in the State of California. Mr. Coulter submitted to the Committee a copy of an article in favor of drug substitution taken from the Sacramento Bee a copy of which is enclosed (Exhibit 1).

Mr. Coulter also submitted a list of manufacturers and distributors of drug products listing various drugs produced by several manufacturer at different prices a copy of which is enclosed (Exhibit 2). The Nevada Consumers League in 1972 made a survey of drugs in Nevada and they found that identical doses of identical drugs varied as much in price as 567%.

Mr. Coulter went on to say that many of the questions on substitution focus on what the Federal Government is going to do. He said former HEW secretary, Casper Weinberger, went before a Senate Committee and said that within a few years drug substitution would be mandated by the Federal Government and Mr. Coulter said he has been told by two pharmacists associated with manufacturers that it is probably coming within a year.

Mr. Coulter then quoted from an article in a 1973 issue of New Republic Magazine saying "The cost of name brand labels often exceed the cost of the pills themselves. This is the unmistakeable conclusion one draws from recent studies on prescription drug industry by Senator Gaylord Nelson and Congressman Rosenthal. Congressman Rosenthal made an extensive survey in the Queens County District of Washington D.C. comparing prices of brand name drugs with those of chemical or generic equivalence. He concluded that American consumers are forced to pay over one billion dollars annually in unnecessary prescription drug costs because of prohibitions on retail advertising, over-protective patent laws, promotional expenditures by industry and unreasonable markups".

In California, they estimate that the passage of their drug substitutio law will save the consumer $45,000,000 every year. Mr.Coulter added that he did not think the amount would be so great in Nevada but he did think it would be in the hundreds of thousands of dollars. He felt this bill would result in much savings for the Nevada consumer particularly senior citizens.

He went on to quote an article from the California Pharmacist Magazine by Edward Fieldman, an official of the American Pharmaceutical Association which said:

"About 20 years ago, the pharmaceutical industry acting through its primary trade association successfully bamboozled the American people. Among those duped were numerous state legislatures, the medical profession and the pharmacy profession. The American Pharmaceutical Association was so effectively hoodwinked that it even lent its support to the industry in advocating the enactment of various statutes and regulations which are commonly referred to as anti-substitution laws." This official of the American Pharmaceutical Association went on to enumerate some of the problems involved with this anti-substitution. He said, "It eliminated meaningful price competition in the drug industry. For all practical purposes, it extended the patent monopoly into perpetuity. It effectively suspended the pharmacist from functioning on benalf of the patients' economic interest and it eliminated the pharmacists' most basic professional function."

Mr. Coulter went on to say that Casper Weinberger stated in testimony before the Senate and it was reported in the Congressional Quarterly that in terms of quality and therapeutical equivalence, with few exceptions, no significant differences among chemically equivalent drugs has been shown.

Mr. Coulter then submitted to the committee a press release from the National Research Council which is a private organization founded by Congress with the responsibility of advising the Federal Government in science and technology. A copy of this press release is attached hereto (Exhibit 3). This release supported drug substitution.

He went on to say that studies indicate that the national pharmaceutical manufacturers spend a great deal of money in promoting particular brand name drugs. According to an article in Scientific America, in 1973, they spent 1.2 billion dollars that year which amounted to $4,000 in efforts aimed at every single doctor in the United States. Mr. Coulter thought this was an incredible amount of money to tell people that they should buy a particular name brand drug. He said 1.5 billion drug prescriptions were filled in 1973 which is a average of 20 prescriptions for every single family in this Country.

Mr. Coulter then quoted Mr. P.H. Lake, President of Eli Lilly & Co. who was speaking to the National Retail Druggists at their convention in Las Vegas in November 1974. Mr. Lake said: "For reasons that I shall neither defend or deny, you and I (the druggists) have not communicated with the consumer. We have not sought out his concerns, his expectations, his complaints. When questions get tough, we retreat to the back room, we wrap ourselves warmly in the cloak of medical mystic and hope the cold winds of consumer concerns and curiosity will blow away, but they won't, ladied and gentlemen, they simply won't".

Mr. Coulter said testimony may be heard that there are bad generic drugs on the market. He said this is probably true, but the pharmacist in his professional capacity should be able to handle this.

Mr. Coulter said he was told the State Pharmacy Association would not oppose this bill if a few changes were made:

> In Section 1, Subsection 2, the Association wants this changed to provide that the doctor would have to specify that a substitution can be made rather than as the bill now reads that the doctor specify they can't be made so there would not be the occasion when the doctor simply forgets to indicate no substitutions.
>
> In Section 1, Subsection 3, the Association would like this Subsection deleted entirely. (Subsection 3a). They did not believe this could be enforceable.

Mr. Coulter said this bill is a meaningful attempt to solve the problem of drug substitution. There are so few drugs that are not interchangeable that a list could be made up as the Federal Government has declared only 20-30 drugs as not interchangeable. Once this is done, he said, this will be mandated on the Federal level. He felt meaningful savings could be made in areas of high escalating costs for all concerned.

Mr. Demers wondered if the Supreme Court decision involving Coca-Cola and Pepsi would enter into this matter as the decision held that if someone goes into a restaurant and asks for a "Coke", they cannot be given a Pepsi. They first have to be told that there is no coke, would they like a pepsi. Mr. Coulter did not know if this case would be applicable in this situation.

Chairman Robinson wondered about the control there would be on, for example, drugs coming in from outside the Country. Mr. Coulter said the decision would be up to the pharmacist and that this bill does not mandate him to do anything. He may choose not to make any substitutions. He felt this bill might force the pharmacist to act more in his official capacity. He said the pharmacist knows more about the different drugs than a doctor. This would get the doctor and the pharmacist working together to get the best drug for a patient.

Barbara Silberling then spoke on behalf of the Consumer League of Nevada in favor of this bill saying it would reduce the price paid by the consumer and commented that the pharmacist should be able to choose the kind of drug he dispenses. She suggested the use of a formulary of drugs as is presently being used in the State of Massachusetts. She suggested a language change in Section 1, Subsection 1 on line 7 after the word "strength" adding the language "and therapeutic equivalent to". Therapeutical equivalence is defined as chemical equivalence which, when administered to the same individual in the same dosage regime, will provide essentially the same efficacy and/or toxicity. This change would give the consumer assurance as to the reliability of substitution. Ms. Silberling's complete testimony is attached hereto (Exhibit 4). She also said language should be added in Section 1, Subsection 2 providing "in his own writing" be inserted into this section. She said that the Women's Lobby would concur with this written statement submitted by Ms. Silberling.

Mr. Joe Lawler of the Consumer Affairs Division then spoke saying the Consumer Affairs Division supports AB 436 relying on the expertise of the professionals involved to maintain the quality control of prescription drugs and dispensing them at the lowest possible price to the consumer.

Mr. Benkovich wondered how much say a pharmacist in a retail store has in the drugs purchased for the pharmacy. Mr. George Bennett answered this question saying the manager or owner of the store determines what will be ordered and the employee may not have any input into the ordering at all.

Mr. Bennett then came before the committee to testify on this bill commenting that the State Board of Pharmacy is a consumer board, it is empowered by the Legislature to protect the consumers of the State. He said the Board is opposed to AB 436 because they feel it is contrary to the welfare of the patient. He said the Food and Drug Administration does not inspect drug manufacturers prior to their operation. He said existing plants operate under the good practices of the FDA which are woefully inadequate and are in the process of revision by the FDA. He said the major drug manufacturers have much more stringent quality controls than either the FDA or the USP requirements. The USP is the official book that sets the standards for potency, etc. of the drug products and the FDA enforces those standards. Mr. Bennett commented on the equivalency of drugs with an example of a certain company which encased one of their drugs in a capsule which took seven days to dissolve in the stomach. The drug itself was equivalent but there was a difference.

He went on to say that the average person thinks the FDA certifies all the drugs. This is far from true. The FDA only certifies four categories of drugs in all batches. These categories are insulin, biologicals (such as vaccines and anti-toxins), antibiotics and digoxin. There are very few generic manufacturers in these catagories because for the difficult process involved and the fact that there is not very much money in it. Many of the biologicals are made by only one company as a public service. The only category where generics are strong is antibiotics and digoxin. This is a big field and much money involved. Recently the FDA, because of complaints from hospitals and patients and doctors took an unusual step and decided to test all of the digoxin presently on the market by 36 companies. 33 of the 36 companies products failed the FDA's test. The Office of Technology Assessment which is an arm of Congress which studies matters which have a technological impact concluded after studying the generic drug issue that the current standards and regulatory practices to no insure bioavailability. The Fact Sheet of the Office of Technology Assessment is attached hereto (Exhibit 5).

Mr. Bennett also submitted to the committee a copy of a letter from the legal counsel of the FDA stating that the FDA realizes that their good manufacturing practices are inadequate. A copy of this letter is attached hereto (Exhibit 6). Mr. Bennett said that what it boils down to is that at the present time and under the present budget of the FDA which is approximately $200,000,000, they simply cannot insure that generic drugs are bioequivalent.

Mr. Bennett said that until the day that the FDA can assure that generic drugs are bioequivalent, the Board feels the substitution of generic drugs is not in the best interest of the consumer.

He said although the Board is not too interested in price as they are in quality of service and products, if all drugs were prescribed generically today, the INS Service which is the national prescription products, stats that there would be a savings of 6.78%. The average prescription in this country is about $5.00. This means by generic drug, you might pay $4.65. He also commented that the Board could not possibly police the generic prescribing mentioned in AB 436 unless perhaps this was referred to the Finance Committee for the appropriation of the $2,000,000 laboratory. He cited the example that a diamond and a chunk of coal are generically equivalent.

With regard to recalls, the number of recalls is about the same for the major companies as for the generic manufacturers. However, 10% of the companies produce approximately 90% of the drugs. The remainder are produced by the small companies. He said many generic drugs are as good as or even superior to brand names. He said he was not trying to say generic drugs were bad per se. He did not believe, however, that any pharmacist or doctor could pick a generic drug from a generic drug house and say possitively that that drug is as good as the brand name. Until a drug is tested, there is no way of saying this. The small amount of savings does not seem to justify risking the health and welfare of a patient. He added that there is nothing to stop a druggist from charging just as much for a generic drug as a brand name one. Also, some of the more expensive generics cost more than some of the brand names. He felt that if the quality control and the good manufacturing practices were enforced in the future, many generics will cost more than brand names because many of the smaller companies simply don't have the background or technological know-how to have the proper quality control as the larger more experienced companies do. Quality control costs money. He said the major companies spend $4,000 to $5,000 per doctor each year. This is not simply to tell them about the brand name, but to detail the doctor about many things about the drug. Many major companies also produce generics.

Mr. James Edmundson of the State Food and Drug Commission then spoke on this bill saying that the Commission does not at this time have the personnel or the facilities to check the equivalence of drugs in order to enforce the provisions in this bill. He thought a good start would be the $2,000,000 necessary for a laboratory and over and above that, the personnel to staff it. He said under Chapter 585 of the NRS, his department would have the responsiblity of the enforcement of this bill. He said it would require a great deal of study to determine what would be needed for this laboratory. Mr. Bennett said he did file a fiscal note for Section 3, a and b of AB 436 as he felt in order to police this bill, it would require a full time inspector state-wide and also hired "shoppers". The fiscal note calls for $25,000 in 1975-76 and in 1976-77 and continuing.

Minor Kelso, Title XIX, then spoke in opposition to this bill saying the most important issue was the question of reliability. If it was reliable, Title XIX would be in favor of the bill. The FDA has not designed or implemented controls that are routinely exercised by

many reputable companies. One of the problems is that there is nothing on the generic package that the druggists see that tells him that the product will reliably perform under some kind of a national standard. Therefore, you would be placing a huge burden on the individual pharmacist that he is not prepared to meet. If the Federal Government would index generics in terms of reliability, then he felt they would be in a position to accept substitution. He said as he understands it, once chemical composition of equivalence has been established, this is where similarity ends. Other factors such as compacting, heating, mixing, storing, aging, refrigeration, sampling, batch control, etc. all enter into whether this drug will have the same affect each time it is used by a person. He said that at a point in time after the reliability of generics has been established of generics, that some bill like this should be enacted, but until then, he did not believe such a measure should be effected. He felt controls should come first.

Janice Goodhue then spoke in support of this measure stating she felt it was a break for the consumer. She submitted to the committee an article from Consumer Reports. This article is attached hereto (Exhibit 7).

Wally Roanhaus of the Division of Aging Services spoke in favor of the bill saying elderly people just don't have the money to spend and if generic drugs can be purchased for less, it would help the senior citizens in this State. He said by the year 2000, over 50% of the population may be 65 years of age or older and these people are the largest purchasers of prescription drugs. When asked if he felt there were sufficient safeguards, he commented if the drugs are presently being sold daily and over the counter, he could see no problem but if there are problems, he felt the drugs should be proved first.

Mr. John Kimball representing the Commission on Aging testified in favor of this bill and submitted a petition of people also in support of AB 436. This petition is attached hereto (Exhibit 8).

Mr. Elliott King who is a pharmacist then spoke representing the pharmacists of Nevada. He was opposed to AB 436. He said there is nothing that a pharmacist has at his disposal today that he can use to distinguish what represents the quality or lack of quality or how a pill will react, or the toxicity of a drug. It is not printed on the label. The only thing he has to rely on is the reputable manufacturer. There are different standards for drugs in different countries. He spoke about malpractice and that it would become a way of life for the pharmacist with the adoption of generic dispensing. He said when a pharmacist dispenses a brand name drug, the reputation of that drug is on the line and the manufacturer will back up anything that goes wrong with it. However, if a drug is imported or from one of the "slack" houses in this country, he felt the pharmacist would be strictly on his own. He would have to increase his liability insurance in order to settle his own claims. He also said that by the time the generic houses are brought up to standards, generic drugs would cost more than brand name drugs. He said until controls are set up, he thought the expert - the physician - should make the decision of what drugs should be administered.

Mr. Elliott King also commented on the instance when a person comes into a hospital unconsious or comatose from an overdose or toxic reaction to a drug, it is impossible to identify a drug that comes from a generic house beca3se they have no labeling or identification. All major manufacturing houses have codes on the bottle so you can determine what has been taken.

With regard to saving money, he said it was a known fact that when Alberta Canada went to substitution, the cost of the average perscription went up. He added that the major drug manufacturers are inspected by the FDA a couple times a year and the inspectors are in and out all the time but this is not the case with the small manufacture who could go in and out of business before an inspector ever inspected him.

With regard to Mr. Lake's comments referred to by Mr. Coulter, Mr. King did not feel he was referring to hoping we could close our eyes to everything and the winds would blow away consumer complaints, but rather that the public should be made aware of the good deal they are getting in American medicine today because we have the best medical practices in the world.

He said the drug companies are the ones who keep doctors informed of all the new drugs and if this was not the case, doctors would still be prescribing drugs that came out years ago instead of the newer and better ones we have today. Part of the $4,000 to $5,000 referred to earlier spent by major drug manufactures is used to educate doctors on new drugs and for edification as to the side effects and benefits of a drug and what a drug will and won't do. They also do this with the pharmacists. He said he is called upon weekly by detail men from the major drug manufacturers but he has never seen anyone from a generic house.

Mr. Bob Rodgers from the Upjohn Company then spoke in opposition to AB 436. He quoted Mr. Alexander Schmidt, the Commissioner of the Food and Drug Administration, who said in a speech before the U.S. Pharmacopeial Convention on March 22:

> "The implication is clear. Today the FDA cannot assure the uniform quality of drugs on the market because the system relies on a set of standards that are outmoded!! Unless the U.S.P. gets its house in order and rejuvenates their standards, the FDA will be forced to come up with their own set of standards."

He submitted the full statement of the Commissioner to the Committee which is attached hereto (Exhibit 9). He also read and submitted to the Committee an excerpt from The Washington Forum, Inc. Forum Notes which is attached hereto (Exhibit 10). This excerpt spoke to the inabilities of the FDA which was "routinely allowing shipments" of generic drugs which have not received approval of Abbreviated New Drug Applications. This Abbreviated New Drug Application System in effect allows a company to market a drug without going through the extensive New Drug Approval system as long as the original, equivalent product has been cleared through the Drug Efficacy Study Implementation review. Under the ANDA system, a company does not

have to wait for its application to be cleared; it can begin or contin marketing as soon as the application is filed. The system is quasi-legal. FDA considers it a stop-gap until its drug monograph setup is finalized.

Mr. Rodgers said two years ago Upjohn became very involved in looking at the bioinequivalence of drugs. They perused literature to see how much documented evidence was available. They found 73 generic drugs in their first look and of these 73, there are 370 published articles of inequivalency. There were 20 documented studies on digoxin alone which is used by heart patients which showed bioinequivalency. He submitted this list to the committee ~~and is attached hereto~~ (Exhibit 11).

He went on to say that the Bureau of Labor's statistics show that since 1963, of all health care providers, the prescription drug prices are the only ones that show a minus 1.8 on a standard scale of 100. The cost of prescriptions have gone down and have remained more stable than any other health care facility. A copy of these statistics and a related article is attached hereto (Exhibit 12).

He then spoke about the difference in prices for the same drug using arithramycin as an example. One company may sell it for $9 while another may sell it for $3. He said the reason for this is that the company manufacturing it and selling it for $9 has probably been asked by a major manufacturer to make it and the major company probably has their quality men there and this drug must be made to their specifications. The company selling it for $3 may not have any quality standards therefore the cost of production is reduced and he sells the drug for less. This company may not be interested in quality control as long as it meets the U.S.P. which is below standard or out-moded standards.

He cited an example with Upjohn when they asked a company to produce nitrofurantoin for them. Upjohn set up the specifications for the laboratory contracted to make it for them and the product went on the market and distributed about $1,000,000 worth of the product. About 3 months later, out quality control people had been checking the batches constantly and suddenly the curve of demonstrating a level of effectiveness flattened out to almost zero. When we challanged this, we discovered that what had happened is that the manufacturer had decided to manipulate the particle size feeling that this would enhance therapeutic value of the product - it enhanced it to zero! They immediately recalled the $1,000,000 worth of the product. Upjohn felt it was their responsibility to do this--not the FDA. He estimated that the establishment of standards for generics would be set up by the FDA approximately 3 to 5 years from now. When this was done and druggists and physicians could be sure of the reliability of a drug, the savings that would be experienced would not be as much as people have thought. He commented on the $45,000,000 that this substitution was supposed to save California consumers. When taking this figure and dividing it by the 21,000,000 population of that State, it results in a $2.00 per year savings per person in California. He said in the State of Oregon they figured what Mr. Weinberger's proposal would

save each Oregonian and came up with a figure of 35¢. But the administration of the program for the first year would cost the Oregon taxpayer $150,000,000 which averages 75¢ in taxes per person to save 35¢ in prescriptions.

In Kentucky, Maryland and Massachusetts where there is a semi-anti-substitution law, after two years there is no significant sign of savings anywhere. Alberta, Canada in 1962 passed a complete abolition of their substitution laws and in 1970 conducted a survey of equivalence of prescription prices as compared to the other provinces and and they found the cost in Alberta had gone up. Rather than the average cost of prescriptions going down, they had the highest average prescription cost. A copy of this report is attached hereto (Exhibit 13).

In answer to a question from Mr. Hickey regarding competition and control of the market by major companies. Mr. George Bennett commented that there are approximately 100 major companies and about 1100 smaller companies. Mr. Rodgers said there is very definitely competitions between these major companies, not competition among companies that are subsidiaries of the same company.

This concluded testimony on AB 436.

Testimony was then taken on AB 583 and SB 283.

AB 583 - Provides for certification of residential designers 3nder Nevada state board of architecture.

SB 283 - Provides for certification of draftsmen under Nevada state board of architecture.

The following persons were present to speak on the bill:

Mr. Joe Foley
Mr. Jack McCulloch
Mr. Clinton Wooster
Mr. Jim Joyce
Mr. I. R. Ashleman

Mr. McCulloch spoke for this group saying they have met together and have arrived at compromising amendments that will satisfy each of them. They have decided to amend SB 283 rather than AB 583. Chairman Robinson said if both the designers and the architects are in accordance with the amendments to be placed on SB 283, he asked that these amendments be submitted to the bill drafter.

This concluded the hearing for this date.

With regard to AB 455 regarding employment agencies, Mr. Getto moved that Amendment No. 7736 be adopted to AB 455, this was seconded by Mr. Demers and carried the committee. Mr. Schofield moved that AB 455 be "do passed as amended". This was seconded by Mr. Demers and carried the committee unanimously.

SB 84 was then brought up before the committee. Mr. Demers moved "do pass" of SB 84. This was seconded by Mr. Benkovich and carried the committee with Mr. Getto and Mr. Schofield not voting.

Mr. Wittenberg moved a "do pass" of SB 89. This was seconded by Mr. Demers and carried the committee with Mr. Schofield not voting.

Mr. Demers moved a "do pass" of SB 213. This was seconded by Mr. Hickey and carried the committee unanimously.

Mr. Demers moved that the minutes throught April 9 be adopted. This was seconded by Mr. Wittenberg and carried the committee.

The meeting was adjourned at 6:15 P.M.

Respectfully submitted,

Joan Anderson, Secretary

Note: Additional miscellaneous attachments regarding AB 436 submitted to the committee at this hearing have been compiled under separate cover.

ASSEMBLY

HEARING

0686

COMMITTEE ON COMMERCE

Date APRIL 16, 1975 Time 3:00 P.M. Room 316

Bill or Resolution to be considered	Subject
AB 436	Allows prescriptions for drugs designated by trade or brand name to be filled with less expensive drugs selected by generic name, unless otherwise specified.
AB 583	Provides for certification of residential designers under Nevada state board of architecture.
SB 283	Provides for certification of draftsmen under Nevada state board of architecture.

58TH NEVADA LEGISLATURE

0698

COMMERCE COMMITTEE
LEGISLATION ACTION

DATE April 16, 1975

SUBJECT AB 455 - Revises law governing private employment agencies.

MOTION: 1. Adopt Amendment No. 7736 X 2. Do pass as amended X

Do Pass _____ Amend _____ Indefinitely Postpone _____ Reconsider _____

Moved By 1. Getto 2. Schofield Seconded By 1. Demers 2. Demers

AMENDMENT: _____

Moved By _____ Seconded By _____

AMENDMENT: _____

Moved BY _____ Seconded By _____

	MOTION		AMEND		AMEND	
VOTE:	Yes	No	Yes	No	Yes	No
Robinson	x					
Harmon	x					
Demers	x					
Hickey	x					
Moody	x					
Schofield	x					
Wittenberg	x					
Benkovich	x					
Getto	x					

ORIGINAL MOTION: Passed X Defeated _____ Withdrawn _____

AMENDED & PASSED _____ AMENDED & DEFEATED _____

AMENDED & PASSED _____ AMENDED & DEFEATED _____

Attached to Minutes April 16, 1975

58TH NEVADA LEGISLATURE

0689

COMMERCE COMMITTEE
LEGISLATION ACTION

DATE April 16, 1975

SUBJECT SB 84 - Clarifies unlawful acts and increases penalties relating to architecture.

MOTION:

Do Pass X Amend ____ Indefinitely Postpone ____ Reconsider ____

Moved By Demers Seconded By Benkovich

AMENDMENT: ____

Moved By ____ Seconded By ____

AMENDMENT: ____

Moved BY ____ Seconded By ____

	MOTION		AMEND		AMEND	
VOTE:	Yes	No	Yes	No	Yes	No
Robinson	x					
Harmon	x					
Demers	x					
Hickey	x					
Moody	x					
Schofield	Not voting					
Wittenberg	x					
Benkovich	x					
Getto	Not voting					

ORIGINAL MOTION: Passed X Defeated ____ Withdrawn ____

AMENDED & PASSED ____ AMENDED & DEFEATED ____

AMENDED & PASSED ____ AMENDED & DEFEATED ____

Attached to Minutes April 16, 1975

58TH NEVADA LEGISLATURE

0700

COMMERCE COMMITTEE

LEGISLATION ACTION

DATE ~~April 16, 1975~~

SUBJECT SB 89 - Requires firms, partnerships, corporations and associations practicing as architects to have registered architect in residence responsible for work.

MOTION:

Do Pass X Amend ____ Indefinitely Postpone ____ Reconsider ____

Moved By Wittenberg Seconded By Demers

AMENDMENT: ____

Moved By ____ Seconded By ____

AMENDMENT: ____

Moved BY ____ Seconded By ____

	MOTION		AMEND		AMEND	
VOTE:	Yes	No	Yes	No	Yes	No
Robinson	x					
Harmon	x					
Demers	x					
Hickey	x					
Moody	x					
Schofield	Not voting					
Wittenberg	x					
Benkovich	x					
Getto	x					

ORIGINAL MOTION: Passed X Defeated ____ Withdrawn ____

AMENDED & PASSED ____ AMENDED & DEFEATED ____

AMENDED & PASSED ____ AMENDED & DEFEATED ____

Attached to Minutes April 16, 1975

58TH NEVADA LEGISLATURE

COMMERCE COMMITTEE
LEGISLATION ACTION

0701

DATE April 16, 1975

SUBJECT SB 213 - Increases penalty for furnishing a dangerous drug without a prescription and requires pharmacist to sign his name or initials on record for each refill of dangerous drug prescription.

MOTION:

Do Pass X Amend ____ Indefinitely Postpone ____ Reconsider ____

Moved By Demers Seconded By Hickey

AMENDMENT: ____

Moved By ____ Seconded By ____

AMENDMENT: ____

Moved BY ____ Seconded By ____

	MOTION		AMEND		AMEND	
VOTE:	Yes	No	Yes	No	Yes	No
Robinson	x					
Harmon	x					
Demers	x					
Hickey	x					
Moody	x					
Schofield	x					
Wittenberg	x					
Benkovich	x					
Getto	x					

ORIGINAL MOTION: Passed X Defeated ____ Withdrawn ____

AMENDED & PASSED ____ AMENDED & DEFEATED ____

AMENDED & PASSED ____ AMENDED & DEFEATED ____

Attached to Minutes April 16, 1975

GUEST REGISTER

0702

COMMERCE COMMITTEE

DATE: 4/16

ADDRESS & NAME	REPRESENTING	PLEASE CHECK IF YOU WISH TO SPEAK
RALPH A. CASAZZA	A.I.A. RENO	
Edward S. Pappas	A.I.A. RENO	
Jack Sheehan	A.I.A. RENO	
Harley Harmon	AIA Las Vegas	
Tom Roy	—	
RAY TREASE	CONSUMER AFFAIRS DIV.	
JOE LOWLER	" " "	✓ AB-436
Jan Gunman	State Fair Manager	AB-583
GENE CRAWFORD	AIA LAS VEGAS	
ERROL TILL	AIA LAS VEGAS	
Barbara Silverberg	Nevada Consumers League	✓ AB-436
David D. Goodhue	Public citizen	✓ AB 436
RAY HELLMANN	NEV. STATE BD. ARCHITECTURE	
ED HARDEN	NEV ASSOC OF ARCHITECTS	
Robert A. Fielden	American Institute of Architects	
ROBERT B. SIMPSON	MERICAN INSTITUTE OF ARCHITECTS	

GUEST REGISTER

~~0524~~ 0703

COMMERCE COMMITTEE

DATE: 4-16-75

ADDRESS & NAME	REPRESENTING	PLEASE CHECK IF YOU WISH TO SPEAK
STEVEN P BRADFORD, PHARMD	TITLE XIX	
~~GERALD HISE~~	ABBOTT LABS	
FRANK L. TIDUS	NEVADA STATE BOARD PHARMACY	
WALLY ROANHAUS	DIVISION FOR AGING	A-B 436 ✓
Larry A. FARNSWORTH	FARNSWORTH DRAFTING	
VIRGIL M. LARSEN	BLDG DESIGNERS LTD	
J.R. OLIVEIRA	CARSON CITY DESIGNER	
LEO J GRAY	MERCK SHARP DOHME	~~AB~~
ED GASSON	CIBA PHARMACEUTICAL CO	
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J WILLIAM SIMPSON	NEVADA ASSOCIATION OF AIA.	
DOMINGO CAMBEIRO	LAS VEGAS CHAPTER AIA	
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Robert Harris	American Institute of Architects	
H. Leslie Walker, FAIA	Chairman, Governmental Affairs Commission, A.I.A.	
FRED O. DOLVEN	NEVADA ASSOCIATION OF ARCHITECTS	

COULTER — EXHIBIT 3

news from the NATIONAL RESEARCH COUNCIL

070

The National Research Council was organized by the National Academy of Sciences in 1916 in order to provide for a broader participation by American scientists and engineers in the work of the Academy. The Academy was chartered by Congress in 1863 as a private organization with a responsibility for advising the Federal Government in science and technology. Since this responsibility is now shared with the National Academy of Engineering, organized in 1964 under the original NAS charter, the Research Council serves, in effect, as an operating agency for both academies.

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For further information call
Harry Weiss, (202) 389-6511

DRUG BOARD URGES CHANGE IN DRUG SUBSTITUTION LAWS

FOR RELEASE: P.M.'s, Tuesday, January 21, 1975

WASHINGTON--A physician should be required to give to, or explicitly withhold from, the pharmacist the option of substituting one brand of a drug he prescribes for another brand of the same drug--an option which could in many cases provide the same treatment at lower cost--according to a resolution of the National Research Council's Drug Research Board (DRB).

This "substitution" option is allowed by law in only two states--Florida and Michigan. In all others it is illegal for a pharmacist, without checking with the prescribing physician, to replace one brand with another even if both brands are known by the pharmacist to have been made in the same laboratory and even if one costs substantially less than the other, the DRB said in a background statement accompanying its resolution.

The DRB pointed out that "no inherent reason" exists for choosing the more expensive drug product simply because of brand-name familiarity. In the absence of any data indicating the substituted drug is not equivalent, then the pharmacist is "in the best position" to make the final choice, the Board said, with cost an element in the decision.

Following are the resolution and the background statement:

Resolution

WHEREAS, The patient's welfare should be the ultimate goal of statutes and regulations concerning drug product selection, which in operational terms means the best product for the lowest cost, and

WHEREAS, The physician must have the ultimate responsibility and authority in drug product selection, since he has the fullest knowledge of the patient's needs and responses with attendant obligation to be held accountable for his selection of particular drug products, and

-MORE-

COULTER EXHIBIT 1

0705

Sac. Bee 3/4/75

The Drug Name Game

If there had been a strong enough lobby for rubbing sticks, no doubt we wouldn't have matches today.

"Beware," the rubbing stick people would have cried through the halls of the legislature. "Matches will burn the fingers of innocent children, set bathrobes on fire, start forest fires."

Such scare tactics, amply financed and orchestrated with enough dramatic flare, would have kept stick factories working overtime and us, rubbing.

Powerful drug manufacturers have some of their top legislative persuaders "working the halls" of the State Capitol now with orders to defeat or weaken two bills aimed at ending California's antisubstitution laws regarding prescription drugs.

Essentially, the measures authored by Sen. Anthony Beilenson, D-Los Angeles, and Assemblyman Barry Keene, D-Eureka, would permit pharmacists to fill prescriptions generically, using the same chemical compound but not necessarily the same brand the doctor has written out on his pad.

The reason the two legislators have submitted the bills is simple: Filling prescriptions generically would save Californians millions of dollars a year.

The reason the drug manufacturers are battling the legislation also is simple: Their industry is the second most profitable in the nation — generic substitution would cut into those profits.

Drug companies spend more than $1 billion annually on promoting their products. The bulk goes to persuading physicians that requesting "Darvon," for example, instead of its generic name, "Propoxyphene HC1," is somehow a better way of doing things.

The painkiller Darvon, according to Consumers Union, wholesales for $7.10 per hundred capsules. The same painkiller when it is called Propoxyphene HC1 sells for $1.85.

Of the 409 drugs most frequently prescribed for older, lower-income patients — the average price when asked for by brand name is $4.11; when asked for generically, it is $2.02.

It is clear who the big losers are — the ones who can least afford it. The elderly make up 10 per cent of our population; they buy 23 per cent of our prescription drugs.

The industry claims brand names insure higher chemical quality and safer biological results. That scares people. "Generics" become synonymous with "bad pills."

The fact is, of 683 drugs recalled in 1973, 291 were brand names. Drug safety is an issue that must be dealt with. But it should not be allowed to muddle efforts to give Californians a financial break in the drug store.

The California Pharmaceutical Assn. — made up of druggists who know the situation well — support the bills of Beilenson and Keene.

Tomorrow morning, Keene's measure comes up before the Assembly Health Committee. The drug manufacturers will be there in force.

The question to be decided is gain.

Will it be the drug industry's? Or will Californians be given an opportunity to buy what they need at prices that are fair.

Table IV
(Continued)

DRUG	MANUFACTURER	DISTRIBUTOR	AVERAGE WHOLESALE PRICE (/c = per hundred)
Propoxyphene Cmpd 65 caps	Caribe Chemical	Progress Labs	$
		Towne, Paulsen & Co.	3.50/c
		Wolins	2.10/c
		West-ward	3.60/c
Propoxyphene Cmpd 65 caps	Mylan Labs	SKF	3.75/c
		Wolins	2.10/c
Tetracycline HCl caps 250 mg	Richlyn	Columbia Medical	1.60/c
		Richlyn	1.50/c
		Ladco	
		United Pharm.	
Tetracycline HCl caps 250 mg	Heather Drug	Wolins	1.92/c
		H. R. Cenci	2.85/c
Tetracycline HCl caps 250 mg	International Labs	First Texas Pharm.	16.47/M*
		Stayner Corp.	12.00/M*
Tetracycline HCl caps 250 mg	Rachelle Labs	Rachelle Labs	2.85/c
		Stayner Corp.	2.80/c
		Towne, Paulsen & Co.	1.50/c
		Progress Labs	
		Saron Pharmacal	
Tetracycline HCl caps 250 mg	Mylan Labs	A. H. Robins	3.25/c
		Towne, Paulsen & Co.	1.50/c
		Wolins	1.92/c
		Wyeth	2.06/c
		Invenex	
		Rexall	
		American Pharm.	
		Central Pharmacal	
		Hoack Labs	

* /M = per thousand

EXHIBIT 2

Table IV
(Continued)

DRUG	MANUFACTURER	DISTRIBUTOR	AVERAGE WHOLESALE PRICE (/c = per hundred)
Erythromycin Stearate Tabs 250 mg	Mylan Labs	Towne, Paulsen & Co.	$ 8.83/c
		Wyeth	9.35/c
		Progress Labs	
		Rexall Drug	
		Mallinkrodt	9.95/c
		Sherry Pharm.	5.70/c
		SKF	10.15/c
		Alliance	
Erythromycin Stearate Tabs 250 mg	Zenith Labs	West-ward, Inc.	8.30/c
		Zenith Labs	8.69/c
		Columbia Medical	8.45/c
		American Quinine	8.65/c
Erthromycin Stearate Tabs 250 mg	Abbott	Abbott	17.39/c
		Parke Davis	15.87/c
Penicillin G tabs 250 mg	Biocraft	H. R. Cenci Labs	
		Progress Labs	
		Stanlabs, Inc.	3.40/c
		Towne, Paulsen & Co.	2.30/c
		United Pharm.	
Penicillin G tabs 250 mg	Mylan Labs	Towne, Paulsen & Co.	2.30/c
		Alliance	
Penicillin VK tabs 250 mg	Biocraft	Progress Labs	
		A. H. Robins	6.60/c
		Stanlabs	
		West-ward	
Penicillin VK tabs 250 mg	Mylan Labs	Towne, Paulsen & Co.	4.70/c
		Sherry Pharm.	
Penicillin VK tabs 250 mg	John D. Copanos & Co.	Towne, Paulsen & Co.	4.70/c
		McKesson Labs	3.50/c
		Pfizer	8.32/c

EXHIBIT 2

EXHIBIT 2
COULTER

Table IV

MANUFACTURERS AND DISTRIBUTORS OF DRUG PRODUCTS

DRUG	MANUFACTURER	DISTRIBUTOR	AVERAGE WHOLESALE PRICE* (/c = per hundred)
Ampicillin Trihydrate caps 250 mg	Zenith Labs	American Quinine	$ 8.00/c
		Consolidated Midland	7.75/c
		Sherry	4.40/c
		West-ward	8.60/c
		Ladco Labs	
Ampicillin Trihydrate caps 250 mg	Biocraft	Columbia Medical	6.70/c
		Wolins	6.30/c
		H. R. Cenci	11.36/c
		United Pharmaceut	
Chloral Hydrate caps 500 mg	R. P. Scherer	H. R. Cenci Labs	1.60/c
		ICN Pharmaceut	1.60/c
		Invenex Pharm.	
		Ladco Labs	
		Life Labs	
		MSD	4.04/c
		Progress	
		Rexall	
		Squibb	5.00/c
		Stanlabs	2.15/c
		Stayner	1.60/c
		Towne, Paulsen & Co.	1.60/c
		United Pharm.	
		Alliance Labs	
		Hoack Labs	
		McKesson Labs	1.75/c
		Purepak Pharm.	1.48/c

*Average Wholesale Price from 1974 American Druggist Red Book

EXHIBIT 1

8020

WHEREAS, The pharmacist may, in some situations, have greater knowledge of drug products than other health professionals, including knowledge of both quality and costs, and

WHEREAS, It is appropriate that decisions with regard to the choice of drug products be made by the health professional possessing the greatest amount of information involved in the particular selection in question, with the attendant accountability, therefore be it

RESOLVED, That the physician, having selected the chemical entity to be used for therapy, should be required to delegate to the pharmacist, or explicitly to retain to himself, selection of the particular drug product to be dispensed and received by the patient.

Background Statement

Early in 1973, the DRB became interested in the question of the appropriateness of existing drug antisubstitution legislation and its relation to the final application of knowledge concerning drugs. Initially, the DRB considered that the antisubstitution laws which have existed in almost all of the states for several decades remain appropriate at the present time and protect the consumer from inferior products. At that time (early 1973), a resolution strongly endorsing continuation of antisubstitution legislation was considered by the DRB. However, subsequent meetings with representatives of various groups, especially the American Pharmaceutical Association (APhA), brought out important facts with which the DRB had not previously been familiar and which it believes most of the American public and American physicians are not aware of.

Perhaps most important is the fact that it is currently illegal for a pharmacist, often the last health professional to have contact with a patient prior to the latter's taking a prescribed drug, to substitute one brand of a given chemical entity for another (e.g., on the basis of lesser cost to the patient) even if both brands were manufactured in the same laboratory, when only the former brand is specified by the physician on the prescription. The DRB discussions concentrated on the knowledge or information, which goes into such decisions; and many of the discussions focused on how one is to deal with an absence of data on bioavailability and bioequivalence. The DRB did not consider that the cheaper of two drug products of the same chemical entity is necessarily the more desirable. However, in the absence of information to the contrary, it is unreasonable to assume that the less expensive is less desirable. In essence, the resolution finally adopted unanimously by the DRB asserts that, in the absence of data to the contrary, there is no inherent reason for choosing the more expensive drug product simply because of the familiarity of the physician or pharmacist with the brand name. It further asserts that the pharmacist may be the health professional most familiar with the details of cost, the one who has to deal with inventory and similar problems, and because of these, the physician should either delegate to the pharmacist the right to make the choice or explicitly reserve that right for himself.

The DRB resolution, in addition, emphasizes accountability of the health professionals involved--the physician and the pharmacist--for their decisions. For the physician, he must be prepared to defend his decision to restrict the dispensed drug product to the specific brand named in his prescription, should he choose to require such a restriction. For the pharmacist, he must be prepared to defend his substitution of a cheaper drug product than a brand named in the prescription, should substitution be permitted by the physician.

The DRB is aware that it changed its position during the calendar year 1973, so that the final position is almost exactly opposite to that it initially considered taking on this issue. The main reasons for this change were (1) learning that amendment of antisubstitution laws does not mean removing from the physician the prerogative of requiring a particular brand; (2) becoming aware of the data on source manufacturer of a number of different brands of some chemical entities (e.g., tetracycline and chloral hydrate, as recorded in the "Hearings before the Subcommittee on Small Business of the U.S. Senate, 93rd Congress, Second Session, etc., etc.," Part 24, February 20, 21, March 5, and 6, 1974); (3) examining the relative laws recently passed by the states of Florida and Michigan. An important unstated aspect of this issue, however, is the conspicuous absence of data or information of any sort for use by the health professionals in making such decisions, other than cost data. As stated above, however, the DRB decided that, in the absence of data indicating inequivalence, cost would often be the deciding factor; and the pharmacist is often in the best position to make this final choice.

The resolution was passed unanimously by the members of the DRB with one abstention, that of J. Richard Crout, director, Bureau of Drugs, Food and Drug Administration, whose agency has not taken an official stand on the issue. Chairman of the DRB is Frederick E. Shideman, head, department of pharmacology, University of Minnesota. Other members are Daniel L. Azarnoff, professor of medicine and pharmacology, University of Kansas Medical Center; James A. Bain, director, division of basic health sciences, Emory University; Mitchell B. Balter, chief, special studies section, psychopharmacology research branch, National Institute of Mental Health; Allan D. Bass, associate dean for biomedical sciences, Vanderbilt University School of Medicine; Paul Calabresi, physician-in-chief, Roger Williams General Hospital, Brown University; J. Richard Crout, director, Bureau of Drugs, Food and Drug Administration; Victor A. Drill, director, scientific and professional affairs, G.D. Searle & Co., Skokie, Illinois; Robert M. Hodges, vice president, research and development, Parke, Davis & Company, Ann Arbor, Michigan; Hugh H. Hussey, editor emeritus, American Medical Association, Chicago, Illinois; Werner Kalow, chairman, department of pharmacology, University of Toronto; Thomas D. Kinney, professor of pathology, Duke University Medical Center; Kenneth G. Kohlstaedt, professor of medicine, Indiana

University; Emanuel M. Papper, dean, University of Miami School of Medicine; James A. Pittman, Jr., dean, School of Medicine, University of Alabama; James M. Price, vice president, corporate research and experimental therapy, Abbott Laboratories, North Chicago, Illinois; David P. Rall, director, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina; and George W. Thorn, physician-in-chief, emeritus, Peter Bent Brigham Hospital, Boston, Massachusetts.

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SILBERLING
EXHIBIT 4

Testimony of the Consumers League of Nevada
AB 436
Carson City

April 15, 1975

0712

In the 1974 Consumers League of Nevada Prescription Drug Follow-up Report we recommended that a coalition of consumers and pharmacists review the anti-substitution regulation in Nevada and seek ways to repeal that regulation.

It was our belief that a full review of available comment on the subject would have culminated in legislation similar to AB 436.

We agree that generic drug usage will substantially reduce the cost of drugs to the consumer. We agree with the American Pharmaceutical Association that pharmacists should be permitted to select the source of supply of drugs they dispense, and that the pharmacist has a professional responsibility to determine that the drug products he dispenses are therapeutically effective.

Consumers are interested in obtaining the highest quality pharmaceutical services at the lowest possible cost. A substitution bill speaks to this request.

One way to prepare for substitution in the past has been the establishment of a public formulary, such as was done in Massachusetts in 1971. That listing was a result of a 1970 law which established a drug formulary commission in that state, charged with compiling and distributing a formulary or list of brand and generic name drugs no longer protected by patent rights, and considered by the Commission to be therapeutically equivalent. The Massachusetts formulary contains an alphabetical listing of more that 250 commonly prescribed brand names, each followed by its generic name.

We would suggest that there be a language change in subsection (1) which would give consumer assurance with the reliability of substitution. After the word "strength" — line 7 we would like to have added and THERAPEUTICALLY EQUIVALENT to, etc. Therapeutical equivalence is defined as "Chemical equivalence which, when administered to the same individual in the same dosage regime, will provide essentially the same efficacy and/or toxicity." (from the Drug Bioequivalence Study Panel Report, 1974). (pg vi)

On the question of therapeutic equivalence, the HEW task force report of 1969 stated "... on the basis of available evidence, lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health." The 1974 Kennedy-Mosher Report (referred to above- Drug Bioequivalence Study Panel Report) states that, "although the number of instances of demonstrable therapeutic inequivalence is small, the problem is an important one, and in the case of drugs with narrow margins of safety, assurance of bioequivalence is vital."

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We first planned to support this bill with an amendment to require, as a prerequisite to enactment, the establishment of a public formulary for Nevada. However, recalling the statement (APhA) of the American Pharmaceutical Association that they will assist states seeking legislation to allow for substitution, I contacted George Denmark, former President of the APhA and Carl Roberts, attorney for the APhA. Although the formulary approach was at one time considered the best avenue, I was told that this has not proven to be as useful as it had originally been hoped to be. According to Roberts it has been an unnecessarily expensive procedure and is now considered to be replaced by simpler, more effective approaches. It is his belief that the simplest, least costly way to apply the substitution concept is to rely on the judgment of the pharmacist. This kind of legislation, which is what we are considering here, has successfully passed in Michigan, Minnesota, Florida, and Maryland. It is on the verge of passage in California.

We agree with the APhA that the pharmacist should have "the right to select the drug product of the prescribed drug entity regardless of the brand name specified in the prescription, thus allowing him to act as the purchasing agent for the patient instead of the selling agent for the manufacturer."

I have heard some concern that pharmacists employed by chain stores often do not have a say in product selection from the various manufacturers. If this kind of substitution law is to work in the best interest of the patient, we believe that the pharmacist should be assured of protection of his right to use his professional judgment in drug selection, regardless of place of employment. The products from which he selects to dispense must be of the highest quality.

There is another direction possible, as demonstrated by the recent passage of a substitution law in Arkansas . This would direct itself to concerns of therapeutic equivalency. It requires that the state health officer develop, within 180 days, a list from which one could <u>not</u> substitute. If we were to consider this kind of action, we would like to have that listing compiled with imput somehow from the state pharmaceutical association, in addition to state or local health officer.

You are probably familiar with the resolution from the National Research Council of the National Academy of Sciences, supporting generic drug substitution. According to their statement issues January, 1975, "In the absence of any data indicating the substitute drug is not equivalent, then the pharmacist is in the best position to make the final choice," the Board said, "with cost an element in the decision."

It is essential that the physician be given the right to refuse to allow a substitution in a particular drug. This "override" has been a consistent factor in the legislation which has passed in other states. We would strongly urge that you add language to subsection (2) so that portion will read "... In his own handwriting." The importance of this particular phrasing has been stressed to avoid such problems as

- more -

pre-printed prescription tablets from drug manufacturers (stating, for example, NO SUBSTITUTIONS).

In summary, we agree to the need for this kind of legislation, and support it with the recommended language additions in subsections 1 & 2. We believe that the professional responsibilities of the pharmacist to his/her patient include his/her right to product selection and that the law, properly enacted, will serve as a valid means of reducing the cost of health care without sacrificing the high standards of health care.

Thank you for the opportunity to appear before you on this issue today.

Patricia van Betten, Health Chm., Consumers League of Nevada

Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, D.C. 20510

EMILIO Q. DADDARIO
DIRECTOR
DANIEL V. DeSIMONE
DEPUTY DIRECTOR

0715

For Further Information
Contact Dick Kirschten
202-225-0731

FACT SHEET

The Office of Technology Assessment is an advisory arm of the United States Congress. Its basic function is to help legislative policy-makers anticipate and plan for the consequences of technological change. OTA provides Congress independent and timely information about the potential effects and side-effects -- both beneficial and harmful -- of technological applications.

Established by the Technology Assessment Act of 1972, (Public Law 92-484), OTA's mission is to examine the many ways, expected and unexpected, in which technology affects people's lives. The assessment of technology calls for exploration of the physical, biological, economic, social and political impacts which can result from applications of scientific knowledge.

OTA consists of a nonpartisan Congressional board, comprised of six Senators and six House Members, which sets policy; a Director, who also is a member of the board; a Deputy Director and other officers and employees; and a 12-member citizens advisory council, which includes as ex-officio members the Comptroller General of the United States and the Director of the Congressional Research Service of the Library of Congress.

The chairmanship of OTA's Congressional board rotates between the Senate and the House in alternate Congresses. The current Board Chairman is Senator Edward M. Kennedy, Democrat of Massachusetts. The Vice Chairman is Congressman Charles A. Mosher, Republican of Ohio.

The Director of OTA is Emilio Q. Daddario, a former Member of Congress who was instrumental in the development of the Technology Assessment Act. The Deputy Director is Daniel V. DeSimone, a former White House science policy assistant. The Chairman of the citizens advisory council is Dr. Harold Brown, President of the California Institute of Technology. The Vice Chairman is Dr. Edward Wenk, Jr., of the University of Washington.

Early in 1974, OTA began its work for Congress by launching assessments in six areas; food, energy, the oceans, materials resources, health, and urban mass transportation.

CONGRESS OF THE UNITED STATES NEWS RELEASE

For Release After
10:30 a.m., EDT
July 12, 1974

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(202) 225-0731

OTA PANEL PROPOSES REFORMS TO ASSURE DRUG QUALITY

Reforms in Federal regulation are needed to improve the quality and uniformity of the drug products available to the American people, an Office of Technology Assessment study panel reported today.

The OTA panel issued specific recommendations, involving use of the best available technology, to create a system in which consumers will be able to rely upon chemically equivalent drug products to produce equivalent therapeutic effects.

Implementation of the panel's proposals, including establishment of an official list of interchangeable drug products, could lead to a reduction in the average cost of prescription drugs no longer covered by patents, the chairman of the assessment group told Congressional leaders.

The OTA assessment, the first to be delivered to Congress, was conducted by a Drug Bioequivalence Study Panel, comprised of ten leading scientists, under the chairmanship of Dr. Robert W. Berliner, Dean of the Yale University School of Medicine.

The study was authorized by the Technology Assessment Board, led by Senator Edward M. Kennedy, Chairman, and Congressman Charles A. Mosher, Vice Chairman, in response to a request from the Senate Committee on Labor and Public Welfare's Subcommittee on Health.

At issue before the Subcommittee is an Administration proposal to reimburse under the Medicare program for only the lowest priced available drugs deemed to be chemically equivalent under present standards.

The OTA panel reported, however, that the present standards as they currently are applied and enforced are not adequate to assure that drug products containing the same active ingredients can be depended upon to produce the same therapeutic effects.

The report cited studies of "a score or so of drugs in which it has been shown that there were differences in the concentration of the active ingredient in the blood following the administration of chemically equivalent products of different manufacturers."

Similar unequal therapeutic effects have been noted between drugs from different batches produced by the same manufacturer, the panelists said.

The OTA panel was critical of the present manufacturing guidelines of the Federal Food and Drug Administration and the current product standards contained in the nation's two offically recognized drug compendiums, the United States Pharmacopeia (U.S.P.) and the National Formulary.

Present Federal drug standards and regulations, according to the panel, are not sufficiently specific as to all steps of the manufacturing process and are not "in keeping with the potentialities of modern technology."

The Panel recommended the following reforms:

1. Establishment of new quality control standards and manufacturing guidelines for drugs, utilizing the best available technology and subject to continuing revision as technological changes occur.

2. Expansion of research to find improved methods of predicting the biological effects of drug products, particularly test methods involving animals or laboratory techniques which could reduce the need to use human test subjects.

3. Clarification of the Food and Drug Administration's authority to require drug-makers to keep records, and to require submission of information needed by the FDA to set drug standards.

4. Elimination of the grandfather clauses which exempt certain groups of drugs---products marketed prior to 1938 and 1962 (years when more stringent regulations took effect)---from current regulations.

5. Establishment of a single organization to replace the U.S. Pharmacopeia and the National Formulary, in their present form, as the official standard-setting organizations of the Federal Government.

The OTA panel's final recommendation, to be accomplished when the above recommendations have been implemented, calls for the creation of an official list of interchangeable drug products.

Such a list would enable consumers to shop for reliable drugs on a comparative-price basis.

The list would be divided into two classifications. The first, which

could be established quickly and would include a vast majority of drugs now 0843 on the market, would consist of drugs known to produce equivalent therapeutic effects despite variations in patterns of absorption into the bloodstream.

The second and much smaller class would consist of drugs for which evidence of precise biological equivalence is considered critical. Products in this category would be listed as interchangeable only after proof of their therapeutic and biological equivalence has been established.

Staff support for the study panel was provided by Family Health Care, Inc., Washington, D.C., under contract to OTA.

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Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, D.C. 20510

EMILIO Q. DADDARIO
DIRECTOR
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DEPUTY DIRECTOR

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BACKGROUND INFORMATION ON MEMBERS OF DRUG BIOEQUIVALENCE STUDY PANEL

ROBERT W. BERLINER, M.D., Chairman. Dr. Berliner, 59, was named Dean of the Yale University School of Medicine in 1973. He also serves on the faculty as a professor of physiology and medicine. He previously was associated for 23 years with the National Institutes of Health, serving from 1969 to 1973 as Deputy Director for Science. His principal field of research has been kidney disease and renal physiology.

FREDERICK C. ROBBINS, M.D., Ex Officio. Dr. Robbins, 57, is a member of OTA's Technology Assessment Advisory Council. He has been Dean of the Case-Western Reserve University School of Medicine since 1966. Dr. Robbins was co-recipient along with Doctors John F. Enders and Thomas H. Weller of the 1954 Nobel Prize in medicine and physiology, awarded for research involving growth of the poliomyelitis virus in tissue cultures, which led directly to the development of the Salk anti-polio vaccine.

LEIGHTON E. CLUFF, M.D. Dr. Cluff, 50 has been Chairman of the Department of Medicine at the University of Florida College of Medicine since 1966. He has specialized in immunology, allergies and infectious diseases. He has conducted extensive research in the area of adverse reactions to drugs.

JAMES T. DOLUISIO, Ph.D. Dr. Doluisio, 38, is Dean of the College of Pharmacy of the University of Texas at Austin. From 1967 to 1973, he was Assistant Dean and professor of pharmacy at the University of Kentucky College of Pharmacy. His fields of scientific interest include biopharmaceutics and physical pharmacy.

KENNETH L. MELMON, M.D. Dr. Melmon, 39, is Chief, Division of Clinical Pharmacology at the University of California Medical Center, San Francisco. He is a professor of medicine and pharmacology and a senior staff member of the Cardiovascular Research Institute at the University of California Medical Center. He has been a consultant with the Food and Drug Administration.

ALEXANDER S. NADAS, M.D. Dr. Nadas, 60, a pediatric cardiologist, is Chief of the Cardiology Department at Children's Hospital Medical Center, Boston. Since 1949, he has been associated with the pediatrics faculty of the Harvard Medical School. He has written extensively in the area of congenital heart disease.

JOHN A. OATES, M.D. Dr. Oates, 42, an intenist, is a pro fessor of medicine and pharmacology at Vanderbilt University, Nashville. Winner, in 1969, of award for "Outstanding Basic Pharmacologic Investigations in Man" from the American Society for Pharmacology & Experimental Therapeutics.

SIDNEY RIEGELMAN, Ph.D. Dr. Riegelman, 52, is a professor in pharmaceutical chemistry and Chairman of the Department of Pharmacy at the University of California College of Pharmacy, San Francisco. Winner, in 1970, of the American Pharmaceutical Association Foundation's Research Achievement Award in Pharmacodynamics.

FREDERICK E. SHIDEMAN, M.D., Ph.D. Dr. Shideman, 58, is both a physician and the holder of a doctorate in pharmacology. He is a professor and Head of the Department of Pharmacology at the University of Minnesota. He has worked in the field of drug abuse with the New York State Narcotic Addiction Control Commission, the U.S. Department of Justice and the Food and Drug Administration.

MARVIN ZELEN, Ph.D. Dr. Zelen, 47, is a specialist in biometry and mathematical statistics. He is Director of the Statistical Laboratory and a leading professor at the State University of New York at Buffalo. From 1963 to 1967, he was head of the Mathematical Statistics and Applied Mathematics Section at the National Cancer Institute, NIH.

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0722

REPORT OF THE

DRUG BIOEQUIVALENCE STUDY PANEL

TO THE

OFFICE OF TECHNOLOGY ASSESSMENT

CONCLUSIONS AND RECOMMENDATIONS

July 12, 1974

CONCLUSIONS AND RECOMMENDATIONS

~~0547~~

1
Current standards and regulatory practices do not assure bioequivalence for drug products.

2
Variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures. It is probable that other therapeutic failures (or toxicity) of a similar origin have escaped recognition.

3
Most of the analytical methodology and experimental procedures for the conduct of bioavailability studies in man are available. Additional work may be required to develop means of applying them to certain drugs and to special situations of drug use.

4
It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes should be based on clinical importance, ratio of therapeutic to toxic concentration in blood, and certain pharmaceutical characteristics.

5
Present compendial standards and guidelines for Current Good Manufacturing Practice do not insure quality and uniform bioavailability for drug products. Not only may the products of different manufacturers vary, but the product of a single manufacturer may vary from batch to batch or may change during storage.

6
New compendial standards for drug substances, excipients and finished drug products should be developed and revised on a continuing basis to reflect the best available technology to assure quality and uniform bioavailability. Appropriate statistical procedures should be specified to make certain that the purposes of the standards are objectively satisfied. The guidelines for Current Good Manufacturing Practice should be expanded to include specific descriptions of all significant aspects of manufacturing processes from the raw materials to the final product.

7
Additional research aimed at improving the assessment and prediction of bioequivalence is needed. This research should include efforts to develop in vitro tests or animal models that will be valid predictors of bioavailability in man.

8
Current law requiring manufacturers to maintain records and make information available to the FDA is ambiguous or inadequate and should be clarified and strengthened. In particular, manufacturers should be required to submit all information relating the tests they conduct to the bioavailability data they develop in order to help provide information on the factors that modify the bioavailability of drug products. This information should be available to aid in the establishment of compendial standards.

9
Exemptions provided in current law for some drug products based on their year of introduction in relation to amendments in the Food, Drug, and Cosmetic Act (so-called grandfather clauses) have impeded improvement in the quality of these products. Such exemptions should be climinated.

10
A single organization capable of setting standards adequate to assure the quality and uniform bioavailability of drug products should be established to replace the present USP and NF as the official standard-setting organization of the Federal Government.

11
A system should be organized as rapidly as possible to generate an official list of interchangeable drug products. In the development of the list, distinctions should be made between two classes of drugs and drug products:

1. Those for which evidence of bioequivalence is not considered essential and that could be added to the list as soon as standards of pharmaceutical equivalence have been established and satisfied.

2. Those for which evidence of bioequivalence is critical. Such products should be listed only after they have been shown to be bioequivalent or have satisfied standards of pharmaceutical equivalence that have been shown to assure bioequivalence.

OFFICE OF THE SECRETARY
ROCKVILLE, MD. 20852

EXHIBIT 6

OFFICE OF THE
GENERAL COUNSEL

September 16, 1974

0725

Carl Roberts, Esq.
Associate General Counsel
American Pharmaceutical Association
2215 Constitution Avenue, N. W.
Washington, D. C. 20037

Dear Mr. Roberts:

This is in response to your letter of July 23, 1974, relating to the work of the Panel on Drug Equivalence of the Office of Technology Assessment. Your letter arrived shortly before I left for vacation, and in any event before Dr. Riegelman could reply. Accordingly, I delayed responding until my recent return from vacation.

It is, of course, impossible for me to verify whatever discussion you may have had with Dr. Riegelman at the conclusion of the Congressional hearing, or to verify whether his oral views are shared by the Panel. Rather than discuss those issues, therefore, I will simply attempt to set out my own view on our legal authority.

As your letter points out, there are two independent means by which we may enforce standards of safety, effectiveness, and quality upon drugs. First, we may enforce the official compendia standards, which are limited to strength, quality, and purity. Second, we may independently enforce FDA standards relating to the broader aspects of safety, effectiveness, and quality (including good manufacturing practices). We have brought numerous court actions using both of these approaches, and have usually prevailed.

I informed the Panel that, although the FDA views GMP regulations as substantive and binding, the industry views them as mere guidelines. There is no definitive court opinion. In my opinion, the Panel was entirely correct in recommending that this should not remain a subject for litigation, but rather should be clarified by specific Congressional enactment.

I also concur with the Panel conclusion that the present drug GMP regulations are inadequate. FDA has been in the process of revising them to make them more specific, and to incorporate a stricter

#6

standard of manufacture. This process began before the OTA Panel was formed. Because of other priorities, it simply has not yet been completed.

0726

Finally, I concur in the judgment of the Panel that the compendial standards are presently inadequate. Even before I came to FDA, my knowledge of the compendial standards had led me to conclude that they were quite inadequate. Without attempting to go down each of the Panel conclusions and recommendations in detail, I would certainly concur with the thrust of the report. I concur with Dr. Riegelman that it is unfortunate that the compendia do not forthrightly recognize that, just as FDA can improve its regulations, the compendia can improve their standards.

This does not mean, of course, that the American drug supply is a total shambles. The American consumer is not receiving, on a daily basis, unsafe, ineffective, and poor quality drugs. It does mean, however, that all of us should promptly take steps to improve the present regulatory controls.

I do not believe that action only by the official compendia, or only by FDA, is the answer. If the official compendia were to disregard the Panel recommendations, the compendial standards would become relatively useless for purposes of regulatory control. Similarly, if FDA were to disregard the issues of bioequivalence and GMP standards, the best compendial standards might be ineffective.

If I were to differ from the Panel on any issues, it might be with respect to the failure of the Panel to reassure the public about the overall quality of drugs available in this country (particularly as compared with the rest of the world), and its unrealistically optimistic view on how quickly the type of work that it recommended could be undertaken and completed. Certainly, when one considers the number of drugs involved, the lack of resources available to this Agency, the number of equally important or more important competing priorities, the complexity of regulatory proceedings, and the time requirements for due process of law, the suggestion that the work could be completed within two years is wholly unrealistic. On the other hand, the overly optimistic estimate of the Panel does not detract from or undercut the validity of the recommendations it made.

Sincerely yours,

Peter Barton Hutt

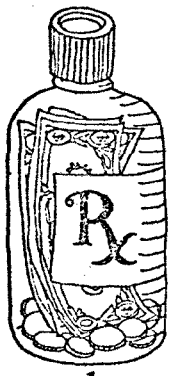
Peter Barton Hutt
Assistant General Counsel
Food and Drug Division

cc: Dr. Sidney Riegelman
Dr. Robert Berliner
Mr. Carl Taylor

EXHIBIT 1

from: Janice Goodlue
Box 462, Carson City
tel: 882-4935

0727



The cost of a prescription varies all around town. You may already know that. But did you know that it can vary in the same drugstore?

How to Pay Less for Prescription Drugs

At Congressional hearings last March, Senator Gaylord Nelson of Wisconsin told of the problems faced by one manufacturer of generic drugs—those marketed without a brand name. According to Senator Nelson, this manufacturer supplies a particular drug to a well-known company that resells it under a brand name. The manufacturer sells the identical drug by generic name directly to pharmacists at a small fraction of the price charged by the brand-name company. But the manufacturer has difficulty convincing physicians to prescribe the unbranded version. He tells them that the two drugs have been made by the same process, at the same plant, on the same day; he shows them photographs of the two products as evidence. But to little avail. Doctors still prefer to prescribe the higher-priced brand-name version. The manufacturer is considering inventing a brand name to slap on the label of his generic drug and boosting its price to the level of the more expensive version.

It may sound strange for a manufacturer to consider raising a price—rather than lowering it—as a way to stimulate sales. But in the topsy-turvy world of prescription-drug economics, it's not strange at all. A just-completed study of the price structure of the antibiotic market suggests that the manufacturer would be heading in a very profitable direction indeed.

One of every five prescriptions written in this country is for an antibiotic. Many antibiotics have been on the market long enough so that they no longer enjoy the monopoly advantage that patents give to new drugs. Widely used antibiotics can be divided into a relative handful of chemical types, many of which are sold both as brand-name drugs and as generics. Thus, if conditions for true price competition were ripe anywhere in the prescription-drug market, they would be ripe in the market for antibiotics. To determine how competition is working in the antibiotics business, Consumers Union helped finance a research study undertaken by the Council on Economic Priorities.

The Council on Economic Priorities (CEP) is a New York-based nonprofit organization that conducts research into the performance of corporations in such areas as environmental quality and consumer practices. Its antibiotic study,* to be released this month, focuses on the seven largest-selling antibiotics that are available from more than one manufacturer. These are penicillin VK, penicillin G, tetracycline, oxytetracycline, ampicillin, erythromycin, and chloramphenicol. To conduct its analysis, the CEP reviewed two important sets of figures compiled by IMS America, a market research firm. The first was each product's "average transaction price"—the average price at which the manufacturer sells the product to the pharmacist. (The price the consumer pays the pharmacist for a drug is generally about double that transaction price.) The second important statistic is the sales volume of each product.

The study's major finding: The brands of antibiotics that cost most dominate the market. More prescriptions are written for them than for similar or identical (but less expensive) competitors, and thus they have greater volume of sales, both in terms of units and of dollars.

Consider the case of penicillin VK. One of the most expensive brands of penicillin VK is Eli Lilly & Co.'s *V-cillin K;* it costs pharmacists $8.32 for 100 250-mg. tablets—its most common dosage form and package size. *V-cillin K* (in all its sizes and forms) has drugstore sales of more than $22-million, or 54 per cent of all sales of the drug. But druggists can also purchase 100 250-mg. tablets of penicillin VK from Sherry Pharmaceutical Co. for just $1.85. The sales of Sherry's penicillin VK—the least expensive one available—were under $300,000, and thus too insignificant to be listed by IMS America.

*"Resistant Prices: A Study of Competitive Strains in the Antibiotic Markets." A condensation of the study is available for $1 from: Council on Economic Priorities, 84 Fifth Ave., New York City 10011.

Sales of tetracycline present another case in point. Lederle Laboratories' *Achromycin V*, one of the most expensive tetracyclines, controls 29 per cent of the market. More prescriptions are written for it than for any other tetracycline. The cheapest tetracycline, sold by H. L. Moore Drug Exchange Inc. for less than one-quarter the price of *Achromycin V*, has insignificant sales.

The story is similar for ampicillin and erythromycin. The most expensive ampicillin, *Polycillin*, sold by Bristol Laboratories, controls the largest share of the market, 24 per cent. Pfizer Laboratories' ampicillin, called *Pen A*, is less than half the price of *Polycillin*—but it has only 8 per cent of the market.

Abbott Laboratories' *Erythrocin*, the highest-priced erythromycin product, controls 60 per cent of the market. Sherry's erythromycin, marketed to pharmacists for less than half *Erythrocin's* price, does not have significant sales.

If the above statistics indicate a problem with price competition in the market for those four antibiotics, consider the situation among the three remaining antibiotics: Squibb's *Pentids*, the most expensive penicillin G, has 78 per cent of the sales of penicillin G. Pfizer's *Terramycin*, the most expensive oxytetracycline, has 99 per cent of the sales of oxytetracycline. Parke, Davis & Co.'s *Chloromycetin*, the most expensive chloramphenicol, has 99 per cent of the sales of chloramphenicol.*

Evidently, certain pharmaceutical firms have the market power to charge a price higher than their competition and still maintain sales. The CEP has labeled that difference in price a "premium" that is granted to the larger firms. The premium is the difference between the lowest price at which the pharmacist can obtain the drug and the price charged by other suppliers of the same drug.

If Sherry can sell penicillin VK for $1.85, for example, that price must at least cover basic costs of manufacturing and distributing, or Sherry would be selling the product at a loss. It probably also includes some money for profit. The extra $6.47 that Lilly charges for penicillin VK is a premium, presumably covering research activities, promotion, and other expenses, plus added profit. That $6.47 premium accounts for 78 per cent of the total Lilly price of $8.32.

All told, the CEP estimates, at least 52 per cent of the $173-million spent by pharmacies for the seven antibiotics, when purchased from 11 major firms, was premium payment. That figures to more than $90-million in premium. Add normal pharmacy markups, and the premium paid by consumers is even greater. Apparently, most prescription dollars are not going for the medication *in* the bottle but for the name *on* it.

WHO'S AFRAID OF GENERIC DRUGS?

In CU's view, most premium dollars are wasted dollars. They contribute neither to the quality of prescription drugs nor to the health of drug consumers.

*There are clinical as well as competitive problems with chloramphenicol. Fatal cases of bone-marrow failure have been reported with use of that drug. Most medical authorities agree that chloramphenicol should be reserved for life-threatening infections. For a fuller report on the drug, see "The Peculiar Success of Chloromycetin," CONSUMER REPORTS, October 1970.

The large, high-premium pharmaceutical firms argue that their products are therapeutically superior to the products of other firms and are therefore worth a premium. Presumably, a firm selling under a brand name manufactures under its own controlled conditions and stands behind its own product. But things don't work that way in the real world of antibiotics, the CEP learned when it examined who manufactures what for whom.

Mylan Laboratories manufactures erythromycin in its final form for several firms, including Sherry, Smith Kline & French, Squibb, and Parke, Davis. Sherry's wholesale price for 100 250-mg. tablets is $5.70; Smith Kline & French's is $10.15; Squibb's is $11.83; and Parke, Davis' is $15.87. One manufacturer; four different prices.

The ampicillin marketplace is stranger still. One company, Zenith Laboratories, Inc., manufactures the final dosage form for six other companies, which then charge from $4.40 to $8.60 for 100 250-mg. capsules of the drug. Another manufacturer, Bristol Laboratories, puts up ampicillin for three firms, with price variation from $7.50 to $14.80. Oddly enough, the lowest price charged for the Bristol product, $7.50, and the highest price, $14.80, are both charged by the same firm, ICN Pharmaceuticals. The lower price is charged by its generic division and the higher price by its brand-name division. The same company can thus buy its product from the same source its competitors do, and then proceed to sell the product for less than its competitors—and for more.

Dr. Henry Simmons, former director of the Food and Drug Administration's Bureau of Drugs, offers further evidence that brand names don't signify better drugs. All antibiotics are batch-certified by the Food and Drug Administration (FDA) for potency, purity, and stability. "Based on many years of experience with this program," said Dr. Simmons, "we are confident that there is no significant difference between so-called generic and brand-name antibiotic products on the American market." On the basis of FDA studies of 19 other classes of drugs, "we cannot conclude there is a significant difference in quality between the generic and brand-name product tested." Dr. Simmons pointed out that defects have been encountered in both brand and generic products manufactured by big and small companies.

The Council on Economic Priorities examined recall data for antibiotics from January 1971 through July 1974. Those recalls indicate that major firms do not have a better record than small firms.

THE ECONOMICS OF EQUIVALENCE

But there is another question that bears on therapeutic superiority. The Pharmaceutical Manufacturers Association (PMA), an organization whose 110 member companies are responsible for approximately 95 per cent of all prescription-drug sales in this country, claims that products that are chemically equivalent (that contain the same amounts of the same active ingredients in the same dosage form) may not be *therapeutically* equivalent. That is, they may not be equally effective in treating the patient's disease.

An important factor in determining therapeutic equivalence is bio-availability—the amount of the product's active ingredient that is absorbed into the bloodstream to perform its function. Bio-availability may be affected by many fac-

tors, including particle size and shape, and the nature of the so-called inert ingredients contained in the drug product. If two drugs have the same bio-availability, they are termed bio-equivalent.

The scientific issue of bio-availability has generated a controversy in the drug industry because of its economic implications. If chemically equivalent drugs are also therapeutically equivalent, there would seem to be no reason for physicians to prescribe a brand-name drug with a "premium" price rather than a cheaper generic version.

The controversy became a significant public issue in December 1973, when Caspar Weinberger, Secretary of the Department of Health, Education, and Welfare (HEW) said his department planned to limit reimbursement for any drug under Medicare and Medicaid "to the lowest cost at which the drug is generally available unless there is a demonstrated difference in therapeutic effect." The reaction of the PMA was quick and critical. Its president, C. Joseph Stetler, termed the proposal a "huge gamble" that could endanger the health of the elderly and the poor. Beneficiaries of Medicaid and Medicare, he said, would be forced to accept drugs that were not therapeutically equivalent to established brand-name drugs.

To settle the issue, a report on drug bio-equivalence was prepared by a panel organized by the Office of Technology Assessment (OTA), a Congressional investigative body. The panel, chaired by Dr. Robert Berliner, Dean of the Yale University School of Medicine, found that variations in bio-availability *have* been demonstrated in chemically equivalent products in a number of drug categories. Those variations have been responsible for a few documented therapeutic failures. Most notably, several different brands of digoxin (a highly potent drug used for treating cardiac failure and certain abnormal cardiac rhythms) were found to differ in bio-availability. Levels of digoxin in the blood just twice as high as therapeutic levels can cause serious, even fatal, reactions. Too little digoxin can also be dangerous, as the dose is then inadequate for therapy. Digoxin is now undergoing batch-by-batch certification by the FDA, and every company marketing the drug must present evidence of bio-availability.

Differences in bio-availability, although not necessarily therapeutic inequivalence, have been documented for a number of other drugs, including diphenylhydantoin, an anticonvulsant; phenylbutazone, an anti-inflammatory drug; prednisone, a cortisone analogue; and tolbutamide, an oral hypoglycemic agent.

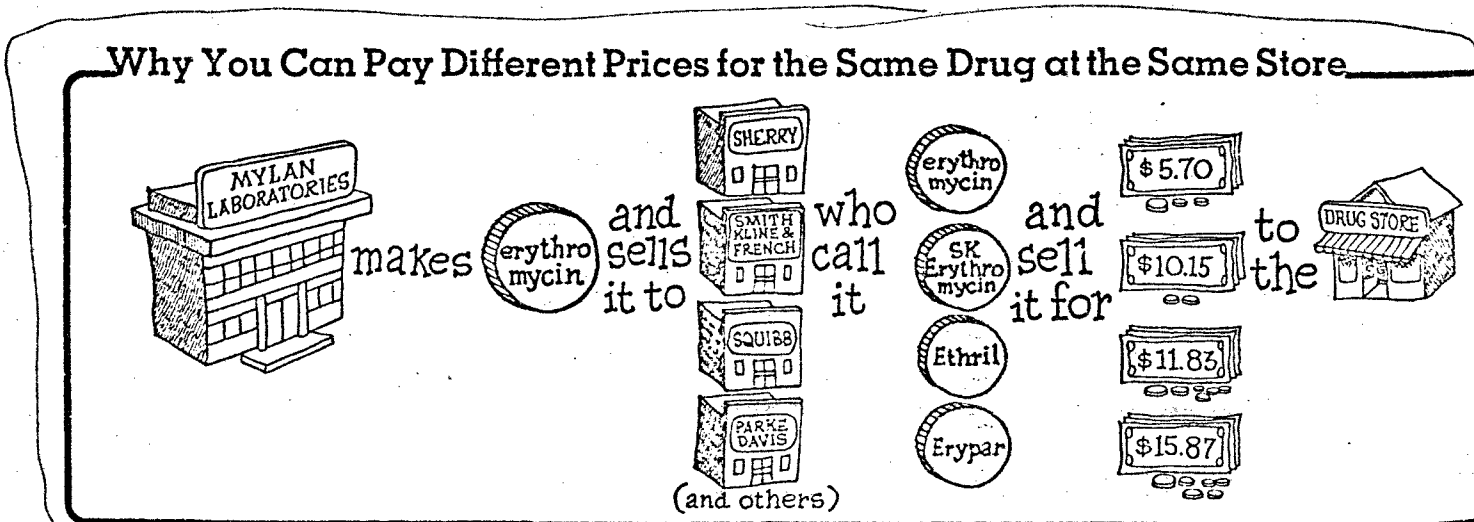
But for most drugs, the gap between therapeutic dose and toxic dose is wider than for digoxin, and any differences in bio-availability would not be so critical. The OTA panel concluded that the great proportion of chemically equivalent products—85 to 90 per cent, according to Dr. Berliner's estimate—presents no problems of therapeutic equivalency and could be used interchangeably. "Most drugs ought to be prescribed generically," Dr. Berliner told CU.

With the controversy over bio-equivalency at last put in perspective, HEW is now going ahead with its lowest-cost reimbursement plans. Formally proposed in mid-November, HEW's policy would establish a pharmaceutical reimbursement board to determine the maximum amounts the Government would pay for drugs under Federal and local health programs. Cost limits would be imposed only on drug products that do not present problems of therapeutic equivalency. According to Government officials, the policy could go into effect by this summer. Meanwhile, the FDA is planning to propose a regulation for identifying and listing inequivalent drugs and for requiring bio-availability data for any drug that is potentially inequivalent.

OTHER ARGUMENTS FOR BRAND NAMES

But high-premium firms have offered another justification for their premiums: The extra price helps cover the cost of the scientific work that goes into the development of new drugs. Basic scientific work is risky business, they contend, and high risk justifies high profits.

The profits have indeed been high. Over the past decade the drug industry has ranked as one of the two most profitable manufacturing industries in the country (the other is soft drinks). In 1973 the profit rate on stockholders' equity after taxes was 18.9 per cent for drug manufacturers, compared with 12.8 per cent for all manufacturing corporations. And the pharmaceutical industry had a 9.4 per cent return on sales, the second highest (after mining)



and more than double the average for all industries.

What about the risk? According to an HEW task force that studied prescription drugs, "The exceptionally high rate of profit which generally marks the drug industry is not accompanied by any peculiar degree of risk or by any unique difficulties in obtaining growth capital." The top firms have been remarkably stable, and their earnings have grown steadily—signs that the industry is relatively risk-free.

It is true that the prescription-drug industry spends heavily on research. According to the PMA, the drug industry spends five times as much of its sales income on research as does American industry as a whole. And the bulk of the research is done by large firms that sell brand-name drugs.

But the HEW task force was not overly impressed with the quality of that research. The task force characterized it as a "waste of skilled research manpower and research facilities," a "waste of chemical facilities needed to test the products," and judged it responsible for a "confusing proliferation of drug products which are promoted to physicians"—all of which results in a "further burden on the taxpayer who in the long run must pay the cost." In an FDA study of more than 800 drugs introduced in the U.S. between 1950 and 1973, two-thirds were found to represent little or no therapeutic gain over existing drugs.

The PMA estimated the cost of basic research (creating new chemical entities) at $100-million in 1971 and the cost of research and development as a whole (including modifying already existing drugs and testing drugs to meet FDA requirements) at $629-million. Those outlays sound high, but they don't measure up to the more than $1-billion the industry spends each year on promotion—persuading physicians that brand A is better than brand B, and that generic nonbrand X just doesn't do the job.

THE NAME GAME

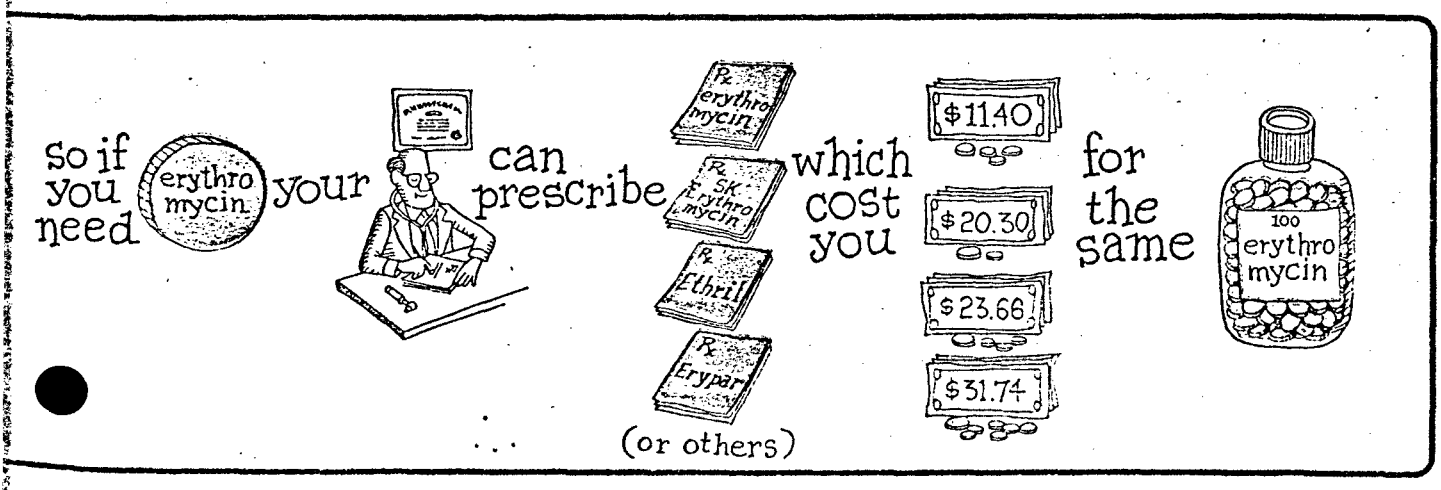
Companies that carry on research and develop new drugs should be rewarded for their contributions to medical progress and human welfare. And they are—by the patent system. The company that has developed a new drug enjoys for 17 years exclusive rights to produce and sell it and to license production and sales to other firms for a fee. (According to the PMA, the life of a patent is actually only 10½ years because of regulatory requirements that delay marketing after the patent has been granted. It's been estimated, however, that most patent drugs pay off the cost of research and development in their first three years on the market.)

Prices and premiums are generally highest during the time of patent-protected monopoly. But even after the patent expires, the original drug usually enjoys such a great advantage that effective price competition is stymied.

That advantage is rooted in the brand-name system. While a drug is undergoing clinical investigation, it is given its *generic* name by the United States Adopted Names Council (a semiofficial organization sponsored by the American Medical Association, the U.S. Pharmacopeial Convention, and the American Pharmaceutical Association). When the drug is ready for marketing, it is given its *brand* name by the pharmaceutical firm, and that name is registered as a trademark. In many cases, generic names are chemical tongue-twisters while brand names are short, simple, and catchy—designed to be remembered easily by physicians.

A patent-holder retains the right to the original brand name after the patent expires. Competing companies must invent their own brand names or market the drug under its generic name. But a drug by any other name doesn't sell the same. The patent-holder typically uses the patent period, and the revenues it derives from monopoly pricing, to mount a massive promotional campaign aimed not only at selling the drug under its brand name while the patent lasts but also at linking its name with the product permanently, so that physicians will continue to prescribe the drug by its original brand name long after the patent period has lapsed. Thus it is that doctors who want to prescribe a sleeping pill may well think first of *Nembutal*, the brand name that Abbott Laboratories pushed without competition for the length of its patent. The generic name, pentobarbital, may not even come to mind. Yet many smaller companies sell their versions of pentobarbital at a fraction of the price charged for *Nembutal*.

To try to catch up to the early favorite, manufacturers of equivalent brand-name products also spend large sums



on promotion. Like the manufacturer that holds the patent, they give presents to medical students and doctors; they sponsor medical conferences; they advertise in medical journals and magazines; they publish quasimedical literature in the form of newspapers and circulars.

At Senate hearings, 20 leading manufacturers said they distributed more than two billion free drug samples to physicians and other professionals in 1973. They also said they distributed some 13 million gifts valued at more than $5-million and 45 million "reminders," such as calendars and rulers, valued at more than $8-million. More than 3000 plant tours were conducted at a cost exceeding $748,000. According to testimony by former industry "detail men"—sort of door-to-door salespersons who promote drug products directly to physicians and pharmacists—freezers, color television sets, bicycles, and camping equipment were offered to doctors and druggists in return for prescribing or buying particular brand-name products.

The drug industry spends an average of $5000 per private practitioner to promote brand-name prescribing. As one result, although about 35 per cent of drugs are no longer under patent, only some 10 per cent of prescriptions are written generically rather than for a specific brand name. And yet brand-name drugs often cost five to ten times more than their generic counterparts—and sometimes up to 30 times more. According to T. Donald Rucker, former head of the Social Security Administration's drug studies unit, the high degree of product loyalty created by promotion directly to physicians is "a dominant factor enabling pharmaceutical manufacturers to exercise control over drug prices."

PRICE PRESSURE AT THE RETAIL LEVEL

That control is extended by antisubstitution laws. In most states, pharmacists must fill a prescription with the exact brand ordered by the physician, even though they may also stock a cheaper, equivalent version of the same drug. If a prescription is written generically, a pharmacist may fill it with either a brand-name or generic version of the drug. Some pharmacists apply a fixed service fee to the basic cost of the drug product. Others charge for their services by adding a fixed percentage to the cost of the prescription. The fixed-percentage markup encourages pharmacists to dispense a high-priced brand-name drug even when a doctor prescribes by generic name. Also, pharmacists can keep their inventory costs down by stocking only one or two of the largest selling brand names and using them to fill both brand-name and generic prescriptions.

Thus at each stage of the process that brings drugs from the scientist's laboratory to patients, there are restraints that limit price competition, keeping drug prices higher than they should be. The patent system provides protection for a new drug for 17 years; the brand-name system, bolstered by promotional blitzes and antisubstitution requirements, protects established, brand-name drugs after the patent period elapses. And retail practices may thwart any savings the doctor may make possible by prescribing generically.

CONGRESSIONAL PRESCRIPTIONS

Over the past few years, legislation has been introduced in Congress designed to compensate for business practices that keep the price of prescriptions drugs unrealistically high. There have been bills in both houses, for example, that would modify the patent system. Manufacturers of new drugs would be required to license other companies to make those drugs if exorbitant pricing practices occurred during the patent period. Legislation has been introduced in the Senate to ban drug-company gifts to physicians and pharmacists; establish a national drug testing and evaluation center; and require the Federal Government to publish a National Drug Compendium containing therapeutic and price information. The FDA has already begun work on a drug compendium, scheduled for publication in 1978. The FDA does not plan, however, to include price information—a serious omission, in CU's view.

A bill in the House would repeal all state antisubstitution laws. And a Senate bill would require prescription-drug labels to bear the manufacturer's name and address, so the person who takes the drug will know whether the brand-name distributor actually made the product.

Those measures all strike at features of the prescription-drug industry that are conducive to overpricing, and they all deserve consumer support. But the best legislative medicine for consumers is a bill that Senator Gaylord Nelson plans to reintroduce in the new Congress. It would eliminate brand names from prescription drugs. Under its provisions, a drug would be prescribed and sold under its generic name only, although a physician could still specify a particular *manufacturer* on a prescription. When no maker is singled out, the use of generic names should help the consumer purchase the least expensive equivalent drug the pharmacist has.

Such a law would help loosen the stranglehold that large, brand-name manufacturers have over the prescription-drug market. First of all, it would take the steam (and the expense) out of their promotional efforts. Why push a drug if a score of other companies are making the same drug and if there's no brand name to distinguish yours from theirs? And it would take the steam out of the antisubstitution laws that so often prevent consumers from obtaining cheaper, equivalent therapy.

The main goal of drug therapy, of course, is not lower prices but better health. Senator Nelson's bill would contribute to that goal by eliminating a source of therapeutic confusion. For every prescription drug there is an average of 30 names—aliases that can obscure the identity of the medication not only from patients but from prescribing physicians.

THE CANADIAN EXAMPLE

Canada, though far behind the U.S. in developing new drugs, is well ahead in developing ways to reduce drug prices. Canada passed a compulsory drug licensing law in 1969. Under it, a company can apply to the government for permission to produce a drug that is still under patent. And several Canadian provinces have passed "product selection" laws permitting pharmacists to substitute for a doctor's prescribed drug either a generic or brand-name equivalent.

In 1970, the province of Ontario implemented a unique, voluntary program called "Parcost" (Prescriptions at a Reasonable Cost). At its core is a Comparable Drug Index—listings of interchangeable drugs that have passed quality

tests and are arranged in order of descending price. Drug quality is evaluated by a committee of medical and drug experts who inspect manufacturing plants and analyze drug samples. Where an equivalency problem is discovered, the Index indicates that the products involved are not interchangeable.

When an Ontario pharmacist substitutes for a prescribed brand-name drug, the substitute product must be one listed in the Index and must be lower in cost than the prescribed product. A generically written prescription must be filled with the lowest-priced interchangeable drug in a pharmacist's inventory.

All Ontario druggists must abide by those substitution rules. More than half the pharmacists in Ontario have also agreed to charge the patient a fixed professional fee for dispensing rather than a percentage mark-up. (The dispensing fee is now set at $2.60.)

If nothing else, the program appears to have made Ontario physicians conscious of the cost of medications. In 1973, about one-third of the prescriptions for drugs marketed by more than one drug company were written generically, up 6 per cent from the year before. Another 31 per cent were written for brands lower in cost than the most expensive, up 2 per cent from 1972.

RECOMMENDATIONS

According to the Consumer Price Index of the Bureau of Labor Statistics, the price of prescription drugs in the U.S. has been rising at a much slower pace than other consumer goods. It has risen only about 4 per cent in the past year and 4½ per cent in the past five years. But those figures are deceptive. The CPI measures a relatively fixed "market basket" of drug products. It was not designed to reflect the impact of expensive new drugs that replace cheaper ones.

Until a rational drug marketplace is developed in the U.S., consumers must fend for themselves when buying prescription drugs. To help you cut prescription costs now, CU offers the following advice:

■ **Ask your doctor to prescribe a drug by its generic name.** As we noted earlier, generic drugs tend to be substantially less expensive than brand-name drugs. Although a pharmacist may not actually sell you the least expensive form of the drug, the CEP study uncovered this interesting fact: Pharmacists often charge less for a generic prescription than for a brand-name prescription *even when the same product from the same manufacturer is used to fill both.*

■ **Ask your doctor to specify the manufacturer who sells the cheapest equivalent product.** That will assure you the lowest-cost therapy, provided the druggist passes on the savings. Unfortunately, price information is not readily available to doctors. But they can try to obtain it by consulting pharmacists, pharmaceutical company representatives, and by obtaining catalogs from generic drug companies. Under the HEW reimbursement plan, price information would be published at least once a year for all physicians and pharmacists and made available to the general public.

■ **If you are going to continue a specific drug for a long period, ask your doctor to prescribe it in a large quantity.** Large-quantity prescriptions are generally more economical and will save repeated trips to the pharmacy. But be sure to check the expiration date of the product with the druggist. If the date will fall before you are scheduled to use up the drug, you should buy a smaller quantity. To preserve the life of a drug as long as possible, ask the pharmacist about the best method of storage.

■ **Shop around.** Numerous surveys, including CU's ("What's the Price of an Rx Drug," CONSUMER REPORTS, May 1970), have documented a wide difference in drug prices from store to store in the same city. But many states restrict retail advertising of prescription-drug prices. So you may have to shop for price. If you prefer to shop by telephone, you may be able to find out drug price information without leaving your home. Organizations that are interested in consumer issues may wish to conduct price surveys of commonly prescribed drugs at local pharmacies.

If it's not an emergency situation, ask a number of pharmacists the cost of a prescription before you have it filled. If it's a generic prescription without a manufacturer specified, ask for the least expensive version of the drug.

If you live in California, Michigan, Minnesota, New Hampshire, New York, Texas, Vermont, Washington, or the city of Boston, your drug shopping will be made somewhat easier by posters listing the prices of the top-selling prescription drugs (though you may have trouble ferreting out the posters in some stores). Price-posting is mandatory in Boston and those eight states; in some other states it is permitted but not required. If your prescription is for a drug not listed on the poster, you'll have to ask for its price.

Wherever you live, inquire about discounts sometimes given routinely to the elderly and to other special categories of patients—but first find out the standard consumer price.

While this report has emphasized drug prices, you should also consider what pharmaceutical services you want—credit, home delivery, personal attention, 24-hour availability in case of emergency, records of your purchases, for example. Such services may be available only at pharmacies that price prescriptions on the high side to cover the extra expense. Only you can decide if such services are worth higher prices.

QUOTE WITHOUT COMMENT

"'The political system is out of balance,' [said William K. Coors, president of Adolph Coors Co., a beer company, at a meeting of Rotarians]. 'And we find our fate increasingly in the hands of a few, relatively small but highly vocal, selfish, interest groups.' As examples of these groups, he cited organized labor, the environmentalists, and consumer groups. 'These groups . . . pursue their own interests with complete disregard for the impact of their wants on the rest of the economy. . . . And while they shout about the environmental impact of almost everything, they have no concern whatever for the economic impact of their corrective legislation.' Examples of what he termed the syndrome of overkill are the Pure Water Bill, the Occupational Safety and Health Act . . . and the probable future ramifications of the Consumer Product Safety Commission."—THE SACRAMENTO (CALIF.) UNION.

KIMBALL
EXHIBIT 8

SIGN UP SHEET -

SUPPORT BILL AB 436 -- Room 316 @ 3:00 PM - April 16, 1975

~~0850~~
0733

This Bill is for reduction of Drug Costs.

John J Nulty -
Aldina C. Partee
Frances Allen
Sam Friedman
M E Gall
Marie E Gall
Jack Gooch
Walter E Deighton
Ina T. Feeley
Lela M. Keller
Nathaniel H. Jones
Dolores L. Hughes
Elinor English
Ingrie Doyle
Pursey Pursey
Theodore W Pursey
Grant P Harris
Ruth Root
Dorothy Walker - Director Sr. Citizens Center -

Mildred Archer
Edwina Archer
George Archer

For Mr. Kimball - Rep. for Aging Services)

DRAFT

Share Committee

EXHIBIT 9

0734

In a speech before the United States Pharmacopeial Convention on March 22, Alexander Schmidt, M.D., the Commissioner of the Food and Drug Administration, took the U.S.P. and N.F. to task for having outdated drug standards.

Referring to the long-standing relationship of the U.S.P. and the Federal agency, he stated, "Traditionally, the U.S.P. has been the private developer (of drug standards) and the FDA has been the government enforcer...." but he continued, "We meet today in a time of change--many changes really--and all of them test us separately and together."

He stated he wanted to preserve this overlapping relationship of U.S.P. and FDA; however, he chided the convention of drug standard setters for not updating their standards.

"Regretfully, too many of the standards that now exist are inadequate or obsolete. A worse problem is that for all too many drugs no standards--obsolete or otherwise--are anywhere to be found."

"Without up-to-date drug standards, the FDA cannot properly do the work assigned it. More precisely, we cannot, without good standards, communicate to the regulated drug industry the conditions that this industry must meet in order to market drugs that live up to their therapeutic expectations."

Carefully couched in suggestions, he left unsaid the fact that the FDA can, at anytime, impose their own standards on the industry. Stating, "the standards we do have must be reviewed, improved and modernized. New public standards must be developed

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and implemented for the many older drugs which today are neither under NDA (Federal controls for safety and efficiency) nor covered by the U.S.P. or N.F. 0735

"This is an unacceptable gap in our system and it will be filled by someone, whether within government or under private auspices."

The implication is clear. Today the FDA cannot assure the uniform quality of drugs on the market because the system relies on a set of standards that are outmoded!! Unless the U.S.P. gets its house in order and rejuvenates their standards, the FDA will be forced to come up with their own set of standards.

He concluded with a commitment of FDA's willingness to work together in good faith, toward the goal of modernized standards. However, he could not resist stating once again, "But the job must be done...by both of us."

R E M A R K S

ALEXANDER M. SCHMIDT, M. D.
COMMISSIONER OF FOOD AND DRUGS

I am honored to be here and to take part in what I feel can be a truly significant meeting.

There have been many meetings of this Convention in years past, but in a very real way this year's meeting is a "first"! For here this weekend, in this place, you will be setting policy and choosing leadership for both the Nation's official drug compendia: The United States Pharmacopia and the National Formulary.

It seems to me especially appropriate that your meeting this year should begin with this second day of spring. Like the season, this is a time of change and transition for your organization. Change for you as for most of us is seldom the most comfortable condition. It brings with it anxieties and even turbulence. But it also brings new opportunities. This is especially true in the spring time with its promise of rejuvenation and renewal. I hope that the season in which you meet will lend strength and vigor to the difficult decisions you must face.

Presented March 22, 1975 before the Quinquennial Meeting of the United States Pharmacopeial Convention, Inc., Washington, D.C.

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This is my first visit to this Convention, but while I am new the association between FDA and the USP is old and deeply rooted.

In much more than a physicial sense, we have been neighbors for a long time. And for all this time, the affiliation between us has worked to the aid of the drug industry, the service of the practicing pharmacist and physician, and the benefit of the American public.

It is my wish that the affiliation between us should continue, and I see no overwhelming reasons that it should not.

We have many overlapping interests, and I could speak on any number of these today. But others wait to be heard and in the ten minutes or so that I have with you I will focus on what I think is the one essential topic upon which all of our relationships are founded.

That topic is drug standards. Traditionally, the USP has been the private developer and FDA has been the government enforcer of drug standards. It has been a good and useful arrangement. It still is!

But, as I said in the beginning, we meet today in a time of change -- many changes really -- and all of them test us separately and together.

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Let me give you a few examples:

Among the most bothersome changes perhaps is the fact that standard setting -- once a quiet and almost private effort -- has become a public issue.

People are watching where they once ignored. And they are watching with critical eyes.

This in itself gives me no reason to lose sleep. Public scrutiny is to me an entirely healthy, if not entirely comfortable, development.

A second change of significance is in the purposes and design of drug standards today as compared to those of our less complicated past.

Regretfully, too many of the standards that now exist are inadequate or obsolete.

A worse problem is that for all too many drugs no standards -- obsolete or otherwise -- are anywhere to be found.

Without up-to-date drug standards, the FDA cannot properly do the work assigned it. More precisely, we cannot, without good standards, communicate to the regulated drug industry the conditions that this industry must meet in order to market drugs that live up to their therapeutic expectations.

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The shape of what we seek in standard setting is easily described, less easily achieved. Our national drug standard setting system is simple in form. It requires only two kinds of drugs standards, public ones applicable to any drug manufacturer, and private standards in an NDA applicable only to the private license holder.

Because of the kinds of changes I have described, it seems clear to me that several important things need doing if we are to preserve the present system and at the same time improve the product of that system.

First, the standards we do have, NDA, USP and NF must be reviewed, improved and modernized.

Second, new public standards must be developed, proved and implemented for the many older drugs which today are neither under NDA's nor covered by the USP or NF.

This is an unacceptable gap in our system and it is a gap that eventually will be filled by someone, whether within government or under private auspices.

Third, all public standards must be publically promulgated by a process which is open and accountable. The evidence from which such standards are evolved must be available to all.

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Fourth, better in vitro standards must be found which are known to assure the bioequivalence of every batch meeting the standard.

Fifth, we must assure that all standards, whether developed from scratch or wrought through change of existing standards, must be responsive to the progress of technology -- to new instrumentation and to automation.

So much for what I think must be done. One might add or substract something here or there. One might debate priorities. But I think that most of us can agree on the general list of things to do.

The question really is not what needs doing so much as who will do it and how.

The now famous OTA Report says we ought to go back to square one and start all over with a brand new institution for standard setting. The idea is not without a following.

But, I believe that a better, more reasonable and less disruptive course is to continue if we can with the historical system we already have in place.

The recent merger of USP and the National Formulary is a big plus for preservation and I congratulate both

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organizations for this positive evidence of a combined determination to face the changes that today's world imposes.

There is only one absolute assurance I can give you here today: The FDA will continue to work with you in good faith and with commitment of its own resources to improve and, thus, preserve the traditional system as the first choice approach to solving the problems before us.

We believe in the fundamental integrity of our system and of the merits of its two dimensional approach -- one side setting and the other enforcing standards. But, the job must be done -- by both of us.

Because it is spring, because I believe in what we're attempting, and perhaps because I am an optimist -- whatever the season -- I look forward to the challenge we face in meeting the changes that must be made.

Together, I just feel we can do the job.

Thank you.

ROGERS

EXHIBIT 10

0742

Drugs: MAC program hits roadblock, may be dead --

HEW's Maximum Allowable Cost (MAC) program suddenly is in big trouble probably dead, but at least delayed indefinitely.

The death blow did not result from intense lobbying based on the program's costs; instead, it resulted from the realization by HEW that the Food and Drug Administration cannot insure that all generic drugs on the market meet the standards of FDA's intensive New Drug Application clearance system.

This inability by FDA was illustrated pointedly when a leading industry trade publication, "F-D-C" Reports, reported FDA's Bureau of Drugs Compliance Director Theodore Byers stated that FDA is "routinely allowing shipments" of generic drugs which have not received approval of Abbreviated New Drug Applications.

The Abbreviated New Drug Application (ANDA) system, about three years old, in effect allows a company to market a drug without going through the extensive New Drug Approval (NDA) system, as long as the original, equivalent product has been cleared through the Drug Efficacy Study Implementation (DESI) review, conducted by the National Academy of Science and the National Research Council. Under the ANDA system, a company does not have to wait for its application to be cleared; it can begin or continue marketing as soon as the application is filed. The system is quasi-legal, FDA considers it a stop-gap until its drug monograph setup is finalized.

Amazingly, this policy was not communicated to, or understood properly by, the MAC supporters within HEW, who now are dismayed to discover FDA cannot back up its assurances to them that the agency can guarantee all generic products on the market are quality products.

A consensus is developing within HEW that the government could not at this time win a lawsuit challenging the MAC program on the grounds that it provides for less than quality care for the poor and the aged in Medicare and Medicaid programs.

HEW apparently has two choices. It can drastically revise the MAC program, making it applicable only to antibiotics, because every batch of antibiotics is routinely checked for quality by FDA. Or, the MAC program could be dropped until FDA gets its long-awaited monograph program going. This program would establish monographs (long papers on exactly how each product must be made) for every product cleared through the DESI program. This is by no means imminent.

About the only certain result of this new MAC roadblock will be very thorough grillings of FDA and HEW officials by Senators Edward Kennedy and Gaylord Nelson, and very probably Rep. L.H. Fountain, whose House subcommittee has oversight authority over FDA. In the words of one high-ranking HEW official -- "the shit is really going to hit the fan" once Congress discovers MAC is stalled.

(Further information: Mark Melcher or Greg Valliere, 202/337-0110).

BASICS OF BIOAVAILABILITY

D. J. Chodos, M.D.
A. R. DiSanto, Ph.D.

Published by The Upjohn Company, Kalamazoo, Michigan

numbers at right of drug indicate study number. Studies are in numerical order on following pages.

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ROGERS 0744

EXHIBIT 11

TABLE I

DRUGS WITH COMPARATIVE BIOAVAILABILITY DATA AVAILABLE

INEQUIVALENCE—Drugs with Human Comparative Bioavailability Data Which Definitively Document or Suggest Differences Among Like Formulations of the Same Drug

Studies Which Definitively Document Differences Among Like Marketed Generic Oral Formulations		
acetaminophen (1-2)	diphenylhydantoin (84-94)	phenylbutazone (207-213)
acetylsalicylic acid (3-17)	erythromycin (96-120)	riboflavin (225-231)
ampicillin (22-34)	nitrofurantoin (152-161)	sulfadiazine (244-246)
chloramphenicol (35-45)	oxytetracycline (167-174)	sulfisoxazole (253-256)
chlordiazepoxide (46)	para-aminosalicylic acid (175-183)	tetracycline (259-277)
digoxin (63-83)		warfarin (295-297)
Subtotal=17		
Studies Which Demonstrate or Suggest Differences Among Any Other Like Oral Formulations		
aminophylline (18-19)	lincomycin (144)	phenylpropanolone (215)
aminorex (20)	lithium carbonate (145)	prednisone (216-220)
chlortetracycline (49-51)	medroxyprogesterone acetate (146-147)	propoxyphene (222)
cyanidanol (53)	methaqualone (148)	salicylamide (232-234)
dextroamphetamine (55-58)	norephedrine (162)	spironolactone (237-242)
diazoxide (59)	paracetamol (184-185)	sulfadimethoxine (247)
ethionamide (122)	penicillin G (186-192)	sulfameter (248)
griseofulvin (126-133)	penicillin V (193-198)	sulfathiazole (257)
hydrochlorthiazide (134-135)	pentobarbital (199)	theophylline (278-280)
hyoscyamine (136)	phenacetin (201-202)	thiamine (281)
indoxole (139)	phenylindanedione (214)	tolbutamide (285-291)
iron (140-141)		triampterene (292)
Subtotal=36		vitamin A (293-294)
Total=53		
Studies Which Demonstrate or Suggest Differences Only Among Like Parenteral Formulations		
	procaine penicillin G (221)	
Subtotal=1		
Total=54		
Studies Which Demonstrate or Suggest Differences Only Among Like Topical Formulations		
dexamethasone (54)	fluocinolone acetonide (124)	
Subtotal=2		
Total=56		
Studies Which Demonstrate or Suggest Differences Only Due to Salt or Ester Formation		
novobiocin (165-166)	quinidine (224)	
Subtotal=2		
Total=58		
Studies Where Only Clinical Data (Efficacy, Adverse Effects, etc.) Are Available Which Suggest Differences Among Like Formulations in Man		
amphotericin B (21)	indomethacin (137-138)	tetracaine (258)
cortisone acetate (52)	L-dopa (143)	thyroid (282-284)
dicumarol (60-62)	sodium salicylate (236)	
Subtotal=8		
Total=66		
Drugs With Only Animal Studies Which Demonstrate or Suggest Differences Among Different Formulations of the Same Drug		
methylprednisolone (150)	phenothiazine (204-205)	salicylic acid (235)
norethisterone (163)	quinalbarbitone (223)	sulfaethylthiadiazole (243)
Subtotal=7		sulfapyridine (252)
Grand Total=73		

INDETERMINATE—Drugs with only Indeterminate Human Comparative Bioavailability Data Available

chlorpromazine (47-48)	furosemide (125)	pentaerythritol tetranicotinate (200)
ephedrine (95)	methicillin (149)	phenethicillin (203)
estrone (121)	nicotinic acid (151)	phentermine (206)
ethylamphetamine (123)	noscapine (164)	

EQUIVALENCE—Drugs with Human Comparative Bioavailability Data Which Only Definitively Document or Suggest No Difference Among Like Formulations of the Same Drug

Studies Which Only Definitively Document No Difference Among Like Marketed Generic Oral Formulations	
isoniazid (142)	sulfamethizole (250-251)
Studies Which Only Demonstrate or Suggest No Difference Among Any Other Like Formulations	
sulfamethazine (249)	

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[redacted]

COMPARATIVE BIOAVAILABILITY REFERENCE LIST

0745

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*Definitive human studies available documenting inequivalence among formulations of marketed generic drugs.

**Clinical evidence for inequivalency among formulations.

††All studies available demonstrate equivalence among formulations.

†††Only animal data isolated.

#11

0753

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Fees and Prescription Charges 1963-1974 #12

0754

Price Indices

The Consumer Price Index (CPI) measures changes in prices of goods and services typically purchased by families with moderate incomes living in large urban areas (2). The most common cited measure of these prices is the composite index covering selling prices for all items included in the survey. This composite index is the Consumer Price Index frequently designated as CPI. But, in addition to the composite index, price indices are subdivided are published for the following commodity groups: (a) food, (b) housing, (c) apparel and upkeep, (d) transportation, and (e) health and recreation. All of the prices series used in this paper are included in the CPI, except the pharmacist's professional fees which are computed from the Kentucky Surveys (3).

Cost of Living Increases

Increases in the price indices for the four major categories reported in the CPI — those of medical care, food, apparel and upkeep, and housing — are presented in Table I. Examination of these data indicate that the overall cost of living has advanced by 60.3% from 1963 through November 1974. During this same period — and for the first time since 1963 — food prices have increased more rapidly (76.5%) than those for medical care (74.8%), apparel and upkeep (47.6% and housing (61.4%). In fact, since 1965, food and medical care have both increased at a rate of almost 1¼ times that of the overall average cost of living — while apparel and upkeep have increased at the rate ofonly ¾ that of the overall cost of living.

It is no surprise to the consuming public that the cost of living has risen rapidly in the last year. During the first 11 months of 1974, food alone, increased over 20%! In fact, the 21.5% increase in food for only the first 11 months of 1974 was greater than the 6 year increase from 1963 to 1969! During this same 11 month period medical care rose 12.8% apparel and upkeep rose 9.6% and housing rose 15.9% The overall cost of living increased 15.2% for the first 11 months in 1974.

The tragedy of "run away inflation" is the hardship imposed upon "fixed income" families. People depending upon social security and retirement incomes are finding it extremely more difficult to make ends meet.

The Pharmacist's Professional Fee

Much has been written about what the professional fee of a pharmacist should be under ideal circumstances and about what the fee is in terms of its current usage (4). The purpose of this paper is not to critique the professional fee issue. Rather, the authors are concerned with a measure of the charge by pharmacists for services rendered, which is comparable with similar charges of other professionals in the area of medical care.

Unlike physicians' fees, dentists' fees and optometrists' fees, there is no price index within the CPI that measures the professional fee of pharmacists (2). Additionally, data are not available for pharmacists fees from various national surveys (5-6). For this reason, the average professional fees for Kentucky pharmacists for 1963 through 1973 are included in Table III for comparison with the fees of other professions. Although national average fees for community pharmacists would be desirable, information of this type is not available. Additionally, data will not be available for the 1974 Kentucky Prescription Survey until April 1975.

The fees resulting from the Kentucky surveys are generally similar to pharmacists fees in other areas of the country (7). Since national fee data are not available, the fees resulting from the Kentucky Surveys are included for comparison purposes in Table III.

It should be noted that the Knetucky prescription surveys reflect the prescription charge regardless of the quantity of drug dispensed, while the CPI values are based on a price for a given brand, strength and quantity of drug. Although the measure of pharmacists' fees is conceptually comparable to the measure of other professional medical care fees, the sampling technique used for collection of data concerning pharmacist's fees differs from the technique used by the Bureau of Labor Statistics. However, differences between the rate of increase of pharmacists' fees and other fees used for comparison is so great, it is doubtful that the conclusions reached would be altered if there were small errors induced by various sampling techniques.

VARIATIONS IN MEDICAL CARE PRICES

Within the medical care industry there have been wide variations in the rate of price increases (8). This discussion will focus on a comparison of price indices of selected medical care service charges and professional medical care fees.

Medical Care Service Charges

Price indices of medical care service charges from 1963 through Nov. 1974, excluding professional fees, are presented in Table II. The base period for these indices is the annual average for 1963, except for the items otherwise noted — and for these items the base period is December 1963.

The item "all medical care charges" in Table II is a composite index of all Medical care service charges and professional fees, except for pharmacists' fees. This index is a weighted average rather than a simple mean of the price indices of the subgroups. Therefore, it is not possible to derive this value through an average of the subgroups in Tables II and III unless the appropriate weights are applied to all categories.

Service charges for hospital rooms increased more rapidly than did any other medical service. Semiprivate rooms increased in price by 191.6%. from 1963 through November 1974. The increase in operating room service charges was 156.1%, dental charges for dentures rose by 58.8%, and X-ray for upper G.I. series increased by 57.1% during this same time period.

In contrast to these large increases in the above medical care service charges, the drugs and prescriptions component has, on the whole, remained stable in price over the same period. Over-the-counter drug items increased by a modest 21.0% from December 1963 through November 1974, and prescription drugs actually declined by 1.8% during this period. Drugs and prescriptions are considered to have dampened, to some extent, the overall upward movement in medical care prices.

Medical Care Fees

In Table III, changes in professional fees of physicians', dentists', and other professional medical fees are compared over the period 1963 through November 1974. Kentucky pharmacists' fees are compared from 1963 through 1973. Examination of Table III indicates that physicians' fees have risen at the most rapid rate of 80.5% for the 1963 through November 1974 reference period. Dentists' fees were second with a 67.6% increase. Other professional medical fees included a

See "Fee" — Page 10

53.9% increase for optometrists' and 47.8% increase for routine laboratory tests for the same time period.

Studies by the authors indicates only a 23.1% increase in pharmacists' fees in Kentucky for the 1963 through 1973 period (3). Although the pharmacists' fees in Kentucky would vary from the fees of pharmacists in other areas of the country, the authors feel that the trend noted in Kentucky would be generally similar to that of other states over the 1963 through 1973 period. It is especially significant to note that while pharmacists' fees have risen only 23.1% since 1963 — food prices rose nearly this much (21.5%) in the first 11 months of 1974 alone!

STABILIZING FACTORS IN PHARMACY PRICES

According to a recent report of the Joint Economic Committee, the rapidly rising cost of medical care, can be explained partially by the following three factors:

(a) an increase in the quality of medical care,
(b) the process of bringing wages of hospital workers in line with wages of workers in comparable occupations, and
(c) the advent of medicare and medicaid programs (9)

The Committee report added: "These partial explanations of rising medical costs must not be allowed to mask the serious structural inefficiencies which exist in the health care industry and which will continue to cause excessive cost increases if they are not corrected" (9). It should be emphasized, however, that the Joint Economic Committee was referring to the overall increase in the cost of medical care. The wide range of price increases noted in this study is an indication that those forces causing price changes have not been uniform throughout the medical care industry.

The charges for retail pharmacy products and services have remained stable relative to other medical care charges. The reasons for this relative stability insight into the stabilizing forces in retail pharmacy.

Average salaries have increased faster for hospital workers than for workers in pharmacies over the period of study (10-11). For example, from 1963 through 1968 the increase in average earnings for pharmacy workers was smaller in 5 years than was noted in only 3 years for hospital workers (11).

Increasing competition has also influenced the stability of charge for pharmacy products and services. Many over-the-counter drug items which were formerly sold exclusively by pharmacies are now sold in non-pharmacy retail stores (12). Since these items are not the main line of business of non-pharmacy retail outlets, they are often sold at little or no markup — and sometimes even as a "loss leader". This increase in the intensity of competition has had some stabilizing effect on the price of over-the-counter drugs. Likewise, the sale of prescription drugs is competitive in most communities — far less competition, if any, exists with respect to most other types of medical care services.

Close government scrutiny of the drug industry is another factor that has played an important role in stabilizing prescription prices. Since the Kefauver hearings in the 1950's, there has been considerable public criticism of drug prices. This criticism seems to be unwarranted in recent years as evidenced by the stability of retail and wholesale drug prices (2).

Other factors probably have been important in stabilizing pharmacy prices. One would expect that medicare and medicaid programs have had a lesser impact on the demand for over-the-counter and prescription drugs than they have had on the demand for other types of medical care — particularly hospital facilities and physicians' time.

SUMMARY AND CONCLUSIONS

For the first time since 1963 food prices have increased more rapidly (76.5%) than those for medical care (74.8%), apparel and upkeep (47.6%), and housing (61.4%). Food and medical care have both increased at a rate almost 1¼ times that of the overall average cost of living (60.3%). The overall cost of living has increased by 60.3% since 1963 — with a 15.2% jump in the first 11 months of 1974.

There were considerable differences in the rate of price increases among various types of medical care service charges within the medical profession. At one extreme, semi-private rooms increased in price by 191.6% from 1963 through November 1974 — while at the other extreme, the prices of drugs and prescriptions increased by only 8.3% over this same period. **Prescription prices actually decreased by 1.8% for this same period.** Dental charges for dentures (full upper) increased by 58.8%.

Considerable differences were also noted among various medical care fees. For example, the composite index of physicians' fees rose by 80.5% from 1963 through November 1974 — with an increase of 14.2% for the first 11 months of [redacted]one. Kentucky pharmacists' fees increased by only 23.1% from 1963 through December 1973. Dentists' fees, optometrists' fees, and charges for routine laboratory tests increased by 67.6%, 53.9% and 47.0% respectively over the 1963 through November 1974 period.

The wide variation in the rate of increase for medical care service charges (Table II) and professional medical care fees (Table III) is only a manfiestation of underlying economic and social forces. The pressure of these forces varies within the medical care industry. Regardless of the casuality — **the only two groups to remain relatively stable** over the period covered were the price of drugs and prescriptions, and pharmacists' fees as represented by the Kentucky Prescription Surveys.

As a result of this study, prescription are considered to be a "best buy" when compared with charges for other goods and services.

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EXHIBIT 12

0756

TABLE I

PRICE INDICES OF MEDICAL CARE, FOOD, APPAREL AND UPKEEP, HOUSING AND ALL ITEMS 1963 THROUGH 1974

Item	1963[a]	1964	1965	1966	1967	1968	1969	1970	1971[g]	1972[g]	1973	1974[h]	% Increase 1963-1974
Medical care, all[b]	100.0	102.1	104.5	109.1	116.8	123.9	132.5	140.9	150.0	154.8	162.0	174.8	74.8
Food[c]	100.0	101.2	103.5	108.7	109.6	113.4	119.4	126.0	129.8	135.4	155.0	176.5	76.5
Apparel and upkeep[d]	100.0	100.9	101.9	104.6	108.8	114.6	121.3	126.2	130.4	133.1	137.0	147.6	47.6
Housing[e]	100.0	101.1	102.4	104.8	107.8	112.4	119.5	128.2	134.1	139.4	145.5	161.4	61.4
All items[f]	100.0	101.3	103.0	106.0	109.0	113.3	119.7	126.8	132.3	136.6	145.1	160.3	60.3

Source - Monthly Labor Review, U.S. Department of Labor, Bureau of Labor Statistics, various issues.

a. Original indices were reported with the 1967 average as the base period. These indices were shifted to base 1963 for convenience.
b. Covers all forms of medical care including drugs, hospital charges, prescriptions, etc.
c. Includes food consumed away from home (restaurants, cafeterias, etc.) as well as food purchased for consumption in the home.
d. Includes all clothing, footwear and apparel services (i.e., drycleaning).
e. Covers shelter, fuel and utilities, household furnishings and operations.
f. The comprehensive index representing all items listed in the "Consumer Price Index for Urban Wage Earnings and Clerical Workers."
g. Government price controls went into effect on August 15, 1971 and extended through 1972. The increases in this period are due to the fact that not all items or all of the businesses were subjected to price controls.
h. Data for 1974 through first 11 months only.

TABLE II

PRICE INDICES OF SELECTED MEDICAL CARE SERVICE CHARGES FOR 1963 THROUGH 1974

Item	1963	1964	1965	1966	1967	1968	1969	1970	1971[c]	1972[c]	1973	1974[d]	% Change 1963-1974
All Medical Care Charges	100.0[a]	102.1	104.5	109.1	116.8	123.9	132.5	140.9	150.0	154.8	162.0	174.8	+ 74.8
1. Selected hospital charges													
a. Semiprivate rooms	100.0[a]	104.7	110.6	121.7	145.7	165.6	187.6	211.8	237.6	253.4	265.3	291.6	+191.6
b. Operating rooms	100.0[b]	101.9	106.4	113.9	128.4	143.2	165.2	182.8	200.6	216.5	230.0	256.1	+156.1
c. X-ray, diagnostic series (upper G.I.)	100.0[b]	100.7	102.1	105.7	112.3	117.1	122.7	130.5	140.3	145.0	148.0	157.1	+ 57.1
2. Dental charges, dentures (full upper)	100.0[b]	101.7	104.6	107.6	113.4	120.3	127.4	134.1	141.6	146.6	150.4	158.8	+ 58.8
3. Drugs and prescriptions	100.0[a]	99.7	99.4	99.7	99.2	99.4	100.5	102.6	104.6	104.8	105.1	108.3	+ 8.3
a. Prescriptions	100.0[a]	98.7	97.6	97.4	95.7	94.1	95.3	96.9	96.9	96.6	96.2	98.2	- 1.8
b. Over-the-counter drugs	100.0[b]	100.6	101.3	102.4	103.4	106.0	106.9	109.8	113.9	115.1	116.2	121.0	+ 21.0

Source - Monthly Labor Review, U.S. Department of Labor, Bureau of Labor Statistics, various issues.

a. Original indices were reported with the 1967 average as the base period. These indices were shifted to base 1963 for convenience.
b. Base period is December 1963; data are not available for entire year of 1963.
c. Government price controls went into effect on August 15, 1971 and extended through 1972. The increases in this period are due to the fact that not all items or all of the businesses were subjected to price controls.
d. Data for 1974 through first 11 months only.

RODGERS
EXHIBIT 13

0757

Page 15

MANITOBA

REPORT

OF

THE ADVISORY COMMITTEE ON

CENTRAL DRUG PURCHASING AND DISTRIBUTION

PROVINCE OF MANITOBA

APRIL, 1972

#13

[redacted]

0758

MANITOBA

ADVISORY COMMITTEE ON CENTRAL DRUG PURCHASING AND DISTRIBUTION

316 Norquay Building,
York & Kennedy,
Winnipeg 1, Manitoba.
Telephone: 946-7791

Honourable Edward R. Schreyer,
Premier of Manitoba, and
President of the Executive Council,
Room 204, Legislative Building,
Winnipeg 1, Manitoba.

Sir:

In accordance with instructions of your Government as established by Order-in-Council 62/71 dated January 27, 1971 (with attached Terms of Reference) and the subsequent modifications by Orders-in-Council 368/71, 370/71, 664/71, 707/71, 1128/71, we are honoured to submit our Final Report embodying our conclusions and recommendations regarding Central Purchasing and Distribution of Prescription Drugs for the Province of Manitoba.

We have the honour to be,

Sir,

Your obedient Servants,

(Signatures follow:)

#13

0759

AD

MANITOBA

ADVISORY COMMITTEE ON CENTRAL DRUG PURCHASING AND DISTRIBUTION

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#13

0760

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#13

0761

TABLE I

SUMMARY OF FOREIGN DRUG PROCUREMENTS BY
U.S. DEFENCE SUPPLY AGENCY,
DECEMBER 1959 – APRIL 1964

Product (official title)	Number of contracts	Total dollar value of foreign contracts	Total dollar value if domestic	Dollar savings per product
Tetracycline	23	$6,537,488.00	$14,352,292.69	$ 7,814,804.69
Meprobamate.....	8	1,151,573.52	7,585,903.99	6,434,330.47
Nitrofurantoin	9*	717,132.48	2,181,996.48	1,464,864.00
Sulfadiazine	3	589,562.00	983,254.08	393,692.08
Chlortetracycline	4	440,234.88	970,752.00	530,517.12
Oxytetracycline	1	358,502.40	581,529.60	223,027.20
Tetracycline syrup ..	1	88,646.40	106,047.36	17,400.96
Total	48	$9,883,139.68	$26,761,776.20	$16,978,636.52

*Includes two contracts for which no domestic offer was received.

SOURCE: Clapp, *op cit* p. 25

As this table shows, the U.S. Defence Supply Agency through bulk purchasing from foreign sources was able to realize a savings of approximately $17 million within a period of five years for a savings of 63 per cent.

5. The Alberta Amendment

In 1962 the Province of Alberta legislated the following amendment in the Alberta Pharmaceutical Association Act:

> *Section 45 "where a prescription refers to a drug or drug combination by a brand name or a name other than its generic name, a pharmaceutical chemist, in dispensing the prescription, may use a drug or drug combination in its generic or brand name equivalent of that named in the prescription, unless the prescriber indicated otherwise,*
>
> *(a) by designating the name of the manufacturer or*
> *(b) by specifying that no equivalent is to be dispensed.*
> *(1962, c. 61, s. 3)*

At the time of this enactment, it was anticipated that a substantial decrease in the cost of prescriptions would follow.

The Advisory Committee has examined the record and can find no evidence that the average cost of prescriptions had been reduced in the Province of Alberta. Indeed, the average price of a prescription in Alberta leads all other provinces and in 1970 was $4.46 compared with the nation-wide average of $3.89. [23]

Although this amendment is a step in the right direction, it is halting and limited in its effect. The phrase "no substitution" appearing on the face of the prescription has blocked change in prescribing habits and defeated the purpose of the legislation. It seems

23 See page 76.

ASSEMBLY ACTION	SENATE ACTION	ASSEMBLY / SENATE AMENDMENT BLANK
Adopted ☐	Adopted ☐	Amendments to Assembly / Senate
Lost ☐	Lost ☐	Bill / Joint Resolution No. 455 (BDR 53-1020)
Date:	Date:	0762
Initial:	Initial:	
Concurred in ☐	Concurred in ☐	Proposed by Committee on Commerce
Not concurred in ☐	Not concurred in ☐	
Date:	Date:	
Initial:	Initial:	

Amendment No. 7736

Amend sec. 3, page 1, by deleting lines 16 and 17 and inserting:

"~~(c) Upon determining that the applicant is a resident of this state; and~~".

Amend sec. 3, page 1, line 20, by inserting after "2." and before "A" the following:

"The labor commissioner shall complete his investigation of the applicant within 60 days after such applicant has submitted his application.

3.".

Amend sec. 3, page 1, line 24, by deleting "3." and insert: "4.".

Form 1a (Amendment Blank) 3044A Drafted 4-10-75 By JNX (more) To Journal (3) CFB

Amendment No. 7736 to Assembly Bill No. 455 (BDR 53-1020) Page 2

Amend sec. 10, page 4, by deleting lines 10 and 11 and inserting:

"(b) Proof that the applicant is a resident of this state.".

ASSEMBLY

HEARING

0764

COMMITTEE ON COMMERCE

Date APRIL 18, 1975 Time 3:00 P.M. Room 316

Bill or Resolution to be considered	Subject
AB 513	Alters composition of state board of pharmacy.
AB 515	Increases district court reporter fees.
AB 539	Permits registered representatives to offer subdivision land for sale.
AB 595	Provides for regulation of property appraisers and makes an appropriation.
ACR 42	Directs commissioner of insurance to investigate adequacy of prepaid comprehensive health programs offered in Nevada and, where appropriate, to inform public of misleading advertising or inadequate programs.

I.P.
DO PASS

TALLY OF BILLS IN COMMITTEE

ASSEMBLY COMMERCE COMMITTEE

58TH SESSION

AS OF April 18, 1975

Bills

Assembly Bills	106	
Assembly Joint Resolutions	5	
Senate Bills	9	
Senate Joint Resolutions	1	
Assembly Concurrent Res.	1	122

Passed by Committee

Assembly Bills	31	
Assembly Joint Resolutions	2	
Senate Bills	5	
Senate Joint Resolutions	1	
Assembly Concurrent Res.	0	39

Indefinitely postponed

Assembly Bills	3	
Assembly Joint Resolutions	0	
Senate Bills	0	
Senate Joint Resolutions	0	
Assembly Concurrent Res.	0	3

Hold for consideration

Assembly Bills	21	
Assembly Joint Resolutions	0	
Senate Bills	3	
Senate Joint Resolutions	0	
Assembly Concurrent Res.	1	25

Bills scheduled for hearing

Assembly Bills	10	
Assembly Joint Resolutions	1	
Senate Bills	0	
Senate Joint Resolutions	0	
Assembly Concurrent Res.	0	11

Bills not scheduled for hearing

Assembly Bills	41		
Assembly Joint Resolutions	2		
Senate Bills	1		
Senate Joint Resolutions	0		
Assembly Concurrent Res.	0	44	122

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MANITOBA

REPORT

OF

THE ADVISORY COMMITTEE ON

CENTRAL DRUG PURCHASING AND DISTRIBUTION

PROVINCE OF MANITOBA

APRIL, 1972

0767

MANITOBA

ADVISORY COMMITTEE ON CENTRAL DRUG PURCHASING AND DISTRIBUTION

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F.R.C.S. (EDIN.) F.R.C.S.(C)
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John R. Troniak

TABLE I

SUMMARY OF FOREIGN DRUG PROCUREMENTS BY
U.S. DEFENCE SUPPLY AGENCY,
DECEMBER 1959 – APRIL 1964

Product (official title)	Number of contracts	Total dollar value of foreign contracts	Total dollar value if domestic	Dollar savings per product
Tetracycline	23	$6,537,488.00	$14,352,292.69	$ 7,814,804.69
Meprobamate.....	8	1,151,573.52	7,585,903.99	6,434,330.47
Nitrofurantoin	9*	717,132.48	2,181,996.48	1,464,864.00
Sulfadiazine	3	589,562.00	983,254.08	393,692.08
Chlortetracycline	4	440,234.88	970,752.00	530,517.12
Oxytetracycline	1	358,502.40	581,529.60	223,027.20
Tetracycline syrup ..	1	88,646.40	106,047.36	17,400.96
Total	48	$9,883,139.68	$26,761,776.20	$16,978,636.52

*Includes two contracts for which no domestic offer was received.

SOURCE: Clapp, *op cit* p. 25

As this table shows, the U.S. Defence Supply Agency through bulk purchasing from foreign sources was able to realize a savings of approximately $17 million within a period of five years for a savings of 63 per cent.

5. The Alberta Amendment

In 1962 the Province of Alberta legislated the following amendment in the Alberta Pharmaceutical Association Act:

> *Section 45 "where a prescription refers to a drug or drug combination by a brand name or a name other than its generic name, a pharmaceutical chemist, in dispensing the prescription, may use a drug or drug combination in its generic or brand name equivalent of that named in the prescription, unless the prescriber indicated otherwise,*
>
> *(a) by designating the name of the manufacturer or*
> *(b) by specifying that no equivalent is to be dispensed.*
> *(1962, c. 61, s. 3)*

At the time of this enactment, it was anticipated that a substantial decrease in the cost of prescriptions would follow.

The Advisory Committee has examined the record and can find no evidence that the average cost of prescriptions had been reduced in the Province of Alberta. Indeed, the average price of a prescription in Alberta leads all other provinces and in 1970 was $4.46 compared with the nation-wide average of $3.89. [23]

Although this amendment is a step in the right direction, it is halting and limited in its effect. The phrase "no substitution" appearing on the face of the prescription has blocked change in prescribing habits and defeated the purpose of the legislation. It seems

23 See page 76.

legalized substitution

1. The present law requiring the pharmacist to fill the prescription exactly as specified by the physician is basically a consumer protection measure, to assure the patient's getting exactly the medication the doctor ordered based upon his experience with that particular product.

2. It (the law) protects the patient's health by assuring that a product which may act differently is not substituted.

3. It protects the patient against fraud. (Substitution of a cheaper product by the pharmacist, gaining him more profit, a competitive advantage, or both, without necessarily passing on the "theoretical" savings to the patient).

4. Under the pharmacist's "fee" system, only the basic drug cost would be reduced if a cheaper drug were dispensed and if the difference were passed on to the consumer. The pharmacist's fee, which represents, on the average, about 50% of the prescription price, would remain the same. Thus, the "savings" to the patient, per dose, would be an infinitesimal amount, and the patient would still run the risk that the "cheaper" drug would not act as the doctor had intended when he prescribed the original product.

5. If prescription drugs are included in a labor union's medical benefits plan, the union should insist upon getting the best drugs for the specific condition being treated, as determined by the physician - not something cheap which a pharmacist might guess is "just as good", thereby bringing the pharmacist more profit or the benefits plan a theoretical savings. Union members have earned, and paid for, the right to first class medical care through (1) dues payments (2) hard negotiation (3) co-payment or co-insurance, neither of which would be reduced for the patient by substituting cheaper, less reliable, ingredients in the prescription.

6. The assumption that the Food and Drug Administration assures therapeutic equivalency among various "generic" equivalent products on the market is an error. (See FDA statements in attached PROPOSED BIOAVAILABILITY REQUIREMENTS, FDA, Jan. 5, 1973

7. With the Food and Drug Administration as yet unable to assure therapeutic equivalency among similar products, it is extremely unlikely that a pharmacist, or a committee acting in his behalf, will be able to do so without jeopardizing the patient's well-being.

8. There is a profit motive involved in the substitution issue. But it is primarily a profit-motive on the part of the minority among pharmacists who want to profit directly by substituting a cheaper product, or indirectly by reducing line-items in their inventories.

   Bear in mind, while the physician has a responsibility to keep the patient's economic well-being as well as his health in mind when he prescribes treatment, the physician stands to make no profit one way or another on the medication he prescribes. He has no incentive to prescribe a high-priced product if he believes a cheaper one will do as well. The pharmacist does stand to profit, more or less, depending upon the cost of the product dispensed in proportion to the price he charges. Legal authority to dispense a different product than the one ordered can lead to abuses by those who would profit thereby. And the chances are that in too many cases, the one who profits by substitution will not be the patient.

9. "Molecular manipulation" is scientifically valid research and often has resulted in improved products with fewer or less severe side effects, lowered dosage, and greater therapeutic efficacy. Without "molecular manipulation", we would still be using sulfanilamide, the wonder-drug of the late 1930's, instead of the vastly improved and safer anti-infectives we use today.

0492

0770

Is It True About Pills?

By RUTH DEAN
Star-News Staff Writer

Who's right?

Those who say United States has become an over-drugged nation?

Or the doctors who claim the average patient takes a pill only when he needs it and then half the time resists or forgets it when it is prescribed?

Dr. Michael J. Halberstam, internist and author of "The Pills In Your Life," holds to the second view which he emphasized in a speech to the Woman's National Democratic Club yesterday He took to task Senate investigating committees, even President Nixon, for promoting the first view.

Halberstam quoted President Nixon as having told the American Medical Association, "we have created a culture of drugs, a pill for every problem." He also referred to Federal Drug Administrator Charles Edwards description of "an over-drugged nation" and Sen. Gaylord Nelson's claim that "we've become massively addicted to drugs whether we need them or not."

HALBERSTAM CALLED these "unsubstantiated notions" which differ from what physicians see in daily practice. He investigated the disparity and found an NIH study of patient compliance showing "perhaps 20-40 percent of the medicines prescribed are taken" and "between 10 and 20 percent are never filled."

The one exception, he said, is "we do prescribe more tranquilizers and anti-depressants than in our past history. But perhaps part of this can be attributed to improved psychiatric treatment which allows psychotic patients who once spent a lifetime in an institution to resume productive lives in the community under enormous dosages of drugs prescribed for their treatment."

Halberstam said hearings conducted by Nelson and statements made by Sen. Edward Kennedy were based on "inadequate investigation and unsubstantiated slogans." He said he would hope "people looking into these problems would apply the same standards physicians apply to their patients.

"If we go into these issues with gross exaggerations and false information, we'll only obscure the main problem and solidify the errors of the past and harm the research and patient benefits of the future," he warned.

An example of how the drug issue is being fogged by exaggeration, Halberstam cited FDA Commissioner Edwards statement three years ago that "five percent of hospital patients are admitted for drug reactions."

WHEN HE investigated the study on which the statistic was based, Halberstam said he found it hadn't been broken down correctly and was not all-inclusive "because it had been made only on the medical floor of a hospital that included attempted suicide cases and leukemia patients being treated with high drug dosages."

A more accurate study, he said, was made by Dr. Nathan Kline, the father of neuropharmacology, "and it's the only study that has measured drug reactions as the reason for admission to hospitals. It showed only one percent."

Halberstam said he wrote Edwards a letter, suggesting a correction, "but nothing has been done about it. So the figure keeps being quoted as gospel. Perpetuation of such an exaggeration," he maintained, "is a disservice to patients and doctors."

Halberstam also accused the FDA of "significantly interfering with the only major medical advance in 100 years for patients with angina pectoris."

Since the introduction into the United States three years ago of propranolol, a drug used for heart disease and high blood pressure, Halberstam said "the FDA still has not released this medication for use, yet thousands are using it."

In effect this means physicians are operating "outside the law," he said, "but I think they will continue to do so until the FDA backs down. This is not a trivial matter. This is a significant treatment for a life-threatening condition."

KIDDY ABSENTEEISM

KIRBY, England (WNS) — School officials who investigated school absenteeism here reported that one student in three is absent at least one day a week.

But fewer than 10 percent of the absentees missed school because of illness.

"Sleepy parents who don't get their children to school are the real culprits," said education officer Peter Neafsey.

"Next are working parents who keep the youngsters at home to answer the doorbell when the TV repair man or the plumber comes to call."

MEDICAL SOCIETY OF THE STATE OF NEW YORK

HOUSE OF DELEGATES, 1973

Number 73-83

Referred to Reference Committee on Medical Services

RESOLUTION

SUBJECT: Medicaid Action to Mandate the Use of Generic Prescriptions

INTRODUCED BY: Medical Society of the County of Queens

WHEREAS, For Medicaid patients in New York City, the new regulation requiring the sole use of a new Medicaid Prescription-Order and Invoice (Form W 304 J) as a prescription blank specifically for Medicaid patients, demanding that if a physician desires to order a medication by a trade name not listed in a new formulary, he is mandated to either accept the alleged generic "equivalent" or call a pre-set telephone number for permission to order the medication, and justify his judgment for the medication he considers best for his patient; and

WHEREAS, There is no knowledge as to whether the person answering the phone to give permission or deny it, is a doctor or a clerk nor, if the phone will be covered 24 hours a day for emergency treatment; and

WHEREAS, It has been amply testified by various prominent medical authorities that "generics" are NOT equivalent; and

WHEREAS, In California a similar "generic substitution regulation" by Medi-Cal was rejected by the courts; and

WHEREAS, Many drug "generics" substituting for trade name products such as: generic Dioxin for Lanoxin, Dilantin made by a different manufacturer with a cheap base; generic Chloromycetin, the foreign made generic of Aureomycin, and many others, including Riboflavin, Acetyl Salicylic Acid, and certain forms of Tetracyclines were all proven to be inferior, non-therapeutic and, in some cases, even toxic as compared to the trade name product; and

WHEREAS, Even in a Federal Drug Administration statement by Charles Edward, M.D., there was the admission that the release of an active drug from a product may be greatly influenced by a physico-chemical factor in a product and its formulation, and that "it is not possible to specify ... the frequency with which lack of equivalence in bioavailability ...may occur;" and

WHEREAS, Compliance with the regulation could require that a physician permit a pharmacist or other person to substitute for the medication of his judgment, thus breaching the Education Law which does not permit a physician to delegate his authority or responsibility and it would breach Sec.6816 ..Sept. 1971, of the Pharmacy Law of the State of New York, Chap. 937 as amended by Chap. 994, which states that it is a misdemeanor for a pharmacist to change a prescription; and

WHEREAS, Implementation of this Medicaid regulation would result in two classes of treatment -- an inferior one for Medicaid patients as contrasted with private patients who would receive reliable medication; therefore be it

Resolved, That the Medical Society of the State of New York object to the concept mandated by the Medicaid regulation which mandates the physician to order generics from a pre-set formulary, or, having to justify his objections by phone to someone who may not even be a physician; and be it further

Resolved, That the Medical Society of the State of New York declare the regulation (a) dangerous, (b) interference with the rights of patients to be properly treated and (c) an untenable attempt to deprive the physicians and the pharmacists the legally granted right to practice their profession; and be it further

Resolved, That this house advise its members to refrain from participation with the Regulation, and so advise the Medicaid authorities.

The best-selling prescription drugs

Beginning with this issue, *Chain Store Age* will report on the fastest-moving prescription drugs each month at the nation's chain drug prescription counters, along with the retail prices chain pharmacists are charging for these drugs. This first list, which reports on the fastest-moving drugs for the month of December, was compiled from prescription counters in some 2,000 chain drug stores throughout the U.S.

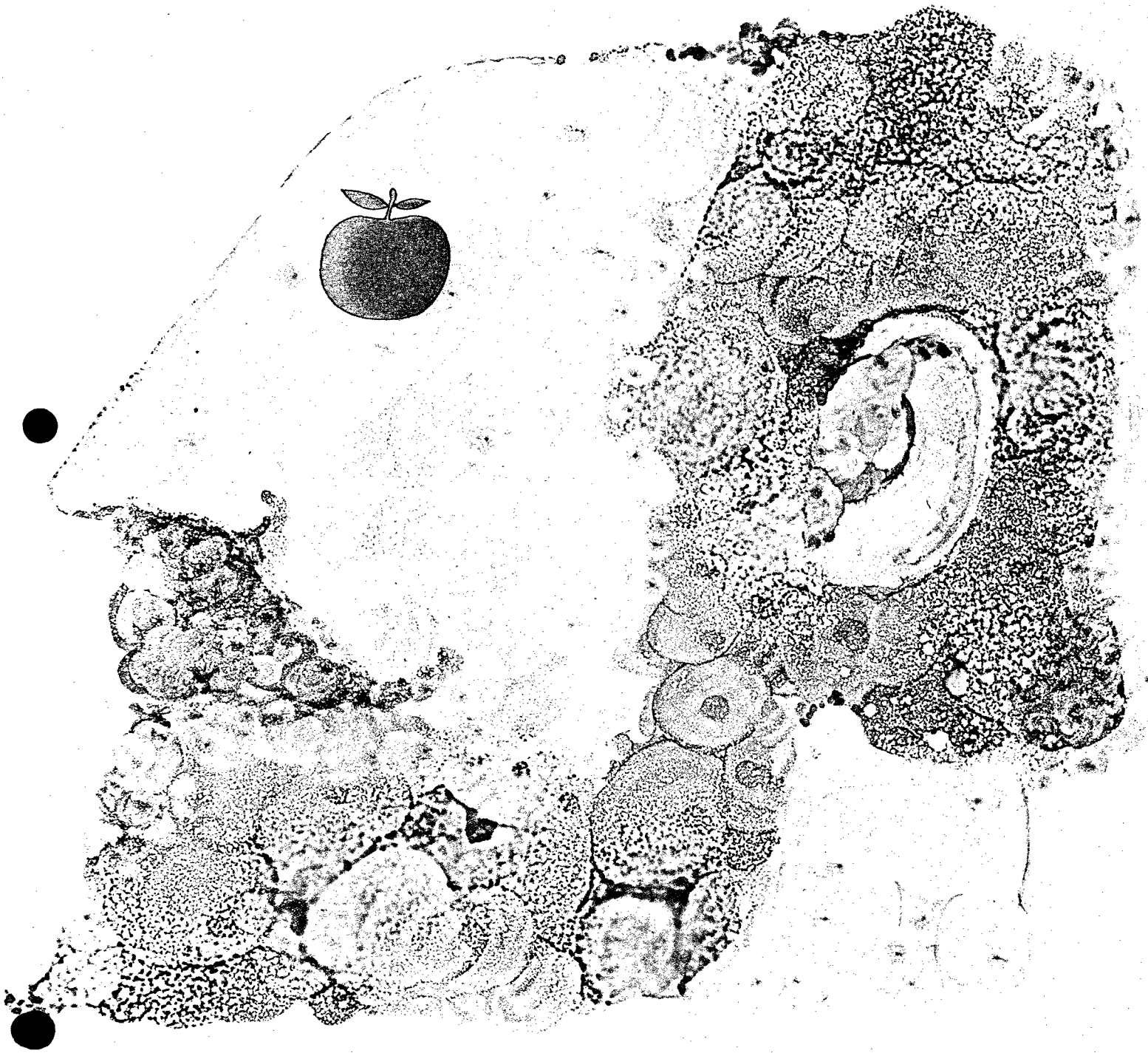
Drug and quantity	Manufacturer	Price charged	
		low	high
Valium Tabs. 5mg. (50s)	Roche	$3.90	$5.85
Librium Caps. 10mg. (50s)	Roche	3.06	6.15
Darvon Comp.-65 Caps (100s)	Lilly	7.29	9.55
Ovral (one-month supply)	Wyeth	1.65	2.19
Lasix Tabs. (50s)	Hoechst	3.13	6.15
Premarin Tabs. 1.25mg. (100s)	Ayerst	6.86	8.52
Indocin Caps. 25mg. (100s)	MSD	7.75	9.25
Librax Caps. (50s)	Roche	3.13	5.05
Diuril Tabs. 500mg. (100s)	MSD	5.85	7.25
Butazolidin Alka Caps. (30s)	Geigy	2.82	3.80
Ornade Caps. (30s)	SK&F	3.24	4.60
Ilosone Caps. 250mg. (16s)	Lilly	3.60	5.10

Recognizing that generic drugs are becoming an increasingly important part of chain drug prescription volume, *Chain Store Age* will report monthly on the most frequently prescribed generic drugs, their prices, and whether these generics are being filled with branded or unbranded products. This first list traces the leading generically-filled prescriptions for the month of December, as assembled from the records of chain pharmacists representing about 2,000 units nationwide.

Drug and quantity	Dispensed products of		Price charged	
	branded	unbranded mftr.	low	high
Ampicillin Caps. 250mg. (16s)	50%	50%	$1.90	$4.60
Tetracycline Caps. 250mg. (16s)	17%	83%	.64	3.20
Meprobamate Tabs. 400mg. (100s)	0	100%	2.24	6.20
Digoxin Tabs. 0.25mg. (100s)	67%	33%	1.25	2.90
Prednisone Tabs. 5mg. (100s)	0	100%	1.68	5.20
Phenobarbital Tabs. 30mg. (100s)	67%	33%	.64	2.50
Reserpine Tabs. 0.25mg. (100s)	0	100%	.64	2.50
Erythromycin Tabs. 250mg. (16s)	90%	10%	2.35	5.20
Chloral Hydrate Caps 500mg. (100s)	50%	50%	1.82	8.20
Potas. Pen. G. Tabs. 400,000U. (50s)	17%	83%	1.75	5.20
Paregoric 4oz.	80%	20%	.64	2.50
Thyroid Tabs. 1 grain (100s)	83%	17%	.70	2.40

FDA CONSUMER

DEC. 1974—JAN. 1975



New Year's Resolutions For Health And Safety

sonment suspended, and probation. (F.D.C. No. 58376; S. Nos. 53-438/9 F, 53-641 F; N.J. No. 53)

Super Valu Stores, Inc., Green Bay, E. Dist. Wis.
Charged 9-14-73: rice, Great Northern beans, corn flakes cereal, flour, and salt were held in a building accessible to rodents and were contaminated with rodent filth; 402(a)(3), 402(a)(4). Nolo contendere plea; fine. (F.D.C. No. 57904; S. Nos. 34-868/70 E et al.; N.J. No. 54)

NOTICES OF JUDGMENT on Criminal Actions

DRUGS

Agri-Lines Corp., t/a Prescription Premix of Billings, Billings, Dist. Mont.
Charged 9-25-73: liquid animal feed was manufactured from bulk urea and molasses (which had been shipped in interstate commerce) and was held in a bulk storage tank; which manufacturing and holding resulted in the feed being contaminated with the new animal drug diethylstilbestrol, and with respect to the use and intended use of such contaminated feed, there was no approval in effect of a New Animal Drug Application; and which manufacturing and holding resulted in the feed being prepared and held under insanitary conditions whereby it may have been rendered injurious to health; 402(a)(2)(D), 402(a)(4). Nolo contendere plea; fine. (F.D.C. No. 58082; S. Nos. 33-213 F, 33-968 F; N.J. No. 55)

Barrows Chemical Co., Inc., Inwood, E. Dist. N.Y.
Charged 6-20-67 by grand jury: when shipped, the strength of dextroamphetamine sulfate capsules differed from its purported strength, and its labeling was false and misleading, since the capsules contained more than the declared 15 mg dextro-amphetamine sulfate, and the circumstances of the article's manufacture, processing, packing, and holding failed to conform to current good manufacturing practice; 501(c), 501(a)(2)(B), 502(a). Guilty plea; fine. (F.D.C. No. 53042; S. No. 1-022 B et al.; N.J. No. 56)

NOTICES OF JUDGMENT on Injunction Actions

Marshall Pharmacal Corp., and Gustave A. Godinez, president and general manager, South Hackensack, Dist. N.J.
Charged 4-21-72 in complaint for injunction: that the defendants were engaged at their plant at South Hackensack, N.J., in manufacturing, processing, packing, labeling, and holding articles of drugs for human use (such as digoxin tablets, digitoxin tablets, prednisolone tablets, prednisone tablets, reserpine tablets, ethinyl estradiol tablets, isoniazid tablets, and phenobarbital and belladonna alkaloid combination tablets), in distributing such articles in interstate commerce, and in holding for sale a number of such articles after shipment of one or more of their components in interstate commerce; that FDA analyses had indicated that the content uniformity of a number of the defendants' digoxin tablets and prednisolone tablets failed to comply with U.S.P. standards, and, pursuant to a survey of the defendants' digoxin tablets, FDA analyses of approximately 43 lots showed that approximately 24 lots failed the U.S.P. tests including 5 lots that the defendants had reworked; that such failures to meet U.S.P. standards were routinely not revealed by any of the defendants' analyses; that FDA inspections showed a number of inadequacies in the methods, facilities, and controls used by said defendants; that a number of defendants' drugs had been found to be in violation of the Federal Food, Drug, and Cosmetic Act; that the defendants had recalled a number of violative drugs; that the circumstances used for the manufacture, processing, packing, and holding of drugs failed to conform to current good manufacturing practice; that the strength of a number of the defendants' drugs differed from and their quality and purity fell below the compendium standards, and their labeling was false and misleading with respect to the strength of the articles; that the defendants' isoniazid tablets was a new drug without an effective approved New Drug Application; and that the defendants were well aware that their activities were in violation of the law; 501(a)(2)(B), 501(b), 502(a), 505(a).

The defendants entered into a consent decree of permanent injunction that enjoined the violations complained of and enjoined the shipment of drugs or the production of drugs at the defendants' plant using ingredients shipped in interstate commerce, unless and until a number of specified current good manufacturing practices were put into practice at the plant, all drugs on hand at the plant were examined by FDA, necessary assays were made, necessary recalls were made of drugs distributed from the assayed lots as determined by FDA, and such assayed and recalled drugs were destroyed or otherwise brought into compliance. (Inj. No. 624; S. Nos. 202-643 C, 52-250 D, 96-766 E et al.; N.J. No. 57)

Sunshine Biscuits, Inc., Charles Holland, manufacturing services director, and Herbert F. Berlin, plant manager, Dayton, S. Dist. Ohio.
Charged 3-31-72 in complaint for injunction: that the defendants were engaged at their plant at Dayton, Ohio, in manufacturing, processing, packing, holding, and distributing in interstate commerce crackers, cracker meal, cookies, cereals, and specialty foods; that in February 1972, FDA analysis showed the presence of the pesticide chemical Ronnel in saltine crackers from such plant; that a February-March 1972 FDA inspection disclosed that the firm's insect control program involved spraying the pesticide chemical Ronnel and that the cracker meal room had been fogged with piperonyl butoxide; that subsequent inspections in March 1972 revealed Ronnel on various surfaces of the plant, in piperonyl butoxide, in finished cracker meal (0.04 parts per million of Ronnel), and in other finished food (0.02 parts per million of Ronnel); that the defendants' foods contained the nonconforming food additive Ronnel, that such foods were prepared, packed, and held under insanitary conditions, and that the defendants were well aware that their activities were in violation of the law; 402(a)(2)(C); 402(a)(4).

A consent decree of permanent injunction enjoined the violations complained of, and enjoined the interstate shipment of any food from the Dayton, Ohio, plant (except temporarily warehoused, finished, and packaged foods which had been manufactured, processed, and packaged at other plants), unless and until a number of specified provisions to assure against food being contaminated with pesticides were established, and all stocks of food on hand which had been processed at the plant were destroyed or disposed of under FDA supervision. (Inj. No. 625; S. No. 26-294 F et al.; N.J. No. 58)

NOTICES OF JUDGMENT on Miscellaneous Actions

Birth control pill warnings, suit for declaratory judgment and injunction, Washington, Dist. Columbia.
Charged 7-2-70 and amended 8-14-70: in complaint for declaratory and injunctive relief by James S. Turner (Center for Study of Responsive Law consultant), Carolyn D. Smith, Judy Holmberg, and Judith Edes (as representatives of the class of women who have taken, are taking, or are considering taking birth control pills—a class so numerous that joinder of all members was impracticable), and American Patients Association, against FDA Commissioner Charles C. Edwards and the Food and Drug Administration: that oral contraceptives were prescription drugs which, in some users, caused harmful side effects and which might cause cancer and damaging metabolic change; that oral contraceptives should not be used at all by women with certain medical conditions, and should be used only under special medical supervision by women with certain other medical conditions; that many users of oral contraceptives did not obtain such drugs by a physician's prescription; that many users of oral contraceptives had not been fully and accurately informed of the potential harmful side effects of using oral contraceptives; that the FDA Commissioner proposed, but never published in the **Federal Register**, a 600-word labeling on the hazards of oral contraceptives; that the defendants proposed and published in the **Federal Register** a shorter proposed labeling on such hazards; that plaintiffs Turner and Smith commented against such shorter labeling, submitted alternative labeling, and requested a public hearing, as did others; that defendants published a regulation ordering specified brief labeling to be in packages of oral contraceptives commencing September 9, 1970, and requiring preparation of a fuller informational statement (pamphlet) for dissemination by prescribing physicians to their patients, upon request and at the physicians' discretion; that the defendants' regulation did not ensure that the information statement for patients would provide adequate directions for use or adequate warnings against unsafe use, or would not be misleading; that, because the defendants' labeling was misleading, lacked adequate directions for use and warnings against unsafe use, and because the labeling regulation was not supported by the facts of the record, was inconsistent and contradictory, and was based on an irrelevant factor, the order was null and void; that the defendants should be ordered to issue a new regulation requiring a labeling fully disclosing the potential harmful side effects, contraindications, and symptoms of serious disorders related to the use of oral contraceptives, or alternatively the defendants should be ordered to hold a public hearing.

The district court denied the plaintiffs' motion for a preliminary injunction on the grounds that the plaintiffs had not shown a substantial likelihood of ultimately prevailing on the merits, that the court was not persuaded that placing copies of the longer pamphlet in the packages was required to protect the consumer, and that a preliminary injunction would, indeed, delay the regulated distribution of copies of the warning pamphlet (which at the time of the hearing on the preliminary injunction were in the hands of physicians for distribution under the regulations effective the next day).

FDA moved to dismiss the action for summary judgment. After initially deferring ruling on such motion, the court ruled in favor of FDA, saying:

"Plaintiffs brought this action to review certain regulations of the Food and Drug Administration governing the labeling of birth control pills. Those regulations require that a short warning of potential side effects of the pill be inserted in each package, along with a statement that the user should consult her doctor for further information; a longer, more comprehensive discussion [pamphlet] of the health hazards of the pill, prepared in cooperation with the AMA, is distributed by physicians who prescribe the pill.

"At a hearing in September, 1970, the Court denied plaintiffs' motion for a preliminary injunction, on the grounds that plaintiffs had not demonstrated a likelihood of success on the merits and had not shown any threat of irreparable harm. The Court found at that time that the FDA's regulations were developed after adequate study and appropriate administrative proceedings, and that the challenged regulations met the legal standards for labeling of prescription drugs. The complaint asserted, however, that birth control pills were being extensively distributed outside prescription channels. If that were true, different standards of labeling might be applicable under the rule in such cases as **Davis v. Wyeth Laboratories, Inc.**, 399 F.2d 121, 133 (9th Cir. 1968), and **United States v. Articles of Drug, Thyrodig Tablets**, 306 F. Supp. 247, 251 (D. Colo. 1969).

"Without deciding whether the existing warnings are adequate even for nonprescription drugs, the Court deferred ruling on the FDA's motion to dismiss or for summary judgment, in order to give the agency an opportunity to conduct a limited market survey to determine the extent to which birth control pills are being distributed outside prescription channels. This was done. The survey disclosed that by and large the pills are being dispensed only on prescription, and that the new warning pamphlets are being effectively distributed by physicians.

"Plaintiffs have requested extensive further discovery on the manner of distribution of the pills and the pamphlets, but the agency's survey taken in good faith adequately demonstrates the absence of special circumstances suggested by the cases cited. The motion for further discovery is denied. Defendants' motion for summary judgment is granted, and the complaint is dismissed."

The plaintiffs filed a notice of appeal, but subsequently obtained the dismissal of their appeal. (Misc. No. 147; N.J. No. 59)

Cothyrobal thyroxine and vitamin B_{12} combination injectable, suit for damages and injunction, Washington, Dist. Columbia.
Charged 12-24-69 in complaint for damages and injunction by Murray Israel, M.D., Roslyn Heights, N.Y., Vascular Pharmaceutical Co., Williston Park, N.Y., and Edison Pharmaceutical Co., New York, N.Y., [proponents of Cothyrobal], against Baxter Laboratories, Inc., and Travenol Laboratories, Inc., [distributors of Choloxin], Morton Grove, Ill., Marion Finkel, M.D., [FDA Medical Officer], Washington, D.C., and David Kritchevsky, M.D., [FDA consultant], Philadelphia, Pa.: that Cothyrobal was a patented drug containing the natural thyroid hormone L-thyroxin, vitamin B_{12}, and other ingredients; that Cothyrobal was used and recommended for the prevention and treatment of certain diseases of the heart and blood vessels; that Cothyrobal was in competition with Choloxin, which contained D-thyroxin; that the defendants conspired to illegally restrain trade; that Dr. Finkel conspired by denying approval, acceptance, and/or clearance from HEW and other Federal agencies, or by arbitrarily making such approval, acceptance, and/or clearance extremely difficult or impossible; that Dr. Kritchevsky, while a consultant, employee, and/or

TO: Members of the Assembly Commerce Committee

FROM: Assemblyman Coulter

Attached is an editorial appearing in today's edition of the Nevada State Journal in support of AB 436 - allowing drug substitution under certain conditions.

Amendments I proposed to the committee would tighten even further the doctors' control of prescribing the drug of his choice. No substitution could be allowed if the doctor didn't think it in the best interest of the patient.

Suggestions that another $25,000 or even $2,000,000 would be needed to enforce such a bill, I believe, are a deliberate smoke screen. I discussed the bill with both the head of the Nevada FDA and the State Board of Pharmacy before the hearing. No mention was ever made of this kind of money. In fact, it was never said any additional money would be needed at all.

Thank you for your consideration.

STEVE COULTER

Nevada State Journal

A Speidel Newspaper

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Friday, April 18, 1975

Editorials

Drug Substitution

A bill that is important for consumers and particularly for the elderly is facing an uphill fight in the Assembly.

The bill is AB 436, introduced by Steve Coulter. It would allow pharmacists to fill prescriptions for drugs designated by trade or brand name with less expensive drugs selected by generic name, unless otherwise specified.

Extreme variations in drug prices are a scandal in the health field. According to figures contained in the American Druggist Red Book, Ampicillin Trihydrate, manufactured by, among other companies, Zenith Labs, is sold per one hundred at prices between $8 and $4.40.

AB 436 would allow the pharmacist to supply a customer with the least expensive drug, although the physician might have suggested a higher priced label. The physician, however, would have the power to specify, if he wished, that only a certain brand be used.

A common objection to such legislation is that the Federal Drug Administration does not test all batches of all drugs — it tests only four varieties. It is believed by some that only large companies, with the well known brand names most often recommended by physicians, have a safe degree of quality control.

In fact, however, many of the widely used drugs are manufactured by a few suppliers and sold to distributors such as Sherry or Squibb. Also, pharmacists, who are drug professionals, (unlike physicians) know their field and could be expected to recommend quality prescription drugs.

Antisubstitution laws, such as are now in effect in Nevada, are a result of widespread drug counterfeiting that occured after World War II. Such counterfeiting has been outlawed, however. Antisubstitution laws now protect big companies with well known brand names, not the comsumer.

Legislation similar to AB 436 has been enacted in Florida and is accepted by the California health program, Medi-Cal. Such legislation has the endorsement of the American Pharmaceutical Association, which is the professional society of pharmacists. It also has the endorsement of the Department of Health, Education and Welfare.

The Federal Drug Administration will, in the next four years, probably have the capability to inspect all drug batches in the nation and insure the strictest quality control. But we believe there are already sufficient safeguards in the drug industry and expertise in the pharmaceutical profession to safely allow drug substitution now.

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April 16, 1975

TO: MEMBERS OF THE ASSEMBLY COMMITTEE ON COMMERCE

FROM: JOHN P. SANDE. M.D., CHAIRMAN, NEVADA STATE MEDICAL ASSOCIATION'S LEGISLATIVE COMMITTEE

SUBJECT: AB:436

Nevada State Medical Association physicians applaud efforts of Assemblyman Steve Coulter to reduce the ever spiraling cost of health care and we appreciate your Commerce Committee's interest in our input regarding AB 436 to allow the substitution of generic drugs by pharmacists. We are pleased to comment on this subject.

The concern of all Nevada physicians is that the best chemical agents be used in the alleviation of pain. We are fearful that drug substitution by pharmacists may not be in the best interests of our patients, as many generic drugs often do not meet the rigorous standards established by the Food and Drug Administration. Drug quality often suffers.

Name-brand quality pharmaceuticals undoubtedly cost more than mass-produced generics; however, this expense is absolutely necessary for research and quality control. Each time a new drug is introduced on the market, millions of dollars and several years of research have been expended for testing in order to guarantee to the public predictable and quality results. These incurred costs must unfortunately be passed on to the consumer, our patients. However, it is our feeling that these costs are entirely necessary and justified.

We ask you to weigh carefully this balance between <u>costs</u> and <u>quality</u>, for it is our opinion that unrestricted drug substitution by pharmacists would not be in the best interests of our patients, the people of Nevada.

JPS:dlh

Journal Private Practice – April 1975

0777

Who Should Select Your Patients' Drugs?

by Francis A. Davis, MD

Who has the qualifications and experience necessary to select drugs in the best interest of patients — physicians or pharmacists? For most of us, the answer is obvious. But for some — legislators and others — the answer seems to be pharmacists. How do they arrive at this conclusion? To start with, by succumbing to three myths:

* Pharmacists are more knowledgeable than physicians about the drug products available to patients;
* What knowledge physicians have comes from detailmen who "brainwash" them into prescribing "high-priced" brand-name drugs;
* Consumers would reap large savings if "generically equivalent" drugs were substituted in place of brand-name products.

Building on this quicksand, some are proposing legislation that would permit pharmacists to substitute drugs for the ones you originally prescribed. This would be done without your prior knowledge or consent.

Although some politicians seem to be unaware of the fact that differently manufactured versions of the same drug vary in therapeutic effectiveness, as physicians, we cannot ignore the myths that have led to such risky proposals. First, the real question is not who is more knowledgeable about drug products — though when it comes to how drugs work in *people*, doctors are — but what is best for the patient. Changing present laws that require pharmacists to fill prescriptions exactly as we intend would surely impair our traditional relationship with pharmacists to the detriment of patients.

Second, the contention that physicians are "brainwashed" into prescribing higher priced brand-name drugs is nonsense on many counts. Brand-name drugs are not always necessarily high-priced. In fact, some identified by brand are less expensive than generically sold equivalents. Few low-cost generics are widely available since they are most likely to come from repackagers and distributors who sell either by catalog or in limited areas. And how much do we know about their quality assurance?

On the whole, the average tablet or dose costs less today than it did in 1960. What else can you say that about? As a result, prescription drugs account for only about 8 percent of consumer expenditures, compared to 12 percent a few years ago. Little enough for the good they do.

Aside from the obvious insult to our ability to distinguish helpful information from promotional puffery, "brainwashing" of doctors would be pretty tough. Frankly, I don't know one practicing physician who could be successfully gulled by detailmen. Only one things keeps us prescribing a drug: when we find it helps our patients. If it doesn't, all the promotion in the world isn't going to make us use it. And the drug companies are careful to see that we get balanced information about drugs — shortcomings as well as favorable qualities. If they weren't, we might not believe them the next time.

Finally, the claim that huge consumer savings will result due to substitution has been proven a myth. A 1973 study by an independent research firm revealed that savings would average only 1.7% if all prescriptions were written generically — essentially the same as permitting pharmacists to substitute. Experience appears to bear this out. Savings on prescription drugs are nonexistent in the three states and five Canadian provinces where substitution is legal. In fact, a study of Saskatchewan conducted by Professor William Tindall of Creighton University revealed that instead of prices going down for those prescrip-

WHO SHOULD SELECT YOUR PATIENTS' DRUGS?

tions in which the pharmacist dispensed products not specified by the physician, they went up 19 percent. The study cited pharmacists' increased liability insurance as a possible reason. In this country, a substitution agreement between physicians and pharmacists in Kane County, Illinois, was cancelled by the county medical society after 15 months when a survey showed (among other failures) no consumer savings. Maryland, Kentucky, and Massachusetts have yet to document any consumer savings as a result of their substitution laws.

If patients are to save on prescriptions, the solution seems to be in our hands. And prescribing generically is not the answer, especially when you consider the high cost in health. An awareness of drug prices and the manufacturers can help. When price and source have been considered, a selective use of brand-names among multi-source drugs can mean savings. Better communication with pharmacists about prices and available products can be of assistance. Repeal of antisubstitution laws would only serve to disrupt such communications.

But let's get to the critical issue at hand — the health risks inherent in substitution proposals and what can be done to stop these proposals. Unfortunately for our patients, these ventures disregard overwhelming scientific evidence concerning drug product inequivalency. Most recently, in a special report to Congress in July 1974, the Office of Technology Assessment of the U.S. Congress concluded, "Current standards and regulatory practices do not insure bioequivalency for drug products . . . the problem of bioinequivalency in chemically equivalent products is a real one . . ." Even more disturbing, the report said that additional undetected cases of inequivalency were likely.

While disregarding scientific factors, substitution proponents would cast aside the only current proven safeguard to the dangers on inequivalency. And that is to depend on your judgment, based on practical experience with particular drug products and clinical knowledge of individual patients. With the repeal of state antisubstitution laws, your decision to select specific drug products for your patients would be dramatically converted into a meaningless exercise.

Imagine how this could affect your day-to-day practice. Suppose the medication that the pharmacist substituted for your prescribed brand doesn't work. How are you to gauge what's wrong? You know how the prescribed brand works, but since the pharmacist substituted without your knowledge, you have no way of judging the substitute. Did the substituted drug deliver as much of its potency — or less — to the patient as the brand that you prescribed? There's no telling. And meanwhile your patient may be incurring additional expenses due to prolonged illness.

This is only the beginning. Now, suppose your patient suffers an injury due to using the substituted drug. Today, the laws regarding liability are well defined. If the drug was misprescribed, you're liable. If it was incorrectly dispensed, the pharmacist is liable. And if it was improperly produced, the manufacturer is liable. But if the injury involves a substituted drug, somebody — physician, pharmacist, or patient — will have the almost impossible task of proving that the products invoived are either equivalent or inequivalent. There's no telling who may end up responsible in a case like this. But if the court decides the burden of proof is on you, as it could since there is no precedent, the chances of avoiding a damaging suit would be pretty slim.

But substitution legislation can and has been defeated in state legislatures. The major reason: the combined efforts of individual physicians on the local level. Here's a check list on how you can help fight dangerous substitution legislation:

* Contact pharmacists. If they have views on substitution similar to yours, seek their help, and make sure they understand that you want *all* prescriptions filled exactly as written — no substitutions without your prior consent;
* If you notice an article on substitution or generic prescribing in your local newspaper that doesn't give all the facts, or distorts them, write a letter to the editor giving the truth;
* Air your views about substitution at your county society meetings. Offer to serve as your society's spokesman on the issue. Encourage society officers and other members to become active;
* When you hear of hearings on prescription drugs, offer your expertise either as a witness or as a source of information for the hearing's investigative staff. Let your state or county medical society know that you are willing to serve as a source. They may have some special legislative or public relations programs where your expertise and views on substitution are needed;
* When you have the opportunity to address groups in your community, make the subject substitution. It's a timely and interesting subject that can be related directly to the individual. Typical groups might be medical school classes, hospital staffs, local medical societies, Rotary, Kiwanis, and other club groups. Urge your audience to talk to their legislative representatives and oppose substitution legislation;
* Most important, talk to your fellow physicians — whether it's just a casual phone call or at a society event. Encourage them to voice their opinions on substitution.

Without our combined individual efforts, substitution could win without the legislature or public realizing the consequences. It's up to us to inform them. The more the facts are made known and the louder the voices, the more likely the defeat of substitution legislation. □

A MEMO TO MY PATIENTS WHO HAVE ASKED FOR GENERIC PRESCRIPTIONS

may occur; the antibiotic tetracycline, if dispensed in relatively acid capsules, will slowly transform into a deadly kidney poison. Without appropriate — and costly safeguards — problems do occur;

7) Absorption of medications from pills depends on how rapidly they dissolve, the choice of non-active ingredients used, stability of the drug in the digestive juices, whether it reacts with food residues, etc.

Here are some specific examples from the medical literature, that also got attention from the lay press:

1) A few years ago, it was discovered that while Parke-Davis's Chloromycetin (brandname) is a very powerful and effective antibiotic for certain indications, all the generic equivalents of chloramphenicol (generic name) failed to achieve comparable bloodlevels of the antibiotic, no matter *how much* was given to patients;
2) Digoxin (generic name) is used by millions of Americans to help their hearts beat more forcefully. Last winter the FDA discovered that some manufacturers' digoxin varied so much in absorption rate that patients could get dangerously low or high bloodlevels of the drug when given the same dosage. The FDA also noted that Burroughs Wellcome, which makes most of the digoxin under its own brandname, had no problems at all with its products;
3) Alan E. Tasoff, MD, has told of his experiences as an Air Force flight surgeon in Thailand in 1972: "Struggling to contain a penicillin-resistant gonorrhea epidemic among airmen — of the magnitude of twenty new cases per day — we were armed with an Italian-manufactured tetracycline, purchased in massive quantities by Congress. Undoubtedly the drug was 'USP' and, therefore, equivalent — in the judgement of consumer groups — to brand name drugs. The failure of this product to dissolve in the alimentary tract was known to all physicians prescribing it, but supplies had to be consumed before a replacement could be made available. The ultimate cost to the airmen involved was chronic, intractable urethritis and prostatitis, which undoubtedly contributed to the horror stories we occasionally hear of 'incurable VD.' "

Senator Edward M. Kennedy (Dem.-Mass.) heard conflicting testimony on this whole question before his Senate Health Subcommittee. So he asked an agency of Congress, the Office of Technology Assessment (OTA), to study the whole matter of drug bioequivalence (whether chemically equivalent drugs are always equally available in the body, therefore allowing them to be therapeutically equivalent).

The OTA set up a Drug Bioequivalence Study Panel headed by Robert M. Berliner, MD, Dean of the Yale University School of Medicine. After months of study, the panel released its report, "Drug Bioequivalence," in July. Among its findings:

> "Current standards and regulatory practices do not assure bioequivalence for drug products."
>
> "Variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures. It is probable that other therapeutic failures (or toxicity) of similar origin have escaped recognition."
>
> "Present compendial standards and guidelines for Current Good Manufacturing Practice do not insure quality and uniform bioavailability for drug products. Not only may the products of different manufacturers vary, but the product of a single manufacturer may vary from batch to batch or may change during storage."

The 78-page OTA report also noted that:

> "The problem of bioinequivalency in chemically equivalent products is a real one . . . documented instances constitute unequivocal evidence that neither the present standards for testing the finished product nor the specifications for materials, manufacturing process, and controls are adequate to ensure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability."

When patients ask for the lower-cost generic drug, they are often asking for a product from a low-quality-control, no-research, minimum-distribution, sometimes fly-by-night company. Thus a small dollar savings may be purchased at a very high cost to their health.

As a physician sworn to the Oath of Hippocrates, I cannot do anything that might in the least endanger your health. I will not prescribe cheap drugs from unknown firms, but only from companies whose products I know, from experience, to be highly reliable. I will not take chances with your health for the sake of a little money. A diamond and a chunk of coal are both 100% carbon, and therefore generically equivalent. But they are hardly the same. □

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IMS America

0779

IMS America Ltd.
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August 30, 1974

Mr. Armistead M. Lee
Assistant Vice-President
Pharmaceutical Manufacturers Assoc.
1155 Fifteenth St., N.W.
Washington, D.C. 20005

Dear Armie,

For a number of reasons that we've discussed, rather than reviewing and revising the Firestone analysis, I decided to start from scratch.

As a beginning point, I listed out the leading 50 generically prescribed drugs for 1973 (Attachment A) and then established criteria for inclusion in the analysis. The first qualification involved multi-source availability at the drug level per se. On the basis of a lack of multi-source availability. I eliminated Lente Insulin from the list, "Lente" being a trademark of Eli Lilly.

A second criterion was that the drug must be prescribed frequently enough on both a generic and branded basis to allow for reasonable comparisons. Only rarely are the following prescribed by brand or manufacturer specification and these were not included in the analysis - paregoric, codeine sulfate, terpin hydrate with codeine, saturated solution of potassium iodide, aminophyllin, vitamin B_{12}, thiamine, morphine, quinine sulfate, tincture of belladonna, nicotinic acid, digitalis, colchicine, and sodium salicylate.

A third factor was the status of the drug-legend or OTC. I arbitrarily excluded OTC items; aspirin falls off the list on this basis as do ascorbic acid and NPH Insulin. Finally, promethazine DC with codeine was excluded as it appears to represent a coding error.

For the remaining products, which represent 82% of all generically written new prescriptions, 75% of total (new and refill) generically written prescriptions and 87% of consumer dollars paid for these prescriptions, the following methodology was utilized. For each of the major forms and strengths of the generically prescribed drugs, we used the NPA Basic Data report to find the most frequently prescribed quantity, then recorded for that quantity the average retail price. This process was repeated for branded or manufacturer-specified prescriptions for the same drug in the same quantity. I should point out here that comparisons were made only with comparable forms and strengths. I do not, for example, feel it valid to compare generic quinidine sulfate with the long-acting Quinidex Extentabs.

The third step was to weight the average retail price of the branded products on the basis of the number of prescriptions for each in the quantities analyzed. This weighted average retail price was then divided by the average retail price of the generic. Further, since we considered all major forms and strengths, the final ratio represents a weighting of the import of these forms and strengths.

The results of the analysis are shown in Attachment B. Generally speaking, for the products that are common to our and Firestone's analysis, our results appear to be somewhat lower. The overall brand/generic ratio as we calculate it for these 30 drugs comes out to 110.62. With regard to what this represents in absolutes, I calculate that roughly 25% of total consumer dollars paid for prescriptions in 1973 was represented by multi-source drugs. As shown below, this results in a figure of $1,696,767,750.00.

National Prescription Audit
1973

Total Consumer Dollars Paid for Prescriptions (New & Refill)		$6,787,071,000.00
Multi-Source % = 25%	x	.25
Total Consumer Dollars - Multi-Source Drugs		$1,696,767,750.00

Of the multi-source total, $498,000,000 was reflective of consumer dollars paid for the generically prescribed segment, leaving a total of $1,198,767,750.00 for multi-source drugs prescribed by brand or manufacturer specification.

Total Consumer Dollars - Multi-Source Drugs	$1,696,767,750.00
Total Consumer Dollars - Generically Prescribed Drugs	498,000,000.00
Total Consumer Dollars - Branded Multi-Source Drugs	$1,198,767,750.00

If I apply the above-determined premium of 10.62% for brand name prescribing to total consumer dollars for the branded segment, I come up with a differential of $115,086,906 as demonstrated in the following:

Total Consumer Dollars - Branded Multi-Source Drugs = $1,198,767,750.00
Brand/Generic Ratio = 110.62

Therefore:

1. $\frac{\$1,198,767,750}{110.62} = \frac{x}{100}$

   x = $1,083,680,844 at Generic Pricing

2. $1,198,767,750
   - 1,083,680,844
   $ 115,086,906 Net Saving

This net savings can then be applied to whatever base you choose. On the basis of total consumer dollars paid for prescriptions, the savings represent 1.69%. On a base of total multi-source drug consumer dollars, the percentage saving would be 6.78%.

I hope this fills your needs. MAC is comig next.

Cordially,

Stephen C. Chappell
Vice-President

Encl.
SCC:ecc

FDA talk paper*

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

T75-9
February 3, 1975

FDA BUDGET

The Administration's proposed budget for FDA for fiscal year 1975 is $203.46 million. This compares with an overall budget of $200.86 for the current fiscal year, and will permit FDA to operate at about its present level.

Eighty-eight additional positions are included -- most of them in the field. The increased staffing will permit FDA to:

Intensify enforcement of new standards for the manufacture and installation of diagnostic x-ray equipment;

Better manage the growing volume of court actions and legal cases;

Cope with added applications from veterinary drug manufacturers;

Increase inspection of pharmaceutical firms, with 1,400 to receive the customary inspection and 3,100 a full review of all manufacturing practices.

The proposed budget will also allow FDA to:

Maintain surveillance of food, cosmetic, medical device and radiologic products at present levels;

Continue long-term studies of known cancer-causing substances;

Enforce new standards for certain over-the-counter drugs;

Undertake studies of generic drugs, testing their equivalency compared with brand-name items.

-MORE-

*FDA Talk Papers are issued by the FDA Press Office to provide guidance to FDA personnel in responding to requests for information on subjects of current interest. They are subject to change as more information or data becomes available.

TO Assemblyman Steven A. Coulter

FROM Jessie M. King (Mrs.)

Memo 0783

DATE April 4, 1975

SUBJECT A.B. 436

I feel that A.B. 436 is a good consumer bill that would help curb the high price of prescriptions. While on a visit to Germany last summer, my son, who is a doctor, advised me of the price difference between trade and brand names and generic names in drugs. This was the first time I was aware of it, which I think is typical of the average consumer.

c: Assemblymen Robert E. Robinson
Harley L. Harmon
Daniel J. Demers
Thomas J. Hickey
Don A. Moody
James W. Schofield
Albert W. Wittenberg
Robert M. Benkovich
Virgil M. Getto
Alan Glover

FACTS ABOUT BRAND AND GENERIC DRUGS

ARE THERE DIFFERENCES?

WHAT IS A GENERIC DRUG?

- "Generic" refers to the scientific or common name given to drug products. A generic name is assigned to every drug entity and must appear on every drug product label. A "generic drug," then, is not a specific type or category of drugs; the term is used merely to describe those drug products labeled with only the generic name, as distinct from those that are labeled with both the generic name and a trademark name.

WHAT IS A BRAND NAME DRUG?

- A brand or trademark is the exclusive name given to some products to identify them with their manufacturers. Reputable manufacturers are proud of their products and want to be known as their producer. (Use of the generic name alone does not identify the producer of that product.)

- Here are two examples of drugs showing their brand and generic names:

  1. Generic name - hydrochlorothiazide Brand name - Oretic

  2. Generic name - tetracycline Brand name - Tetrex

ARE BRAND NAME DRUGS GENERALLY MORE EXPENSIVE THAN THOSE SOLD UNDER GENERIC NAMES?

- Yes, in many cases, and for good reasons. Companies that spend millions of dollars annually on research and development market most of their drugs under brand names. Since the government pays for only about 1% of the research, compared to 43% for all industry, the costs must be reflected in the prices of those branded products.

- Drugs that are essential to the cure or treatment of uncommon diseases are often manufactured with little or no profit by research-oriented firms. Those costs must be covered through the sale of more widely prescribed branded products.

- In order to make their products known and available on a nationwide basis, drug firms incur informational, service and distribution costs, which are also covered in the prices of drugs.

- Generically marketed drugs may be less expensive because their manufacturers: (1) do not engage in research and development, (2) produce only the most frequently used dosage forms of widely prescribed drugs, (3) do not distribute their products nationwide (many low cost drugs are available on a local or regional basis only), and (4) do not promote their products extensively, since the market has been created for them by the original developers.

- The notion that all generic drugs are less expensive than brand name drugs is false. For instance: the lowest priced brand of tetracycline sells for 66% less than the highest priced generic version; the lowest priced brand of penicillin G costs 59% less than the highest priced generic.

HOW MUCH COULD CONSUMERS SAVE IF ALL RX's WERE WRITTEN GENERICALLY?

- Savings on prescriptions if all Rx's were written generically are estimated at 1.7%. This would average out to about 8 cents on the average Rx of $4.45.

  Source: IMS America Ltd., independent marketing and research firm (1973 study).

ARE GENERIC DRUGS INFERIOR IN QUALITY COMPARED TO BRAND NAME DRUGS?

- Not necessarily. Variation in quality can exist between differently manufacturered versions of the same drug whether they are sold under a brand or generic name. There are high quality generics and low quality brands, and the opposite is also true.

- Quality depends on the source of the drug. Who manufactured the product and standards of quality control determine a drug's safety and effectiveness--not the name it's sold under. A brand name simply helps identify the source of the drug.

WHAT IS THE OVERALL QUALITY OF U.S. DRUG PRODUCTS?

- Excellent. Most drugs sold in the U.S. are made by companies that provide safe, effective and economical drug products by following good quality control and good manufacturing practices. However, there are some products on the market that are produced cheaply by manufacturers who put less emphasis on quality control. This puts the patient at risk. Although small in number, one unreliable drug product on the market is one too many.

- The only safeguard to this is to depend on the prescribing doctor's judgment which is based on his experience with a particular drug and his knowledge of the individual patient.

- Fortunately, most states have laws that prohibit the substitution of a different drug product for the one originally prescribed by a doctor. These laws protect consumers from receiving unreliable drugs. Without them, the doctor's decision to select a specific drug product for his patient would be meaningless.

DRUG BIOEQUIVALENCE

A REPORT OF THE

OFFICE OF TECHNOLOGY ASSESSMENT

DRUG BIOEQUIVALENCE STUDY PANEL

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402 - Price 95 cents

OFFICE OF TECHNOLOGY ASSESSMENT

Emilio Q. Daddario, Director
Daniel De Simone, Deputy Director

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Emilio Q. Daddario

LETTER OF TRANSMITTAL

Congress of the United States
Office of Technology Assessment
Washington, D.C., July 15, 1974

The Hon. Harrison A. Williams
Chairman, Senate Committee on
Labor & Public Welfare
United States Senate
Washington, D.C. 20510

The Hon. Harley O. Staggers
Chairman, House Committee on
Interstate & Foreign Commerce
U. S. House of Representatives
Washington, D.C. 20515

Sirs: On behalf of the Board of the Office of Technology Assessment, we are pleased to forward to you the following report of the Drug Bioequivalence Study Panel, which was assembled on April 12, 1974, under the chairmanship of Dr. Robert Berliner. The Panel was asked to determine whether or not the technological capability is now available to assure that drug products with the same physical and chemical composition will produce comparable therapeutic effects.

This report is being made available to your Committees in accordance with Public Law 92-484, with appreciation and thanks to Dr. Berliner and his colleagues on the OTA Drug Bioequivalence Study Panel.

Respectfully yours,

Edward M. Kennedy
Chairman

Respectfully yours,

Charles A. Mosher
Vice-Chairman

panel members

Robert W. Berliner, M.D., Dean
School of Medicine
Yale University
(Chairman)

Leighton E. Cluff, M.D., Chairman
Department of Medicine
University of Florida

James T. Doluisio, Ph.D., Dean
College of Pharmacy
The University of Texas at Austin

Kenneth L. Melmon, M.D., Chief
Division of Clinical Pharmacology
University of California, San Francisco

Alexander S. Nadas, M.D., Chief
Cardiology Department
Children's Hospital Medical Center, Boston

John A. Oates, M.D., Professor
Medicine and Pharmacology
Vanderbilt University

Sidney Riegelman, Ph.D., Chairman
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University of California, San Francisco

Frederick E. Shideman, M.D., Ph.D., Head
Department of Pharmacology
University of Minnesota

Marvin Zelen, Ph.D., Director
Statistical Laboratory
State University of New York at Buffalo

Frederick C. Robbins, M.D., Dean
Case Western Reserve Medical School
Case Western Reserve University
(Ex Officio Member)

conclusions and recommendations

1

Current standards and regulatory practices do not insure bioequivalence for drug products.

2

Variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures. It is probable that other therapeutic failures (or toxicity) of a similar origin have escaped recognition.

3

Most of the analytical methodology and experimental procedures for the conduct of bioavailability studies in man are available. Additional work may be required to develop means of applying them to certain drugs and to special situations of drug use.

4

It is neither feasible nor desirable that studies of bioavailability be conducted for all drugs or drug products. Certain classes of drugs for which evidence of bioequivalence is critical should be identified. Selection of these classes should be based on clinical importance, ratio of therapeutic to toxic concentration in blood, and certain pharmaceutical characteristics.

5

Present compendial standards and guidelines for Current Good Manufacturing Practice do not insure quality and uniform bioavailability for drug products. Not only may the products of different manufacturers vary, but the product of a single manufacturer may vary from batch to batch or may change during storage.

6

New compendial standards for active ingredients, excipients and finished drug products should be developed and revised on a continuing basis to reflect the best available technology to insure quality and uniform bioavailability. Appropriate statistical procedures should be specified to make certain that the purposes of the standards are objectively satisfied. The guidelines for Current Good Manufacturing Practice should be expanded to include specific descriptions of all significant aspects of manufacturing processes from the raw materials to the final product.

7

Additional research aimed at improving the assessment and prediction of bioequivalence is needed. This research should include efforts to develop in vitro tests or animal models that will be valid predictors of bioavailability in man.

8

Current law requiring manufacturers to maintain records and make information available to the FDA is ambiguous or inadequate and should be clarified and strengthened. In particular, manufacturers should be required to submit all information relating the tests they conduct to the bioavailability data they develop in order to help provide information on the factors that modify the bioavailability of drug products. This information should be available to aid in the establishment of compendial standards.

9

Exemptions provided in current law for some drug products based on their year of introduction in relation to amendments in the Food, Drug, and Cosmetic Act (so-called grandfather clauses) have impeded improvement in the quality of these products. Such exemptions should be eliminated.

10

A single organization capable of setting standards adequate to insure the quality and uniform bioavailability of drug products should be established to replace the present USP and NF as the official standard-setting organization of the Federal Government.

11

A system should be organized as rapidly as possible to generate an official list of interchangeable drug products. In the development of the list, distinctions should be made between two classes of drugs and drug products:

1. Those for which evidence of bioequivalence is not considered essential and that could be added to the list as soon as standards of pharmaceutical equivalence have been established and satisfied.

2. Those for which evidence of bioequivalence is critical. Such products should be listed only after they have been shown to be bioequivalent or have satisfied standards of pharmaceutical equivalence that have been shown to insure bioequivalence.

biopharmaceutics and dosage form design

edited by Gerald E. Schumacher, Pharm.D., Ph.D.

This column covers a broad range of topics pertinent to dosage form and biopharmaceutical design. It emphasizes (1) the pharmaceutic and biopharmaceutic principles required for dosage form design in hospital pharmacy, (2) topics in these areas which are of general interest to the clinical pharmacist in his interpretation of dosage form effects and (3) brief research projects in these areas.

Formulations published in this column are intended only as guides to preliminary evaluation in individual laboratories. Since no program of bulk compounding should be conducted without the provision for quality control, all formulations are considered incomplete until individual laboratories judge their merit on the basis of appropriate analytical procedures.

Contributions of 500-2,000 words are invited if they demonstrate the practical application of sound dosage form and biopharmaceutical design theory. The theoretical justification for all procedures, formulations and interpretations is required. Address all correspondence to:

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Variations in Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets Manufactured by Thirteen Firms

by JOHN L. LACH, TING-FONG CHIN and EUGENE L. PARROTT

► A MONOGRAPH OF THE NATIONAL FORMULARY OR THE United States Pharmacopeia for a specific dosage form of a drug(s), such as Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF, does not specify the excipients to be used or the method of manufacture. The approval of the Food and Drug Administration of a pharmaceutical (drug) product is for a specific dosage form manufactured by a specific process with specific drug(s) and excipients. Another firm may manufacture the same dosage form having an identical drug content and satisfying the official specifications, and although the two products are chemically equivalent, they were designed with different formulations consisting of different excipients and were prepared using different equipment and different procedures.

The effect that the excipients and the manufacturing procedure may have on absorption of drug(s) and subsequent therapeutic efficacy has been seriously considered for only a decade. Poole[1] presented an overview of biologic and physicochemical factors that may modify bioavailability. Monkhouse and Lach[2] recently reviewed the literature on the effect of excipients on drug absorption. In seven of nine humans Bettis, Lach and Hood[3] found significantly different serum levels of theophylline between a single oral administration of equivalent doses of free theophylline and an isolated 2:1 theophylline-phenobarbital complex. Such a difference points out that two drugs in a single dosage form may interact and alter drug absorption (bioavailability). The Academy of Pharmaceutical Sciences in "Guidelines for Biopharmaceutical Studies in Man"[4] identifies some of the physiologic factors and dosage form factors that may influence bioavailability.

Based on economic considerations there are those who advocate the use of the cheapest dosage form which is labeled to contain the prescribed quantity of drug(s). This concept does not appear to be in the best interest of the public health because controlled studies in man (in which two or more commercial pharmaceutical products containing the same drug in the same dosage form were used) have shown that factors other than drug content (chemical equivalency) are responsible for variability in drug absorption. Wagner[5] has summarized these studies on commercial products containing riboflavin, aspirin, aminosalicylic acid, chloramphenicol, sodium diphenylhydantoin, sulfisoxazole, tetracycline hydrochloride, oxytetracycline

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hydrochloride, isoniazid, chlordiazepoxide hydrochloride, warfarin and ephedrine sulfate. Recently Lindenbaum et al.[6] found as much as four-to seven-fold difference in serum digoxin level after oral administration of tablets manufactured by different firms. They also reported lot-to-lot variation. Similarly, in their study, Bettis, Lach and Hood[3] showed that bioavailability, as determined by serum theophylline, varied upon the administration of three commercial theophylline, ephedrine hydrochloride and phenobarbital tablets. The in-vitro dissolution data for theophylline from these tablets followed rank-order correlation with the serum levels.

Theophylline is a gastric irritant and frequently causes nausea upon oral administration. For this reason it is frequently administered in complex dosage forms (enteric coated or sustained release products). Theophylline and ephedrine are widely used in the treatment of bronchial asthma. Ephedrine is an effective drug in bronchial asthma, and combinations of ephedrine and phenobarbital are often useful in patients with mild episodic asthma.[7] In such a disease state a rapid onset of therapeutic response is vital; therefore, solid dosage forms should be designed so they have a fast dissolution. Biological availability differs following the oral administration of commercial tablets containing theophylline, ephedrine hydrochloride and phenobarbital. Based on these considerations, which indicate a high potential for therapeutic inequivalences of pharmaceutical products, Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF were selected for investigation.

It is not the purpose of this report to evaluate bioavailability or therapeutic efficacy of these tablets but to demonstrate that between various firms and even within a given firm there exists a problem in satisfying in vitro specifications for Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF.

Experimental

Commercial Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets. Twenty lots of uncoated Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF manufactured by 13 pharmaceutical firms within the United States and labeled to contain 130 mg theophylline, 24 mg ephedrine hydrochloride, and 8 mg phenobarbital were obtained from pharmacies. The firms and lot numbers of the tablets tested are given in Table 1.

Weight Variation. Twenty tablets were weighed and the average weight was calculated. In order to meet NF specifications for compressed tablets, not more than two of the individually weighed tablets may deviate from the average weight by more than 7.5%.[8]

Analytical Methods. The chemical analyses were performed in duplicate. Samples were taken from 20 tablets that had been weighed and pulverized. The concentration of each drug was calculated by means of a standard absorbance-concentration curve determined for the official reference standard of each drug. Ephederine was determined by a modification of the periodate oxidation method reported by Chafetz:[9] An accurately weighed quantity of pulverized tablets representing approximately 2 mg of ephedrine was shaken for 30 minutes with 100 ml of distilled water in a glass-stoppered, 250-ml conical flask. The mixture was filtered through a sintered-glass filter, and the first 20 ml of the filtrate were discarded. To a 5.0-ml aliquot of the filtrate, 1.0 ml of saturated sodium bicarbonate solution and 2.0 ml of 2% sodium metaperiodate solution were added, and the mixture was shaken. The mixture was shaken for 30 seconds with 20.0 ml of n-hexane. The hexane layer was filtered through dry filter paper (Whatman No. 1). The absorbance of ephedrine in the hexane was determined spectrophotometrically at 240 nm in a 1-cm cell.

Assay for Theophylline. An accurately weighed sample of the powdered tablets was transferred to a 250-ml volumetric flask and shaken for 30 minutes with 200 ml of distilled water, after which the volume was adjusted to 250 ml with distilled water. The solution was filtered through a sintered-glass filter and adjusted to a concentration of approximately 8 μg/ml of theophylline. The absorbance was determined spectrophotometrically at 275 nm. At this dilution the interference of ephedrine and phenobarbital is negligible.

Table 1. Code for Manufacturers of Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF

CODE	MANUFACTURER	LOT NUMBER
A	Aberdeen Pharmacals Corp.	374705
B	American Pharmaceutical Co.	1F16172
C	B & B Drug Co.	021139
D	Davis-Edwards	E16244
E	Spencer Mead, Inc.	031239
F	Richlyn Laboratory	19077
G	Rugby	051443
H	Stayner Corp.	1LR643D
I	Sheraton Labs., Inc.	1LR643-11
J	Warner-Chilcott Laboratories	0152P108C
K-1	Towne, Paulsen & Co., Inc.	127051
K-2	Towne, Paulsen & Co., Inc.	037131
L-1	Robinson Laboratory, Inc.	20360340
L-2	Robinson Laboratory, Inc.	10521138
L-3	Robinson Laboratory, Inc.	10160340
M-1	Progress Labs., Inc.	C212
M-2	Progress Labs., Inc.	B203
M-3	Progress Labs., Inc.	N121
M-4	Progress Labs., Inc.	E101
M-5	Progress Labs., Inc.	2953A

Assay for Phenobarbital. An accurately weighed quantity of powdered tablets representing approximately 16 mg of phenobarbital was shaken for 30 minutes with 50.0 ml of 10% barium hydroxide solution in a 100-ml volumetric flask. Sufficient distilled water was added to adjust the volume to 100 ml. The solution was filtered through a sintered-glass filter. Twenty milliliters of the filtrate were pipetted into a separatory funnel, and 10 ml of concentrated hydrochloric acid were cautiously added. The solution was extracted three times with 50 ml of ether. The combined etheral extract was evaporated to dryness on a steam bath. The residue was dissolved with gentle heating in 50 ml of a borate buffer at *p*H 9.5. After cooling, the resulting solution was transferred to a volumetric flask and diluted to 100 ml with the buffer. The solution was filtered, and the first 20 ml were discarded. Twenty milliliters of the filtrate were pipetted into a volumetric flask and the volume was adjusted to 100 ml with the buffer. The absorbance of the phenobarbital was determined spectrophotometrically in 240 nm.

Disintegration Test. The NF Tablet Disintegration Test for uncoated tablets[8] was carried out in simulated gastric fluid T. S. on all lots of tablets. The disintegration time limit of the NF monograph is 10 minutes.

Dissolution Test. The Dissolution Test, Method II, using six tablets in 750 ml of simulated gastric fluid T. S. at 37 C was used as specified in the NF monograph.[8] At 2, 5 and 10 minutes a 2.0-ml sample was withdrawn by pipet and diluted in a volumetric flask to 500 ml with distilled water. The absorbance of the solution was determined at 275 nm, and the concentration was calculated by means of a standard absorbance-concentration curve. The reported dissolution is the average of two tests. The NF monograph specifies that not less than 66% of the labeled amount of theophylline dissolves within 2.0 minutes.

Results and Discussion

The acceptable quantity of drugs in Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF is not less than 90.0% and not more than 110.0% of the labeled amount of each drug. It is generally considered that the drug content of a tablet is readily maintained within the legally permissible limits of the labeled quantity if good manufacturing practices are employed; yet in this study chemical analyses showed that 45% (nine out of 20) of the lots of tablets were not chemically equivalent. Three of the 20 lots did not meet the weight variation specification (Table 2).

The recently introduced dissolution specification is a sensitive test and a step forward in refining the methods of insuring equivalency of tablets. As shown in Table 3, eight out of 20 lots did not meet NF specifications that not less than 66% of the theophylline be dissolved within 2.0 minutes.

Table 2. Percent of Labeled Amount and Weight Variation of Drugs in Some Commercial Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF

	% LABELED AMOUNT			WEIGHT VARIATION	
MANUFACTURER	THEOPHYLLINE	PHENOBARBITAL	EPHEDRINE HYDROCHLORIDE	AVERAGE (MG)	RANGE (MG)
A	108.2	107.4	86.8[a]	222.4	213.4-230.9
B	99.3	102.3	111.7[a]	194.3	170.3-203.3[a]
C	105.7	102.1	100.0	205.5	195.5-221.7
D	106.0	102.4	121.7[a]	238.4	223.3-245.7
E	99.3	105.6	100.4	204.3	195.9-216.2
F	84.2[a]	100.1	97.9	210.7	194.0-226.2
G	91.2	94.1	93.3	186.7	157.6-202.0[a]
H	112.0[a]	102.4	96.8	230.4	224.0-238.3
I	105.9	99.6	106.3	226.6	218.8-237.3
J	98.6	100.3	109.2	210.9	202.0-219.7
K-1	114.0[a]	105.6	95.0	241.7	236.4-246.8
K-2	111.1[a]	98.4	93.8	238.2	231.4-245.3
L-1	109.5	98.6	92.5	239.8	233.5-247.7
L-2	100.7	93.1	100.4	202.7	152.0-216.3
L-3	102.8	103.3	99.6	239.3	230.5-243.5
M-1	91.1	97.1	106.7	203.9	188.3-229.9
M-2	99.3	100.9	96.3	187.8	178.4-196.4
M-3	108.2	104.5	86.8[a]	283.8	275.3-296.8
M-4	111.3[a]	100.3	100.5	212.8	208.3-217.1
M-5	108.1	101.1	109.2	240.5	209.0-291.3[a]

[a]Does not meet NF specification

Table 3 Dissolution and Disintegration of Some Commercial Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF

MANUFACTURER	% THEOPHYLLINE DISSOLVED 2 MIN	5 MIN	10 MIN	DISINTEGRATION TIME (MIN)
A	52.8[a]	68.4	81.2	2
B	28.0[a]	60.3	95.3	10
C	98.7	103.1	103.9	2
D	27.6[a]	46.0	73.8	12[a]
E	91.0	101.6	102.2	3
F	12.4[a]	27.1	52.4	17[a]
G	97.5	98.1	98.1	2
H	103.6	108.9	111.4	2
I	104.5	106.4	109.0	2
J	99.5	101.7	101.7	2
K-1	110.7	112.8	113.5	2
K-2	108.8	110.5	111.7	2
L-1	26.1[a]	44.2	73.0	12[a]
L-2	92.7	104.3	104.3	5
L-3	23.9[a]	39.2	67.6	14[a]
M-1	21.1[a]	41.2	70.0	13[a]
M-2	54.9[a]	92.1	101.7	10
M-3	78.8	107.8	110.2	5
M-4	98.6	110.8	111.3	3
M-5	99.5	109.3	109.3	2

[a]Does not meet NF specification.

Based on the oldest control test of chemical analysis and the newest control test of dissolution, 65% (13 out of 20) of the lots did not meet legal specifications. Certainly the presence of the labeled quantity of the drug in the tablet and the specified dissolution of the drug from the tablet are essential to the desired bioavailability and therapeutic result. In the treatment of acute bronchial asthma by means of theophylline, ephedrine hydrochloride and phenobarbital tablets, it is vital that the labeled quantity of the drugs be administered and be rapidly dissolved from the tablet so they are rapidly available for absorption.

Five lots of tablets did not meet NF specifications that the tablet disintegrate in 10 minutes. It is interesting to notice that the five lots which did not meet the specification for disintegration also did not meet the specification for dissolution.

The four specifications—drug content, weight variation, disintegration and dissolution—may be used to compare a pharmaceutical product made by several firms. Five lots (C, E, I, J and L-2) met the four specifications. Eight lots (G, H, K-1, K-2, M-2, M-3, M-4 and M-5) failed to meet one specification. Four lots (A, L-1, L-3 and M-1) failed to meet three specifications.

Lot L-2 met all specifications, but L-1 and L-3 did not meet dissolution and disintegration specifications. With manufacturer M, at least one of the four specifications was not met in each of the five lots tested. In this study conducted prior to the introduction of dissolution tests into the official compendia the extent of lot-to-lot variation was further examined in 11 lots of manufacturer M. Diffuse reflectance spectra of the 11 lots did not show significant variations, which indicated that if any drug-drug and/or drug-excipient interactions occurred, they were the same in all lots. Dissolution and hardness varied considerably from lot-to-lot as shown in Table 4. As illustrated in Figure 1, only two lots met NF dissolution specifications. There appears to be no correlation between hardness and dissolution as the two lots with the hardness of 5.8 and 5.1 kg were the two fastest dissolving tablets.

Table 4. Lot-to-lot Variation in Hardness[a] and Dissolution of Eleven Lots of Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF Manufactured by Company M

LOT NUMBER	HARDNESS (KG)	% THEOPHYLLINE DISSOLVED 2 MIN	5 MIN	10 MIN
07626	5.8 ± 0.5	75.2	91.1	93.0
08010	1.3	39.0[b]	47.5	53.0
08861	2.7	66.0	85.0	88.0
046986	2.5	49.6[b]	57.8	64.0
109716	2.2	55.0[b]	69.6	74.6
08322	0.8	42.0[b]	50.0	57.0
09716	4.4	51.5[b]	82.0	86.2
10999	3.3	48.5[b]	66.0	71.5
10998	4.7	59.0[b]	75.5	80.0
0185W	2.7	61.0[b]	79.0	83.0
08864	2.0	28.5[b]	38.0	46.5

[a]Average of five determinations by means of Pfizer Tablet Hardness Tester.
[b]Does not meet NF specification.

Conclusion

In recent years in vivo testing of dosage forms has been emphasized. The use of in vivo evaluation and the correlation of in vivo and in vitro data are desirable; however, the value of in vitro specifications is not to be ignored. In some cases, in vitro specifications should be expanded. For example, only 11 of the monographs for tablets in the official compendia contain dissolution specifications. Frequently in the evaluation of bioavailability the in vitro characteristics of the dosage form are not reported or considered; thus, the extent to which formulation factors contribute to the particular bioavailability is obscured. The conclusive evaluation requires a knowledge of both in vitro and in vivo properties of the pharmaceutical product.

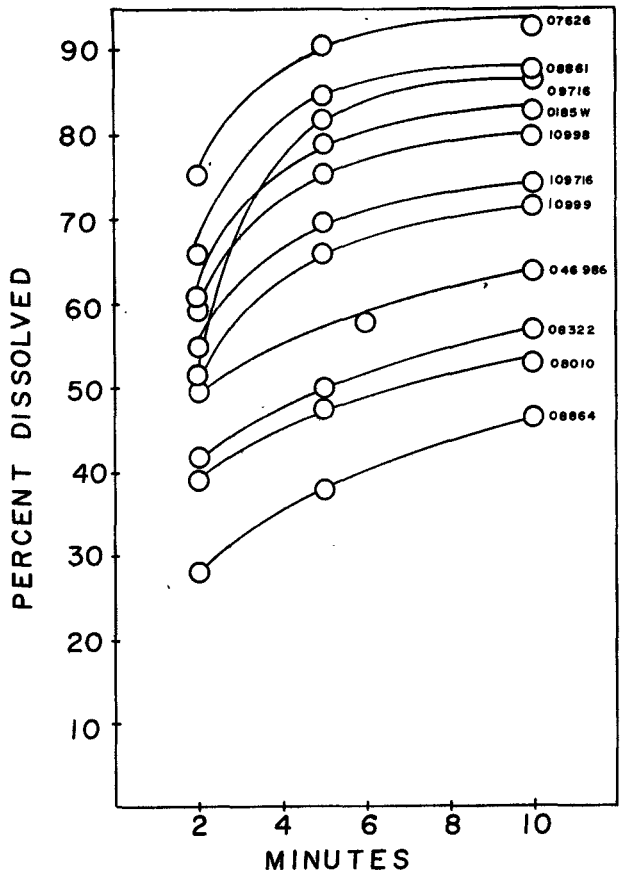

Figure 1. Dissolution profiles of eleven lots of Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF made by company M

Despite professional, scientific and political concern with bioavailability of economical pharmaceutical products, too frequently the product does not satisfy the relatively simple chemical and physical specifications of the official compendia. This investigation of Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF manufactured by 13 firms shows that often legal specifications are not satisfied and that differences in the tablet exist between firms, and at times, a lot-to-lot variation exists within a given firm. The lot-to-lot variation may indicate the need for improvement in manufacturing practices and/or quality control. It may not be practicable that each lot be identical in all respects; however, the degree to which minor variations of specifications significantly contribute to therapeutic response should be established, and the permissible range of any specification should be established on the basis of clinical efficacy.

With Kentucky and California statutes containing the term "quality drugs," the question arises as to what specifications are to be established for determining a quality pharmaceutical product. Are the specifications such as chemical equivalency, weight uniformity, disintegration time and dissolution profile adequate to define a quality product and to allow the pharmacist to intelligenctly select a quality product from those of numerous manufacturers? Perhaps a reference pharmaceutical product should be used as a standard. If so, how is the product to be selected? The reference standard should be one that has been investigated thoroughly and is recognized as being clinically effective. In 1968 the Food and Drug Administration cancelled certification of three manufacturers and five repackers of chloramphenicol capsules because of doubts of safety and efficacy based on the properties of Chloromycetin capsules. Since it was marketed in 1949, Chloromycetin capsules, as the first commercial chloramphenicol product, have undergone the majority of clinical studies as well as extensive physicochemical evaluation, and it was the logical choice as a reference product. Similarly, the Food and Drug Administration used Terramycin capsules as a reference product in evaluating oxytetracycline capsules from all sources in the United States.

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ABSTRACT

Theophylline, Ephedrine Hydrochloride and Phenobarbital Tablets NF manufactured by 13 firms were tested for chemical equivalency, weight variation, disintegration and dissolution.

Sixty-five percent of the lots did not meet NF specifications. Diffuse reflectance spectra, hardness and dissolution profiles were determined for 11 lots of a given manufacturer. The diffuse reflectance spectra demonstrated no significant difference in drug-drug and/or drug-excipient interaction. Hardness and dissolution varied considerably. Only two of the 11 lots met the NF specification for dissolution. The variation between tablets manufactured by different firms and the lot-to-lot variation with a given firm show that in vitro testing is a necessary part of the evaluation of a quality pharmaceutical product.

Ed. Nelson

*DR. BERLINER'S TESTIMONY BEFORE THE SENATE SUBCOMMITTEE ON MONOPOLY

GAYLORD NELSON, CHAIRMAN

March 19, 20, and 21, 1975

Dr. Berliner first read a prepared statement which merely reviewed the major findings of the OTA report. Points he apparently wanted to clarify, or emphasize, were:

> "..two drugs may differ in bioavailability, that is be bio-inequivalent, but may still be therapeutically equivalent." ..."On the other hand, it is also true that in a very few instances, differences in bioavailability have led to well-documented therapeutic failures. The rarity with which such failures have been documented should not mislead one into believing that they are rare occurances."
>
> "We therefore concluded that there are at least some categories of drug products for which it will be necessary to establish adequate and standard bioavailability before interchangeability could even be considered."
>
> "It was our view that considerable tightening of those (USP and NF) standards should be effected and that it would be desirable for the improvement of those compendial standards to precede the development of a list of interchangeable products."

He would have to conclude today, as he had at the time of the release of the OTA report, he said, that "I see no danger of therapeutic inequivalence if the list of drug entities to be included is based on careful selection by appropriate experts. However, I believe that the list will necessarily be more circumscribed than would be possible if the compendial standards were improved to give better assurance of bioequivalence." (emphasis added)

# # # #

* Robert W. Berliner, M.D., Dean, Yale School of Medicine and Chairman, Drug Bioequivalence Study Panel for Office of Technology Assessment, U. S. Congress

CONGRESSIONAL STUDY SHOWS DRUG SUBSTITUTION PROPOSALS UNWISE

The conclusions and recommendations contained in a major report released July 12, 1974 by the Office of Technology Assessment, United States Congress, have cast serious doubt on the wisdom of enacting state legislation to allow pharmacists to substitute "generic" drug products for brand name drugs prescribed by physicians.

A national panel of drug experts was asked by the OTA:

> Can current Government standards assure that chemically equivalent drug products, made by different manufacturers, produce equal therapeutic effects (bioequivalence)?

After careful study, the OTA panel's unanimous answer was:

> "Current standards and regulatory practices do not assure bioequivalence for drug products....The problem of bioinequivalency in chemically equivalent products is a real one...documented instances constitute unequivocal evidence that neither the present standards for testing the finished product nor the specificiations for materials, manufacturing process, and controls are adequate to ensure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability." (time drug takes to act in adequate concentration in a given part of the body)

The panel recommended a number of steps to improve the present system. After these steps have been accomplished, the panel concluded, a system should be organized as rapidly as possible to generate an official list of interchangeable prescription drug products.

The panel stated, however, that:

> "Current staffing and funding levels are not adequate for the FDA to meet the significant new responsibilities proposed in this recommendation. Consequently, additional financial and staffing support will be required to develop and maintain the list of interchangeable drug products and to coordinate these efforts with the agencies involved in setting standards and supporting research."

Thus, only after new federal drug standards and capability to assure equivalence have been established and satisfied, can state legislation authorizing "generic drug" substitution safely be enacted.

[A complete copy of the report Drug Bioequivalence: A Report to the Office of Technology Assessment can be obtained by contacting the Public Relations Department, Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D. C. 20005]

# # #

ABBOTT

0738

Pharmaceutical Products Division

Robert E. Singiser, Ph.D.
Vice President, Scientific Affairs

Abbott Laboratories
14th & Sheridan Road
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March 27, 1975

Mr. Frank Titus
Village Drug
1119 California
Reno, Nevada 89502

Dear Mr. Titus:

Your request for information regarding the advantages of a proprietary erythromycin stearate tablet, Erythrocin® Stearate Filmtab® Tablets, Abbott Laboratories, as compared to the many generic erythromycin stearate tablets on the market, was forwarded to me for reply. We then spoke by telephone so that I could get a clearer picture of your needs. I hope the following will be helpful.

Abbott Laboratories is the only U.S. pharmaceutical company that is a manufacturer of both the erythromycin stearate bulk drug and the final erythromycin stearate tablet product. This allows us to control the quality and efficacy of our Erythrocin Stearate Filmtab Tablets throughout the manufacturing process for both the active ingredient and the dosage form.

Erythromycin stearate tablets are described in monographs contained in the Code of Federal Regulations and the United States Pharmacopeia. As with all erythromycin stearate tablet products, Abbott Laboratories' quality assurance procedures for Erythrocin Stearate Filmtab Tablets conform to those required in these regulations.

Abbott Laboratories' R&D and Quality Assurance programs are designed to exceed the standards established by the Federal Government. Numerous discriminatory in-process testing is performed on each lot of Erythrocin Stearate Filmtab Tablets during the manufacturing process to ensure intra- and inter-batch uniformity. These tests include:

1. Weight variation
2. Tablet hardness (prior to coating)
3. Tablet disintegration (uncoated)
4. Tablet thickness
5. Tablet appearance
6. Tablet shape, color and odor
7. Integrity of the tablet coating
8. Testing to assure that the filmcoating used has been properly dried

Dissolution studies and bioavailability studies are continuously conducted on representative lots of products. Controlled clinical tests are appropriately conducted to confirm product efficacy; an example is the recent study which has removed the "possibly effective" status from the Hemophilus influenzae indication (see Attachment A). Please note the last paragraph of the attachment; even though Abbott Laboratories paid for all of the clinical studies needed to establish this claim, all manufacturers of erythromycin products will likely be permitted by the Food and Drug Administration to use this indication. It must therefore be obvious that the cost of the studies will be borne by the Abbott Laboratories Erythrocin products, and not the generic products.

In addition to the above, to confirm that our product remains efficacious and fully bioavailable throughout the life of the product (to the expiration date), we have performed bioavailability studies on the product at various time periods throughout the five year expiry period. These studies were conducted on freshly made tablets, and then repeated annually up to the end of the five year expiry period. The results of these studies indicate that Erythrocin®Stearate Filmtab®Tablets are well absorbed throughout the shelf life of the product, and there is no significant difference in the bioavailability of the product with product age.

As part of our quality assurance program, representative lots of Erythrocin Stearate Filmtab Tablets are routinely evaluated in stability tests of product and package. These materials are tested to make certain that our tablets continue to meet all the Abbott, FDA, and United States Pharmacopeia chemical and physical specifications throughout the expiry period of the product.

Further, if there is any question about the acceptability of any lot of Erythrocin product produced, that lot will either be destroyed or specific bioavailability tests will be conducted on that lot to establish its in vivo performance. This costly procedure could not be expected from lower cost generics.

Our service to the customer does not end when the product leaves Abbott Laboratories. If the customer has a question regarding our product, at least four areas of our Division are available to assist him. The Abbott professional sales representative is routinely available to our customers and is the first source of information if a question arises. If the representative cannot answer the question, he will forward it to the appropriate area at Abbott Laboratories, North Chicago, for reply. The Product Improvement Coordination group is responsible for those inquiries related to product quality and improvement. Our Medical Information group is available 24 hours a day to answer questions related to the safety and efficacy of the product. Thirdly, the Office of the Vice President, Scientific Affairs, is available

to respond to those inquiries related to formulation and bioavailability aspects of the product. Bioavailability information is routinely provided on all of our dosage forms (tablets, suspensions, granules, chewables, injectables, suppositories, etc.). Copies of the attached paper by Drs. Chun and Seitz are also sent to those practitioners who will be evaluating bioavailability data from various sources. We feel that it is our responsibility to point out the pitfalls involved in such evaluations.

Since Abbott Laboratories is also the source for our bulk erythromycin drug, we rigidly control all aspects of a final dosage form's manufacture, including the bulk drug that goes into it. Bulk drug can meet all compendial and FDA specifications, yet perform differently in vivo, depending on how that bulk drug is produced. In vitro tests will now show these differences. No processing change is permitted in our bulk drug manufacture without first evaluating this change through human bioavailability testing. A generic manufacturer that simply purchases bulk drug has no way to monitor such changes. In fact, such a company may buy drug from two or more different sources, which might result in tablets of differing quality. We are aware of instances where different formulas had to be used for erythromycin tablets, depending on which source of bulk drug was employed. This illustrates the extreme sensitivity of erythromycin products to formulation and manufacturing variables. To maintain leadership in this product line, research must continue after the product is marketed in order to understand these variables. Abbott Laboratories is continually researching our products in an attempt to find ways to make them even better. Up to 100 bioavailability studies are performed annually by Abbott Laboratories. Generic companies generally do not wish to incur this huge expense, so they formulate their products and then forget about any further work on them.

Abbott Laboratories' Erythrocin®Stearate Tablets are cited as the standard of the industry. Many years of intensive work have been devoted to establishing development and quality assurance programs, setting rigid specifications and performing extensive clinical studies to ensure the safety and efficacy of our product. Extensive clinical studies continue to be done on erythrocin to expand its clinical use and broaden its utility in specific disease areas.

I trust you will find this information of use. If you have any additional questions, do not hesitate to contact me. Your interest in our products is appreciated.

Sincerely yours,

R. E. Singiser, Ph.D.

RES:cm

FACTS ABOUT DRUG QUALITY

DO QUALITY DIFFERENCES EXIST AMONG VARIOUS VERSIONS OF THE SAME DRUG?

- Yes. Even though two drugs made by different manufacturers contain the same active ingredients, their effects on patients may vary. Variations can occur in purity, potency, weight, disintegration time, dissolution time, and stability. Nonactive ingredients such as binders, coaters, fillers and lubricants can also vary from manufacturer to manufacturer, and they affect drug quality in important ways.

- All of these factors, and others, determine how fast and thoroughly a drug dissolves and sends its active ingredient to a given part of the body. This is known as bioavailability. Drug products that exhibit comparable bioavailability characteristics are considered to be bioequivalent. Otherwise, they are bioinequivalent and may not have the same therapeutic effect on patients.

ARE THERE KNOWN CASES OF BIOINEQUIVALENCE AMONG DRUGS?

- Yes. Studies have shown that at least 73 drugs have real or potential bioavailability problems. Take the case of digoxin, a drug used to treat certain forms of heart disease. In 1971, the Food and Drug Administration (FDA) discovered that out of 36 firms' digoxin products, 33 failed to meet requirements. Some were not as potent as claimed, and others were too potent to the point of being dangerous.

- Professor John G. Wagner of the University of Michigan published a major review on drug equivalency in 1971 and reported that "for 10 of 12 drugs studied, or 83% of them, different manufacturers' products appear not to be equivalent."

- Presumed equivalents of the important antibiotic oxytetracycline were found by the FDA in 1970 to produce blood serum levels only half that of the original brand. Some 40 million capsules of the inequivalent brands and generics were recalled.

- In 1967, FDA studies confirmed industry reports that several forms of chloramphenicol (used for certain serious and acute infections) produced antibiotic levels in the body significantly lower than those produced by the original brand--despite the fact that they had been certified by FDA and were on the market.

- The Military has experienced numerous product failures over the last decade when different drug products were substituted for the brands physicians preferred. For example, in 1966 at Dow Air Force Base, Maine, physicians submitted a complaint about a new lot of diphenylhydantoin (used to control epilepsy). They said, "patients on this drug are experiencing seizures more frequently than on previously available products."

CAN THE GOVERNMENT ASSURE THE UNIFORM QUALITY OF DRUGS?

- No. A panel of the nation's drug experts, in a July 1974, report to the Office of Technology Assessment (OTA) of the U.S. Congress concluded that "current standards and regulatory practices do not assure bioequivalence for drug products...the problem of bioinequivalence in chemically equivalent products is a real one."

- The OTA Report went on to say that "documented instances constitute unequivocal evidence that neither the present standards for testing the finished product, nor specifications for materials, manufacturing process, and controls are adequate to ensure that ostensibly equivalent drug products are in fact equivalent in bioavailability."

IF THE GOVERNMENT CAN'T ASSURE DRUG QUALITY, THEN WHAT'S BEING DONE ABOUT IT?

- Most states prohibit pharmacists from substituting different drug products (brand or generic) for the ones prescribed unless the doctor consents. These laws protect consumers from exposure to inferior or variable therapy.

- Reliable drug companies are in the forefront of developing standards that assure bioavailability for drug products. Extensive testing and high standards for quality control enabled these companies to back the quality of their products.

- The OTA has recommended a number of steps to improve the current system. Among them is the creation of new standards that will help assure the uniform quality of drug products on the market. Considerable time will be required to develop and implement these recommendations.

WHAT CAN CONSUMERS DO TO ASSURE TREATMENT WITH SAFE, EFFECTIVE AND ECONOMICAL DRUGS?

- In advance of any illness, choose a pharmacy that will best serve you with quality drugs at the best price, and with efficient, professional services.

- Discuss your medication with your doctor. Ask him if several reliable companies produce the medicine he wants you to have (brand name or generic). If so, ask him to call your pharmacist and find out--among those companies whose products he has confidence in--which one you can buy for the lowest price.

- So you can be sure to get the lower priced, but still reliable product, ask your doctor to write your prescription specifying that particular company's product (whether he does this by writing the generic name and the name of the manufacturer, or by writing the brand name of the company's product, if it has one.)

- If the prescription is for a maintenance drug, ask your doctor to write it for a larger amount of the drug. You can save money by buying larger numbers of tablets less frequently.

# # #

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

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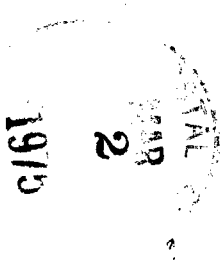

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0804

FOOD & DRUG ADMINISTRATION WEEKLY REPORT OF SEIZURES, PROSECUTIONS, INJUNCTIONS, FIELD CORRECTIONS, AND RECALLS

Issued: February 12, 1975

NOTE: The legal actions listed have been filed with the court indicated. The allegations of the Government have not yet been tried or adjudicated by the court.

Prosecution Actions Filed:

Against: Walk Brokerage, Inc. and Anthony W. Miller, Jr., Denver, Colorado
Charge: Adulteration - Products held under insanitary conditions.
Product: Foods
Filed: February 3, 1975 - U.S. District Court for the District of Colorado; FDC #59842; Criminal #75-CR-43.

- - - -

Complaints for Injunction Filed:

NONE

Seizure Actions Filed:

Product: Orotic Acid Anhydrous
Charge: Adulteration - Product is an unsafe food additive.
Responsible Firm: Private Formula, Inc., St. Louis, Missouri
Filed: January 30, 1975 - U.S. District Court for the Eastern District of Missouri; FDC #60183; Civil #75-93C(1).

- - - -

Product: Macaroni
Charge: Adulteration - Product held under insanitary conditions.
Responsible Firm: BRF Wholesale Company, Black River Falls, Wisconsin
Filed: January 3, 1975 - U.S. District Court for the Western District of Wisconsin; FDC #60126; Civil #75-C-1.

- - - -

MORE

Product: Myotonachol Tablets
Charge: Adulteration - Product contaminated with insect filth.
Responsible
Firm: Glenwood Laboratories, Inc., Tenafly, New Jersey
Filed: February 3, 1975 - U.S. District Court for the District of Minnesota; FDC #60195; Civil #5-75-13.

- - - -

Product: Candy Pacifier
Charge: Adulteration - Product is unfit for food as it is prepared in a manner and shape which present choking and aspiration hazards.
Responsible
Firm: The Paul Spitz Company, Bronx, New York
Filed: February 3, 1975 - U.S. District Court for the Southern District of Texas; FDC #60153; Civil #75-H-202.

- - - -

Product: Brie Cheese and Camembert Cheese
Charge: Adulteration - Product contaminated with decomposed cheese.
Responsible
Firm: (Unknown). (Mfr) - Fromagerie H. Hutin S.A., France; (Dlr) - Crystal Meat and Cheese Company, Inc., East Boston, Massachusetts
Filed: February 5, 1975 - U.S. District Court for the District of Massachusetts; FDC #60199; Civil #75-483-M.

- - - -

Regulatory Letters:

Regulatory Letters are formal legal notices used to advise firms or individuals that specific sections of the law administered by FDA have been violated. The recipient is advised that FDA will pursue legal or administrative sanctions if corrective action is not taken within a stated time period. Copies of all Regulatory Letters are available for public review at the Public Records and Documents Center, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20852.

Recalls and Field Corrections:

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

NONE

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

Product: Recall #F-063-5 has been extended to include one code of "Van Camp's Grated Light Tuna***6-1/4 oz.***," manufactured by Van Camp Sea Food Company, Division of Ralston Purina Company, Terminal Island, California. Lot Number: 7L207/50F3N. Distribution was limited to Topeka, Kansas and Northern California. (Recall #F-063-5).

Reason: Histamine contamination.

- - - -

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

Product: Prophenamine Expectorant with Codeine in one gallon jugs labeled in part "Prophenamine***Expectorant***with Codeine***1 Gal.*** Distributed by Carroll Chemical Co., Smyrna, Tenn.***" Lot number: 40786. Manufactured and recalled by Carroll Chemical Co., Smyrna, Tenn. by letter on January 17, 1975. Distribution was in the Eastern two thirds of the nation with firm estimating that approximately 100 gallon bottles remain on the market. (Recall #D-257-5).

Reason: Subpotent.

- - - -

Product: Normal Saline, mislabeled "Distilled Water" labeled in part "McGaw Distilled Water in Irrigating Container, McGaw Laboratories, Division of American Hospital Supply Corporation, Glendale, Ca.***Single dose container***Packed 12 Units/Case***Exp Sep 77***" Lot number: A4K152. Manufactured and recalled by McGaw Laboratories, Glendale, Ca. by telephone on January 27, 1975. Distribution was to hospitals in Alaska, Arizona, California, Montana and Utah between September 4, 1974 and January 23, 1975 with firm estimating that approximately 300 units remain on the market. (Recall #D-254-5).

Reason: Mislabeled - Normal Saline labeled as Distilled Water Irrigating Solution.

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Product: (Hair shampoo) "Body on Tap", packed in 4 oz. and 8 oz. plastic bottles. Lot numbers: 4004, 4005 and 4006. Manufactured and recalled by Bristol Meyers Products Division, Hillside, N.J. by salesman pick up on December 20, 1974. Distribution was to Colorado, Kansas, Ohio and Wyoming with firm estimated that approximately 7,500 bottles remain on the market. (Recall #F-093-5).

Reason: Bacterial contamination.

- - - -

Product: "Stamyl", an OTC tablet, packaged in strip paks of 167 strips of 6 tablets in a hospital shelf carton, bearing Spanish labeling, as follows in part, "Stamyl Marca Registrada Para: Complementor la Secrecon Insufficiente de Enzimas Pancreaticas Cada Tableta Contiene: Pancreatina a Concentracion Tres Veces Major Que la Indicada en el NF 175 mg.; Hemicelulosa 50 mg., Extractd de Bilis de Buey 25 mg. 1000 tabletsas***Winthrop Products Inc., New York, N. Y. E.U.A." Lot numbers: 580LE and 581LE. Manufactured by Winthrop Products, Inc., Rennselaer, N.Y. Packaged and recalled by Winthrop Products, Inc., Myerstown, Pa. by salesman pickup on January 16, 1975 with followup letter on January 17, 1975. Distribution was to hospitals in Puerto Rico with firm estimating that none remains on the market. (Recall #D-250-5).

Reason: Shelf cartons lack above mandatory labeling.

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Product: Rx drug, "Butamin Tablets***Sodium Butabarbital 30 mg.***manufactured by Mallard, Inc., Detroit, Michigan***", packed in bottles of 100 tablets. Lot number: C005. Manufactured and recalled by Mallard, Inc., Detroit, Michigan by letter on January 7, 1975. Distribution was to Illinois, Indiana, Iowa, Michigan, Missouri, Pennsylvania and New York with firm estimating that approximately 7,000 tablets remain on the market. (Recall #D-259-5).

Reason: Subpotency.

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MORE

Product: Thiamine Hydrochloride Tablets 100 mg. in bottles of 1,000 labeled in part, "Thiamine Hydrochloride Tablets (Vitamin B-1) 100 mg. 1000 Tablets***Distributed by Carroll Chemical Co., Smyrna, Tennessee***" Lot number: 40606. Manufactured by Stanley Drug Products, Portland Oregon. Repacked and recalled by International Drugs, Inc.,D/B/A Carroll Chemical Co., Smyrna, Tennessee by letter on January 17, 1975. Distribution was to Alabama, Florida, Louisiana, Massachusetts, Mississippi, New Hampshire, New Jersey, North Carolina, Tennessee, Virginia, Washington, D. C., and to one foreign country with firm estimating that approximately 15/1000 tablet bottles remain on the market. (Recall #D-255-5).

Reason: Trace contamination with methyltestosterone during repacking operation.

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Product: Calcium Lactate Tablets in bottles of 100, labeled in part:"*** Calcium Lactate***N.F.***10 Grains - 100 Tablets***Distributed by Carroll Chemical Co., Smyrna, Tennessee***" Lot number: 40313. Manufactured by Private Formulations, Inc., Hempstead, N.Y. Repacked and recalled by International Drugs, Inc., D/B/A Carroll Chemical Co., Smyrna, Tennessee by letter on January 17, 1975. Distribution was to the eastern two thirds of the nation with one shipment to Bermuda with firm estimating that approximately 500 bottles remain on the market. (Recall #D-256-6).

Reason: Trace contamination with methyltestosterone during repacking operation.

Product: Estrone Suspension in glass vials labeled in part, "Sterile 30 ml. Multiple Dose Vial Estrone Suspension 5.0 mg/ml***Intramuscular*** Manufactured for Rugby Laboratories, Inc., L.I., N.Y.***." Lot Number: 4A007. Manufactured and recalled by D-M Pharmaceuticals, Inc., Rockville, Maryland on January 27, 1975. (Recall #D-253-5).

Reason: Label mix-up - Some units of Estrone Suspension are labeled as Promethazine HCL Injection.

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Product: Oxytetracycline Hydrochloride Capsules, 250 mg. U.S.P., packed in bottles of 100 and 1,000 capsules under the following labels: (a) Rondex Laboratories, Inc., Guttenberg, N.J.; (b) B.R. Mitchell, Inc., Guttenberg, N.J.; (c) Purepac Pharmaceutical Company, Elizabeth, N.J.; (d) Bioline Laboratories, Inc., Brooklyn, N.Y.; (e) Cooper Drug Company, Troy, Michigan; (f) Geneva Generics, Detroit, Michigan; (g) Midway Medical Company, Glasgow, Kentucky; (h) Henry Schein, Inc., Flushing, N.Y.; and (i) United Research Labs, Inc., Philadelphia, Pa. Lot Number: 23806. Manufactured and recalled by Rondex Laboratories, Elizabeth, New Jersey by letter on January 22, 1975. Distribution was national. (Recall #D-247-5).

Reason: Unsatisfactory bioavailability.

- - - -

Product: Electroplated Nickel Silverware Baby Cup, packaged in brown cardboard carton with yellow and black label which reads in part, "E.P.N.S. Baby Cup***Style 01064***One Piece***Made in India***." Lot Number: 01064. Manufactured by Mysope Electroplating Ltd., Moradabad, India. Imported, distributed, and recalled by Prill Silver Company, Inc., New York, New York by letter on January 23, 1975. Distribution was nationwide. (Recall #F-084-5).

Reason: Excessive lead content.

MORE

Recalls and Field Corrections:

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

Product: Sweet Red and Green Peppers - Federico Brand Pizza Strips in institutional size package, distributed by Suzy Bel Canning Company, Inc., Port Elizabeth, New Jersey in #10 cans, net wt. 6 lbs. 6 oz., 6 cans per case. Lot Number: 2-line code with top line 4PSGR. Manufactured and recalled by Suzy Bel Canning Company, Inc., Port Elizabeth, New Jersey by telephone on December 13, 1974 and follow-up letters on December 14, 1974. Distribution was limited to 4 consignees in New York and Wisconsin. All of the products in which peppers were used were recovered prior to distribution. (Recall #F-091-5).

Reason: Bacterial contamination.

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

Product: Implantable Electronic Pacemakers as follows: (a) Model MIP-40 RT Regular P-Wave Blocked on Demand Pacemaker; (b) Model MIP 41 RT R-Wave Blocked Pacemaker equipped with Hysteresis Circuit; and (c) Model MIP 501 T Standard Asynchronous Pacemaker. Lot Number: Serial Numbers (a) 968 thru 3300; (b) 161 thru 650; and (c) 250 thru 554. Manufactured by Vitatron Medical, Dieren, Holland. Vitatron Medical, Inc., South Boston, Massachusetts contacted physicians advising them of the problem in June, 1974, and recommending replacement of units if preliminary symptoms are noted. FDA learned of the problem through a hospital investigation in December, 1974. Distribution was national with firm estimating that not more than 50 pacemakers remain implanted. (Recall #T-159/161-5).

Reason: Leakage of electrolyte from the batteries, resulting in premature battery depletion, loss of capture, and output loss.

MORE

Product: Akineton (Biperiden HCL) Tablets in 2/4 tablet sample catch covers in a mailing box which is 5 X 3 X 3/4 inches and reads in part, "***For Over a Decade***Relief of Parkinsonian Symptoms***Control of Extra Pyramidal Reactions***." Lot Number: 13500253. Manufactured and recalled by Knoll Pharmaceutical Corporation, Whippany, New Jersey by letter on January 14, 1975. Distribution was in northwestern New York State. (Recall #D-230-5).

Reason: Due to an error in mailing of physician's samples, the above product was mailed to expectant mothers.

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Product: Candy Pacifiers, assorted flavors, packaged in clear cello bag, 48 units to a box, 30 boxes to a case. Made in Hong Kong for Bee Distributing, Beverly Hills, California. Product is labeled as not for infant or baby use. Lot Number: None used. All of product is under recall. Importing broker is James G. Wiley Company, Los Angeles, California. Distributed and recalled by BLS Enterprises Corporation, d/b/a Bee Distributing Company, Beverly Hills, California by letter on January 20, 1975. Distribution was national with firm estimating that none of the product remains on the market. (Recall #F-085-5).

Reason: Product presents a potential choking and aspiration hazard to infants and small children.

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Product: Rx Drug, "Proserum 25 Normal Serum Albumin (Human) Salt Poor U.S.P. ***Distributed by The Dow Chemical Company, Indianapolis, Indiana***," in 50 cc bottles and packaged in a carton which includes an intravenous injection set. Lot Number: 174-077. Manufactured and recalled by Dow Chemical Company, Zionsville, Indiana by telephone and follow-up letter on December 3, 1974. Distribution was national with firm estimating that none of the product remains on the market. (Recall #B-018-5).

Reason: Fever and chills in recipients (pyrogenicity).

MORE

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

Product: "Giant Food Tomato Paste***Net Wt. 6 oz.***Product of Portugal*** Distributed by Giant Food, Inc., Washington, D.C." The 13 oz. similarly labeled cans are also involved. Lot Number: All lots where product label indicates "Product of Portugal" and bottom line of 2 line code contains the numerical series "34." Manufactured by Compal, Lisbon, Portugal. Recalled by Giant Food, Inc., Landover, Maryland by telephone on January 9, 1975. Distribution was in Maryland, Virginia, and Washington, D.C. (Recall #F-087-5).

Reason: Abnormal cans.

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Product: Candy - Holland Chocolate Toffee Eclairs. Candy is individually wrapped in a wax paper wrapper that may or may not be labeled as "Toffee Chocolate." Bulk 5 lb. poly bags labeled in part, "Toffee Chocolate Eclairs Holland's Finest Candy made in Breskens-Holland*** Net Wt. 4-1/2 lbs.***Wt. with Wrappers 5 lbs.***Packaged for Dae-Julie, Inc., Chicago, Illinois." Lot Number: None used. Manufactured by Verduyn Brothers Confectionery Works, Ltd., Breskens, Holland. Recalled by Cheese Barn, Inc., (Hickory Farms), Federal Way, Washington on December 4, 1974. Distribution was to ten Hickory Farms retail stores in Washington State with firm estimating that none of the product remains on the market. (Recall #F-086-5).

Reason: Rancidity/decomposition.

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Product: This is an extension of Recall #F-062-5, Tomato Catsup being recalled by Naas Foods, to include these additional lots distributed by C.B. Ragland Company, Nashville, Tennessee: (a) "Lucky Lady" brand in 14 oz. bottles; (b) "Colonial" brand in 14 oz. bottles; (c) "Lucky Lady" brand in 26 oz. bottles; and (d) "Colonial" brand in 20 oz. bottles. Lot Number: (a) PB456H, PB456J; (b) PC4514P, PC4514K, PC4515H, and PC4515F; (c) PB4520N, PB4520U, PB404G, PB40439, and PB40430; and (d) PK4522G9, PK4522F0, PC4A270, and PC4A275. Manufactured and recalled by Naas Foods, Inc., Portland, Indiana by telephone on December 16, 1974. (Recall #F-062-5).

Reason: Mold contamination.

MORE

DIGOXIN CERTIFICATION PROGRAM STATUS REPORT

The current status of the Digoxin Certification Program is as follows:

1. Thirty-five (35) Digoxin manufacturers have been involved in the program.

2. One hundred and forty-five (145) currently marketed batches from twenty-seven (27) manufacturers have been tested for dissolution and the results reported to the respective manufacturers.

3. Of the one hundred and forty-five (145) currently marketed batches tested, forty-five (45) batches from seventeen (17) manufacturers failed to meet the requirements of the Federal Register statement of 1/22/74. These out-of-limits batches, which represent a failure rate of 31.0 percent of the tested batches have been recalled by their manufacturers. An additional eleven (11) batches, which have not been tested by FDA, have been recalled by two (2) manufacturers who were required to recall all batches of Digoxin Tablets manufactured during the past two (2) years after four (4) consecutive batches tested by FDA all failed the dissolution requirements of the Federal Register statement.

4. To date, fifty-nine (59) batches from seventeen (17) manufacturers have been submitted for pre-marketing certification.

5. Forty-six (46) batches from fourteen (14) manufacturers have been certified and released for distribution.

6. Thirteen (13) batches from five (5) manufacturers failed the dissolution requirements of the Federal Register statement and were denied certification.

7. It has been our policy to temporarily release a manufacturer from the pre-marketing certification requirement when the manufacturer has submitted four (4) consecutive passing batches of Digoxin Tablets of the same strength. Thus far, three (3) manufacturers have been temporarily released from pre-marketing certification. One of the manufacturers has submitted four (4) consecutive passing certification batches for each of its three (3) Digoxin Tablet dosage strengths and has been temporarily released from the pre-marketing certification program for those three Digoxin Tablet dosage strengths.

The other two manufacturers were temporarily released from pre-marketing certification for one dosage strength.

Final release from the certification program will depend on:

a. An in-compliance, CGMP inspection of the manufacturer's plant;

b. Verification of the manufacturing process as submitted to FDA in an ANDA;

c. Compliance with all of the requirements of the Federal Register statement of 1/22/74.

8. Thus far, twenty-four (24) ANDAs have been submitted by nineteen (19) manufacturers.

Stephen P. Molinari Jan. 31, 1975

Stephen P. Molinari

January 31, 1975

Digoxin Certification Samples

Manufacturer	# of batches	# pass	# fail	released
* Barr	4	4		no
Burroughs Wellcome	12 (3 strengths]	12		yes
Cord	2	2		no
Halsey	5	5		yes
J. Davis	1		1	no
Heather	2		2	no
Ketchum	1	1		no
Lanett	2	1	1	no
Lederle	2	2		no
* Marshall	11	4	7	no
Phillips-Roxane	2	2		no
Rondex	2	2		no
SCA - ICN	1	1		no
Towne Paulsen	2		2	no
Vale	1	1		no
West-Ward	1	1		no
Zenith	8	8		yes
Total 17	59	46	13	3

* Even though these manufacturers had 4 consecutive passing batches, they were not released from certification because of too wide a variation among the batches.

Regulatory Letters:

Regulatory Letters are formal legal notices used to advise firms or individuals that specific sections of the law administered by FDA have been violated. The recipient is advised that FDA will pursue legal or administrative sanctions if corrective action is not taken within a stated time period. Copies of all Regulatory Letters are available for public review at the Public Records and Documents Center, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20852.

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Recalls:

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

Product: Recall #F-069-5, S. S. Pierce Red Label Stems and Pieces Mushrooms, appearing on Recall List of 12/11/74, has been extended to include product distributed by Eckerd Drug Stores in Georgia. (Press Release #74-66, 12/26/74).

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

Product: Sodium Diphenylhydantoin U.S.P., 1-1/2 gr. (100 mg.), packaged in plastic bottles containing 1,000 capsules each. Lot Number: 983194. Manufactured and recalled by Kasar Laboratories, Niles, Illinois by telephone on December 31, 1974 and/or January 2, 1975 with follow-up letters on January 8, 1975. Distribution was to State and County Hospitals and distribution centers in Connecticut, Illinois, Minnesota, California, and Arizona. (Recall #D-219-5).

Reason: Label mix-up - Bottle labeled as "1,000 Tablets/Aspirin/U.S.P." instead of Sodium Diphenylhydantoin.

MORE

Product: An in-vitro diagnostic reagent test kit for the quantitative determination of serum urea nitrogen used in conjunction with an automatic analyzer. Kit labeled, "Union Carbide Centrifichem Test Bun (Blood Urea Nitrogen) for the Quantitative Determination of Serum Urea Nitrogen - Diagnostic Reagent for In-Vitro Use Only***Exp. Date 6-1-75*** Contents 12 vials of Reagent***." Each kit contains 12 amber vials containing white powder, labeled "Diagnostic Reagent for In-Vitro Use Only***;" A translucent plastic squeeze bottle, labeled "Standards Glucose 200 mg/100 ml Urea N 40 mg/100 ml***;" and an instruction sheet entitled "Certrifichem Methodology Sheet." Lot Number: D 4201. Kit assembled and being recalled by Union Carbide Corporation, Tuxedo, New York by telephone the week of November 4, 1974. Distribution was national and international with firm estimating that approximately 985 kits remain on the market. (Recall #T-152-5).

Reason: Reagent gives inaccurately low results for samples of extremely high uremic content.

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Product: "Isolette Ventimeter Ventilator." A device which continuously monitors tidal volume and automatically controls ventilation during anesthesia. Lot Number: All units manufactured prior to 1/1/73, as identified by the following serial numbers: Numbers 25164 thru 25303. All numbers prefixes with FB, MB, DB, JB, BB, GB, NB, EU, KU, CU, HU, AU, FU, MU, DU, JU, BU, GU, NU, EM, KM, CM, AM, FM, MM, DM, JM, BM, GM, or NM. Manufactured by Air-Sheilds, Inc., Warminster, Pennsylvania (device distributed under former name, Isolette Division of Narco Medical Company.). Corrective action program was undertaken on December 16, 1974 by letter to all accounts advising that field representatives will inspect devices and replace the bag connector pipe with one containing a pin insert. Distribution was national with firm estimating that approximately 2,250 devices are in use. (Recall #T-151-5).

Reason: Misconnection of hoses to wrong ports causes failure of device to operate efficiently.

- - - -

Product: Ceiling Crane, XD1801, a telescoping ceiling mounted crane to which the X-ray tube or related equipment may be attached. Lot Number: All units. Manufactured in Europe by Philips A.C. for Philips Medical Systems, Inc., Shelton, Connecticut. Philips Medical Systems issued a memorandum to all service managers and dealers on October 25, 1974, instructing them to check all ceiling cranes. The devices are not being physically recalled. Distribution was to hospitals, radiology offices, etc., nationwide. (Recall #T-141-5).

Reason: Faulty installation by manufacturer.

MORE

Product: Internal Cardiac Pacemaker with a rate of 70, Stanicor Model Numbers: 143J7, 143L7 and 143N7. Lot numbers: None use - all model numbers indicated are involved. Manufactured by (Pacemakers): Cordis Corp., Miami, Fla.; (Resistors): C.T.S. Berne, Inc., Berne, Ind. Recalled by Cordis Corp., Miami, Fla. by letter on December 16, 1974 to all affected physicians. Letter recommended that each patient be monitored once a month for 5 months. If significant decrease in rate is noted, removal of pacemaker is recommended. Distribution was national and international with firm estimating that approximately 4,288 remain on the market. Quantity implanted is unknown. (Recall #T-163-5).

Reason: Pacer epoxy becomes saturated with moisture causing it to swell. Lowering of pace rate can result.

- - - -

Product: Liquid in pint and quart amber glass bottles labeled in part, "Tincture of Benzoin Compound U.S.P." Lot number: 41387. Manufactured by National Pharmaceutical Mfg. Co., Inc. (A/K/A Barre Drug Co., Inc.), Baltimore, Maryland. Recalled by Consolidated Midland Corporation (CMC), Brewster, New York by telephone on January 31, 1975. Distribution was to West Virginia with none of the product remaining on the market. (Recall #D-267-5).

Reason: Label mix-up - Part of lot mislabeled as Iodine Tincture by CMC during relabeling operation.

- - - -

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

Product: Soma Tablets, Carisopriodol, 350 Mg. 500 tablets in plastic bottles. Lot number: 4H1001. Manufactured and recalled by Wallace Laboratories, Cranbury, New Jersey by telegram on February 5, 1975. Distribution was nationwide. (Recall #D-266-5).

Reason: Mold contamination.

- - - -

Product: RX Drug, Rauwolfia Serpentina N.F. 50 mg., sugar coated tabs in bottles of 1000 and 5000 tablets and in bulk. Lot Number: 30570. Manufactured and recalled by Cord Laboratories, Inc., Detroit, Michigan by letter on February 10, 1975. Distribution was to Indiana, Iowa, Michigan, Ohio, Pennsylvania, Tennessee and Wisconsin, with firm estimating that approximately 5000 tablets remain on the market. (Recall #D-258-5).

Reason: Subpotent.

- - - -

MORE

Product: 3-P Gest-Plus Decongestant Capsules
Charge: Subpotent
Responsible
Firm: Alpha Pharmacal Co., Inc., St. Louis, Missouri
Filed: February 14, 1975 - U.S. District Court for the Western District of Missouri; FDC #60192; Civil #75-CV-118-W-4.

- - - -

Regulatory Letters:

Regulatory Letters are formal legal notices used to advise firms or individuals that specific sections of the law administered by FDA have been violated. The recipient is advised that FDA will pursue legal or administrative sanctions if corrective action is not taken within a stated time period. Copies of all Regulatory Letters are available for public review at the Public Records and Documents Center, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20852.

Recalls and Field Corrections:

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

Product: Recall #T-068-4, Pacemaker Pulse Generator, General Electric Model A2073, Implantable, Asynchronous, has been extended from 5 lots to include all units of this model. Manufactured and recalled by General Electric Company, Medical Systems Division, Milwaukee, Wisconsin. The extension was announced by letter to all affected physicians on February 1, 1975. The letter recommended replacement 22 to 24 months after implantation. Attached to the letter was a list of each physician's affected patients. Distribution was national and international with firm estimating that approximately 1,241 units are implanted. (Recall #T-068-4).

Reason: Possible copper migration into pacemaker circuits causing excessive pulse rates.

- - - -

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

MORE

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SCHOOL OF PHARMACY
DEPARTMENT OF PHARMACY

SAN FRANCISCO, CALIFORNIA 94143

March 3, 1975

Assemblyman Barry Keene
Chairman
Assembly Committee on Health
Room 5119
Capitol Building
Sacramento, California

Dear Assemblyman Keene:

I have recently been informed that the Assembly Committee on Health is considering a bill, AB 193, which will allow the pharmacist to substitute on a generic basis for drug products prescribed by the physician. I wholeheartedly support the concept of generic prescribing, but it is my opinion that unrestricted substitution of the so-called generic equivalent product for a drug prescribed by a physician could be a serious detriment to the health and welfare of the patient involved. It is my contention that there is a large number of drug products for which generic substitution could be allowed with impunity. Yet, there is a critical set of drugs for which this type of substitution could lead to serious untoward reactions.

I have had the privilege during the past year to be appointed to a special advisory committee to the U. S. Congressional Office of Technology Assessment. This committee drafted a "Drug Bioequivalency Report," which was presented to Senator Edward Kennedy's Subcommittee on Health in July, 1974. The committee supported the concept of "controlled" generic prescribing. However, they proposed that it should be undertaken by establishing an official list of interchangeable drug products, but there is a series of drugs which should not be included on this list as they pose possible hazard to the patient due to the potential variation among the different available brands. This would include drugs which are difficult for the clinician to adjust to the appropriate level for the patient and other drugs which may markedly differ in their bioavailability to the degree that they would seriously modify the intended activity.

As you are probably aware, Secretary Weinberger of HEW is presently developing a procedure to limit federal reimbursement of multiple source drugs to the lowest cost at which chemically equivalent products are available. I am attaching to this letter a letter I wrote to Secretary Weinberger, indicating my support of his policy. It is my understanding that Secretary Weinberger will restrict the list of interchangeable drug products to those drug substances which his experts believe could be substituted without serious risk to the patient.

From my experience as a teacher and professor of pharmacy for over 25 years and a scientist in the area of bioavailability, I can assure you that the practicing pharmacist cannot possibly be aware of all the aspects involved in the dose adjustment and product selection among the critical drugs. In my opinion, it would be much more logical to restrict such substitution to the forthcoming HEW Interchangeable Drug List, rather than to give the pharmacist blanket authority to

substitute on all prescriptions. I hope that your committee will give serious consideration to delaying action on this matter until further information is available on the federal procedure for handling these drug products.

I am attaching for your information a speech which I was invited to give at the 14th Annual International Industrial Pharmacy Conference in Austin, Texas, on February 25, 1975, on the OTA Report. In it I quote from a letter from Mr. Peter Hut Assistant General Counsel for the Food and Drug Administration, in which he indicates he agrees with the OTA Bioequivalency Report that there are important inadequacies in drug standards regulations under which the FDA can undertake recall of drug products. These include the current good manufacturing practices regulations and the official Compendial standards which define minimum specifications for quality, strength, and purity of drug products. My speech goes into details on what I believe to be some of the limitations of the present Compendial and cGMP standards.

While I recognize that this matter of generic substitution has been in front of the state legislature for a number of years, it is my expert opinion that it would be inappropriate to undertake action which is not coordinated fully with the federal plans in this area.

Sincerely,

Sidney Riegelman

Sidney Riegelman, Ph. D.
Professor of Pharmacy and
Pharmaceutical Chemistry
Chairman, Department of Pharmacy

SR/nm
Enc.

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SCHOOL OF PHARMACY
DEPARTMENT OF PHARMACY

SAN FRANCISCO, CALIFORNIA 94143

0815

August 27, 1974

The Honorable Casper Weinberger
Secretary of Health, Education and Welfare
Department of Health, Education and Welfare
Office of the Secretary
Food and Drug Administration
Washington, D.C. 20204

Dear Secretary Weinberger:

It is my understanding that there is a list of approximately forty-odd commonly prescribed, multi-source, orally administered drugs whose solid dosage forms are being considered by you and your associates for inclusion in a maximum allowable cost (MAC) drug reimbursement regulation. As you are probably aware, I was a member of the Office of Technology Assessment Drug Bioequivalence Study Panel. The Panel members support your efforts to establish a MAC list. In our Report we merely wished to express our concern that specific drug products may not be sufficiently pharmaceutically equivalent for immediate inclusion without additional action being taken.

I wish to emphasize personally my unqualified support of your efforts in developing this new regulation. I want to see as many drug products added to this list as possible, commensurate with public health and safety. Yet, I reflect upon what could happen in the future if one of the drugs included in the list turned out to be bioinequivalent. Consider that had the MAC list been drawn up in 1972, digoxin tablets undoubtedly would have been included in the list. The later reports of Lindenbaum et al on the therapeutic ineffectiveness of some of the duplicate manufacturers' digoxin tablets would have caused havoc. Conceivably, the whole concept of a MAC list would have been compromised.

Having given considerable thought to this matter, I would like to propose the following sequence of events which I believe will minimize the probability of drug products being placed on this list without having appropriate controls over their manufacture.

1. Drugs should be included on the list only if they are not critical drugs (as discussed in the Drug Bioequivalence Study Panel Report, Sections IV and XI.

2. The official compendial monographs covering the pure drug substance and the drug products should be reviewed to ascertain (a) where critical deficiencies exist in the standards to a degree that inclusion of the drug should be deferred

until action is taken to correct the deficiency, and (b) in other instances, the drug product should be included on the MAC list, with a report to the compendial revision organization as to the deficiencies identified in the monograph, with a recommendation that appropriate action be taken.

3. A drug product quality assurance plan should be established as a regulation in the CGMP guidelines to be imposed on all manufacturers of MAC list products, including a statistically valid, discriminating dissolution test.

I have expanded on several aspects of the above proposal in the appended material. I hope that you and your associates have an opportunity to review this. I would deem it a privilege to discuss these matters with you and/or your representatives in further detail.

Respectfully,

Sidney Riegelman

Sidney Riegelman, Ph. D.
Professor of Pharmacy and
Pharmaceutical Chemistry
Chairman, Department of Pharmacy

SR/bk

Enc.

cc: Charles Edwards, M.D., Undersecretary of Health,
Education and Welfare
Alexander Schmidt, M.D., Food and Drug Administration Commissioner
Richard Crout, M.D., Director of the Bureau of Drugs
Drug Bioequivalency Study Panel members, Office of Technology
Assessment
William Weller, Ph. D., Executive Director of the United States
Pharmacopeial Convention, Inc.

"THE GREEN SHEET", JULY 15, 1974

"APhA HAS CONFIDENCE THAT PHARMACISTS WILL USE EXTREME CAUTION IN EXERCISING 'DRUG PRODUCT SELECTION' PRIVILEGES GRANTED THEM BY LAW OR PRESCRIBERS WHEN DISPENSING THE IDENTIFIED PROBLEM DRUG," APPLE SAID.

-- William S. Apple
Executive Director, American Pharmaceutical Association

"ACTION REPORT" FROM THE ILLINOIS STATE MEDICAL SOCIETY

"PHARMACISTS VIOLATE DRUG INTERCHANGE PACT IN AURORA

A YEAR-OLD DRUG INTERCHANGE AGREEMENT BETWEEN AURORA, ILL., PHYSICIANS AND PHARMACISTS HAS BEEN TERMINATED FOLLOWING AN INVESTIGATION WHICH REVEALED PHARMACISTS WERE VIOLATING THE PACT. UNDER THE PROGRAM -- INITIATED TO REDUCE PATIENT PRESCRIPTION COSTS -- PARTICIPATING MD'S ALLOWED PHARMACISTS TO INTERCHANGE COMMONLY USED BRAND NAME DRUGS LISTED IN A FORMULARY PREPARED BY A COMMITTEE OF MD'S AND DRUGGISTS. AN INVESTIGATION REVEALED THAT, AMONG OTHER VIOLATIONS, PHARMACISTS WERE INVOLVED IN UNAUTHORIZED INTERCHANGE, IMPROPER LABELING AND THE INTERCHANGE OF DRUGS NOT LISTED IN THE FORMULARY. IN ADDITION, THE AGREEMENT WAS BEING USED BY SOME STATE PHARMACEUTICAL ASSOCIATIONS OUTSIDE ILLINOIS TO SUPPORT ARGUMENTS FOR REPEAL OF ANTI-SUBSTITUTION LAWS. THE PACT BETWEEN THE SOUTHERN BRANCH (AURORA) OF KANE COUNTY MEDICAL SOCIETY AND AURORA AREA PHARMACEUTICAL ASSN. WAS NOT ENDORSED BY THE COUNTY SOCIETY."

8/9/74

ROCHE LABORATORIES

DIVISION OF HOFFMANN-LA ROCHE INC. • NUTLEY, NEW JERSEY 07110

Jerald A. Breitman
Institutional Planning Manager
Western Region

John B. Dalton
Institutional Planner
Central Region

Philip J. Daly
Institutional Planning Manager
Northeastern Region

Paul L. Keating
Institutional Planner
Northwestern Region

Michael L. Labat
Institutional Planner
Southwestern Region

Lewis D. Lepene
Institutional Planning Manager
Eastern Region

Robert L. Moon
Institutional Planner
Southern Region

Mr. George T. Bennett
Secretary
Nevada State Board of Pharmacy
1281 Terminal Way
Suite 217
Reno, Nevada

Dear Mr. Bennett:

I am pleased to send you the full proceedings of a recent Excerpta Medica Colloquium, "The Scientific Evaluation of Drug Equivalency".* Under separate cover you will receive five copies of the abridged version of the colloquium proceedings should you desire to distribute them to the officers of your organization.

The colloquium generated considerable controversy concerning the importance of positively establishing through adequate evidence the equivalency between drug products bearing the same generic name before permitting their interchangeability. These proceedings are of particular relevance today in light of the Health, Education and Welfare Department's recently published regulations regarding the implementation of a Maximum Allowable Cost (MAC) program for drug products reimbursed through federally financed programs.

We at Roche believe that the patient's right to safe, effective, quality assured drug products will be violated should the MAC program be implemented in accordance with the regulations published in the November 15 and November 27 Federal Register. In our opinion, the greatest potential danger to the patient arises from the scientifically invalid premise underlying the drug product equivalency criteria established by the proposed regulations:

- equivalency among drug products within a generic (multisource) category will be assumed unless proven otherwise.

*The mention of any pharmaceutical product in the enclosed colloquium proceedings does not imply any recommendations for such products. Manufacturers' product information should be consulted for specific information.

Many examples of inequivalency have been cited in the literature and documented by scientific experts, which we believe clearly demonstrate that therapeutic equivalency cannot be assumed among chemically equivalent products. In light of the uncertainties in this area, in our judgment, equivalency must be proven, not assumed. We further believe that proof of equivalency must be demonstrated on the basis of adequate objective scientific standards. There is no room for a subjective or nonscientific determination of equivalency when this issue bears so directly on patient health care.

Under the proposed MAC program, physician and pharmacist prerogatives in drug product selection will be severely restricted and will be based essentially on cost considerations. In addition, this program would impose a significant administrative burden upon the existing State Medical Assistance Programs since by regulatory mandate, they would have to be drastically altered in order to comply with the proposed scheme.

We urge all concerned parties, especially professional members of the health care community, to express their views on this far-reaching proposal which could seriously affect the quality of drug products utilized by this nation's disadvantaged and elderly ill.

All comments should be sent to:

Hearing Clerk
Food and Drug Administration
Room 4-65
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20852

Sincerely,

Gerald D. Lore

Gerald D. Lore
Group Manager
Institutional Planning

0820

HOFFMANN-LA ROCHE INC.
Comments on MAC Regulations

Hoffmann-La Roche Inc. has taken an active interest in HEW's efforts to develop a drug reimbursement mechanism which ensures the availability of quality pharmaceuticals in a fiscally responsible manner. Now that the proposed Maximum Allowable Cost (MAC) program has been described in the Federal Register, we wish to offer the following constructive comments and suggestions which address some of the key elements of this program.

The MAC proposal speaks to several very important issues affecting all sectors of health care in federally funded programs. While we at Roche find major problems in some provisions which economically affect individual sectors, we are focusing our response to address those issues which have a direct bearing on the very fabric of health care in this country, that is, the pursuit of quality patient care, especially in programs funded by the government.

As indicated in our previous responses to Dr. C. C. Edwards' questionnaire and our communications with HEW, certain essential modifications are necessary in order to provide an economically and therapeutically responsible drug reimbursement program. We cannot extend our support for the MAC program which has recently been proposed. The Roche position has always been that if drug products are proven to be truly equivalent, the government should not have to pay any more than the lowest price available. This position was fully outlined in our previous correspondence with you and it alerted the Department to the complexities involved with such a proposal. We felt then and we feel now that if the quality of the drug supply were not jeopardized, the specifics of drug product reimbursement could be developed to all parties' satisfaction. To reiterate our position, we believe that only a positive determination based on sound scientific proof should be accepted to resolve the issue of drug product equivalency. The reference standard against which all imitations should be measured would be the drug product which has been the subject of an approved full new drug application. This approval means the drug has undergone extensive clinical study and patient experience and is produced according to exacting quality control protocols and manufacturing procedures.

In order for equivalence to be established, manufacturers of other products within the generic category must provide documentation to the Department which demonstrates their product to have the following attributes in relation to the reference drug standard:

* Chemical equivalence;

* Bioavailability equivalence where appropriate standards and methodology have been established;

  or in the absence of these standards, or where otherwise deemed necessary,

* Therapeutic equivalence in terms of adequate and well-controlled clinical studies.

We further suggested that manufacturers of multisource products should be required to meet minimum standards of technical equivalency which we consider to be essential in guaranteeing consistency in identity, strength, purity, quality and service excellence.

Finally, the logistics of product distribution should be considered since this too plays an important role in maintaining the high quality of products while assuring the continuity of the patients' pharmaceutical health care. The acceptance of return goods to encourage return of outdated, contaminated, or damaged merchandise and drug recall capabilities are indispensable components of logistic equivalency.

We feel these safeguards of drug product quality to be essential in determining what we term "proven equivalence," yet we find them missing from the proposed MAC regulations, and when the quality of drug products for a large segment of the population is concerned, we cannot waiver in our insistence on this guarantee of proven equivalency.

We strongly believe that far more attention must be focused on this controversial but extremely critical aspect of the proposed regulations. In the absence of mandatory bioequivalence standards, it is virtually axiomatic that in any multisource drug class there will be drug products which are inferior to the original product. This can ultimately result in patients receiving an inferior product, having to undergo longer treatment, experiencing unnecessary adverse reactions or possibly even experiencing a treatment failure, all of which increase personal risk to the patient and result in greater costs to the Federal Government. To characterize entire drug classes as not having bioequivalency problems because therapeutic levels are far separated from toxic levels only scratches the surface of inequivalency problems and ignores an opportunity to guarantee consistent quality pharmaceuticals with as predictable a patient response as is possible. No matter which drug class one picks, whether it be antibiotics, analgesics, ataractics or any of the

others, an additional day of discomfort, an unnecessary adverse reaction, or a preventable treatment failure because of a product which does not perform as well as the original is a serious gamble to take for any savings theoretically involved with the price of that one prescription. If in fact our ultimate goal is to reduce the unnecessary and preventable discomfort of patients with disease, then we feel that the ignoring of drug quality standards is counterproductive to that aim.

The "Drug Bioequivalence" report by the Office of Technology Assessment Drug Study Panel appears to have identified a source of equivalency problems when it stated that "...*the number of (bioinequivalents)...has been sufficient to establish that the problem of bioinequivalence in chemically equivalent products is a real one. Since the studies in which lack of bioequivalence was demonstrated involved marketed products that met current compendial standards, these documented instances constitute unequivocal evidence that neither the present standards...nor the specifications...are adequate to ensure that ostensible equivalent drug products are...equivalent in bioavailability.*"

The report went on to further state that "...*variations in the bioavailability of drug products have been recognized as responsible for a few therapeutic failures. It is probable that other therapeutic failures (or toxicity) of a similar origin have escaped recognition.*" Thus, this distinguished panel struck at the heart of one preventable drug failure problem--"*current standards and regulatory practices do not ensure bioequivalence for drug products.*"

In May, 1974, prior to the publication of these supportive OTA findings, Roche communicated its concern to the Department about the standards required for Abbreviated NDA's as being inadequate to determine equivalency. We found that requirements for an Abbreviated NDA do not require clinical studies to determine safety or efficacy of a product nor do they require full descriptions of manufacturing methods, facilities and controls. The FDA is not judging equivalence between an ANDA product and the original NDA product but simply minimal safety and efficacy standards. While both drugs may contain the same active chemical ingredient, the drugs could significantly differ in potency, spectrum or frequency of effectiveness and incidence of side effects. Even though both products met physical and chemical compendium standards, these differences can occur because they are not fully equivalent. We remain convinced that the manufacturer of a product which is not equivalent to an original drug product but which is considered to be safe and effective should file for an NDA because the product is clearly different, and, therefore, a new drug product not an equivalent multisource drug product.

If the bioinequivalent product has not been proven safe and effective, it should not be marketed. However, the proposed MAC regulations fail to distinguish the inequivalency among products introduced through the ANDA process.

One must remember that the interchangeable use of many generic drug products, which is encouraged by these proposed regulations, has not been that prevalent in the past. The increased utilization of questionable source drug products may therefore unleash greater numbers of unpredictable patient therapeutic responses from which the questions of bioequivalency significance will regrettably be answered.

Roche feels that the Department of HEW has placed a heavy accent on the economics of health care and possibly neglected similar consideration to the quality of health care. The proposed regulations are even titled Maximum Allowable Cost; what then about the level of acceptable quality in prescription medicine? It can easily be documented through the professional literature or the drug product recall lists that inferior products exist. The proposed regulations encourage rather than discourage their use.

As the regulations indicate, an incentive of 25 percent is offered to purchase below what appears to be a bottom-level price. The method in which a pharmacist collects this bonus incentive would probably be to purchase from a lower-priced local manufacturer or purchase large quantities from those offering quantity discounts. In the case of local manufacturers, it has come to our attention that intrastate manufacturers of drug products are not subject to any federal quality assurance program and that state certification in many instances is a token measure guaranteeing little in the way of quality assurance. Are these products also going to be reimbursed by the Federal Government for the purposes of treating our elderly and disadvantaged ill? It becomes apparent to us that state drug reimbursement regulations heavily based on price could easily comply with the MAC regulations while seriously jeopardizing the implicit moral commitment to maintaining a drug product supply of unquestionable quality.

In fact, any reimbursement regulations strictly based on price will not provide the economies HEW is seeking. Incentives and ceilings which coerce the pharmacist to maximize his return by dispensing lower quality drug products will establish a false economy where questionable initial savings will exact heavy debts in the future. The pharmacotherapy segment of health care is recognized to be one, if not the most, economical treatment modality in that treatment subsequent to a drug product failure and alternative therapy to drug treatment are virtually always much more costly.

The costs of the program have never been defined. Several states--Kansas, Texas and California--have attempted to employ an actual acquisition cost reimbursement system only to discover the impracticality of such a scheme. They subsequently reverted to a modified average wholesale price (AWP) system because of the huge administrative burden of enforcing actual acquisition. Even the federal guidelines to State Medical Assistance Programs in their "Medical Assistance Manual - Section .29 Requirement for State Plans," November 29, 1973, express pragmatic wisdom based on their own past experience when they state:

> *Some State programs reimburse for the drug product on the basis of "actual acquisition cost" to the dispensing pharmacist. Under the best of circumstances, it is nearly impossible to determine the actual cost at the time of dispensing. This method is also far more expensive to administer under Title XIX than "average wholesale price."*

It seems all agree that the costs of administration overshadow the possible savings from such a measure. An overlying economic consideration which must be recognized is that the squeezing of savings from any one component involved is this relatively closed system will result in the expansion of other component costs, that is, reduction of revenue to pharmacy in employing an actual acquisition cost system must result in an increase in professional fees, especially if the arguments from the pharmacy sector of insufficient recompensation are accurate. An additional administrative cost enters the formula when one considers the expense of processing pharmacy operating data to determine the level of professional fees. Totaling up these considerations would lead one to believe that the suggested economic savings are significantly overstated.

We strongly recommend that the Department critically review all of the ramifications of the present MAC proposal. As Dr. Marvin Zelan of the State University of New York at Buffalo, a member of the OTA Study Panel, testified before the Hearing Subcommittee, *"...One might make a broad blanket decision and say 'let us put 85 percent of the drug products on the interchangeable list' and on the average that might be a very fine decision, but for those particular individuals who are adversely affected, it is very unsatisfactory and the government regulations have not succeeded in protecting them, and perhaps, may have actually harmed them..."*

Because of our concerns iterated in this letter, Roche considers positive proof of full equivalence as defined in terms of scientific, technical and logistic equivalency to be the minimum acceptable level of quality for drug products. Manufacturers who

share our concerns about quality drug health care to all patients, regardless of their economic status, will agree that to avail oneself of consideration for federal reimbursement, the equivalency of a multisource product to the original drug product must be proven. Therefore, we recommend that proven equivalency be the cornerstone of the MAC regulations.

Roche recognizes the administrative demands these criteria for equivalence will place on both government and industry. A critical initial decision concerns the selection of the official body in which should be vested the responsibility for determining equivalence among products within a generic category. The proposed MAC regulations semiutilize the FDA for these determinations. Because of its resources, experience and expertise in handling issues relating to pharmaceutical products, we believe the Food and Drug Administration is the appropriate agency to oversee drug equivalency determinations for the Department's reimbursement programs. Consistent with FDA's philosophy to employ outside expertise on questions which merit the consideration of the scientific and medical community, we also feel an independent and objective scientific body should be appointed by therapeutic category which deliberates the difficult issue of bioequivalency between drug products. This committee would review equivalency data submitted to it by manufacturers and present findings and recommendations of equivalency among drug products within each generic category for adoption by FDA.

In summary, we believe the most critical phase of establishing an MAC is the determination of drug equivalence to ensure that federally reimbursed drug products meet an acceptable level of quality before their interchangeability is permitted. Only those drug products which have been proven equivalent should be considered for federal reimbursement. We further suggest that the government explore ways and means to control the misutilizations and inefficiencies involved with Medical Assistance Programs. Studies have shown as much as 10 percent can be saved by the elimination of wasteful practices such as double billings and patient prescription shopping. We should experiment further with utilization review procedures, programs of close consultative collaboration between physicians and pharmacists and educational programs to improve rationality of therapy beginning in medical schools and extending into private practice on a continuing basis. Every effort should be made to improve the health system for our patients, for therein lies true economy.

HOFFMANN-LA ROCHE INC.
NUTLEY • NEW JERSEY

QUALITY CONTROL DEPARTMENT

0826

Raw Material - PURIFIED WATER

This raw material is tested and shall meet all U.S.P. tests as defined in U.S.P. XVII, page 754, or revision thereof.

HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY

QUALITY CONTROL DEPARTMENT

4529

Raw Material - MAGNESIUM STEARATE*

0827

Specifications

Test No.		
01.0	Appearance	Fine, bulky powder
02.0	Color	White
03.0	Odor	Faint, characteristic
15.0	Identity Test A	Positive
15.1	Identity Test B	Positive
26.0	Loss on Drying	Maximum 4.0%
30.0	Heavy Metals	Maximum 40 ppm
30.1	Lead	Maximum 10 ppm
32.0	Arsenic	Maximum 3 ppm
44.0	Assay: Magnesium Oxide	6.8 - 8.0%
60.0	Microbiological Purity	Satisfactory

*USP XVIII, FCC I

4480•

ck

Raw Material - MAGNESIUM STEARATE

Directions for Testing

15.0 Identity Test A

Place about 1 g of sample into a 50-ml beaker, add a mixture of 25 ml of water and 5 ml of hydrochloric acid, and heat on a hot plate: the fatty acids float as an oily layer on the surface of the liquid. Filter the suspension using a suitable filter. To the clear filtrate add a few mg of ammonium chloride, and then add ammonium carbonate T.S.: no precipitate results. Add sodium phosphate T.S.: a white crystalline precipitate insoluble in ammonia T.S. results.

15.1 Identity Test B

Place about 25 g of sample into a 400-ml beaker and mix with 200 ml of hot water. Add 60 ml of 10% sulfuric acid, and heat the mixture, with frequent stirring, until the fatty acids separate as a transparent layer. Allow the mixture to cool and pour off about 200 ml of liquid, being careful not to lose any fatty acids. Wash the fatty acids remaining in the beaker with boiling water until the wash water does not give a white precipitate when barium chloride T.S. is added. Transfer the fatty acids into a small beaker, and warm on a steam bath until the water has separated and the fatty acids are clear. Allow the fatty acids to cool and again pour off the water layer. Melt the acids, filter, if necessary, using a suitable filter, and dry in an oven at 100°C for 20 minutes. Test for complete saponification of the sample by placing 3 ml of the dry acids into a test tube, adding 15 ml of alcohol, heating to boiling, and adding an equal volume of ammonia T.S.: a clear solution results.

Determination of Solidification Temperature

Apparatus

Congealing Temperature Apparatus: As described in USP XVIII, page 922, equipped with an ASTM 15 C thermometer, or suitable equivalent, a 25 x 100-mm test tube, and a wire stirrer about 30 cm long, bent at its lower end into a horizontal loop around the thermometer.

- cont'd -

Procedure

Adjust the temperature of the sample preparation to about 70°C, and pour into the test tube to a height of 50 - 57 mm. Assemble the apparatus with the bulb of the thermometer immersed midway in the sample. Fill the water bath to about 12 mm from the top of the tube with water at about 49°C, and cool the sample to about 59°C. Then adjust the water temperature to about 46°C, and begin to stir the sample continuously by moving the loop up and down between the top and bottom of the sample, at a regular rate of 20 complete cycles per minute, recording the sample temperature every 30 seconds. Discontinue stirring when the temperature becomes constant or starts to rise slightly, but continue to record the temperature in the test tube every 30 seconds for at least 3 minutes after the temperature again begins to fall after remaining constant. The average of not less than four consecutive readings that lie within a range of 0.2° constitutes the solidification temperature: the solidification temperature of the fatty acids is not below 54°C.

26.0 Loss on Drying

Dry about 1 g of sample, accurately weighed, to constant weight in a 105°C oven.

30.0 Heavy Metals

Reagent

Alcoholic Magnesium Nitrate Solution: Dissolve 25.0 g of magnesium nitrate hexahydrate in 100 ml of ethyl alcohol.

Procedure

Transfer 750 mg of sample into a porcelain dish approximately 2-inches in diameter. Add 250 mg of sample to a second dish to serve as a control. Treat both dishes in the same manner. Add 5.0 ml of alcoholic magnesium nitrate solution and cover with inverted, 3-inch short-stem funnels. Heat on a hot plate at a low setting for 30 minutes and then increase the heat to a medium setting for an additional 30 minutes. Take the dishes from the hot plate, cool and remove the funnels. Add 2.0 ml of Standard Lead Solution, equivalent to 20 micrograms of lead, to the control. Place both dishes over a suitable burner until most of the carbon is burned off and then ignite until the last traces of carbon have disappeared.

- cont'd -

Cool, add 10 ml of nitric acid and transfer the solutions into 250-ml beakers. Add 5 ml of 70% perchloric acid and cautiously evaporate to dryness. Add 2 ml of hydrochloric acid to the residues and wash down the inside of the beakers with small portions of water. Carefully evaporate to dryness again, swirling near the dry point to avoid splattering. Repeat the hydrochloric acid addition, the washings and the evaporation. Cool, and dissolve the residues in about 10 ml of water. Add 1 drop of phenolphthalein T.S. and sufficient 1N sodium hydroxide until the solution just turns pink, and then add 10% hydrochloric acid until each solution becomes colorless. Add 1 ml of 6% acetic acid and a small amount of charcoal to each solution. Filter through Whatman No. 2 filter paper, or suitable equivalent, into 50-ml Nessler tubes. Wash with water, dilute to 40 ml with water, and add 10 ml of hydrogen sulfide T.S. to each solution. The color in the sample solution should not exceed that produced in the control solution (40 ppm).

30.1, 32.0

Lead and Arsenic

X-Ray Fluorescence

Reagents

Arsenic Trioxide: Primary standard, J.T. Baker Chem Co., or suitable equivalent.

Boric Acid: Spex Industries Cat. No. 1218, purity 5-9s, or suitable equivalent.

Magnesium Stearate Reference Sample: Magnesium stearate sample which shows no characteristic fluorescence radiation due to lead or arsenic.

Lead Oxide: Reagent grade, or suitable equivalent.

Standard Preparation

Accurately weigh 0.053 g of arsenic trioxide and 3.947 g of boric acid into a mixing vial suitable for use in a Spex "Freezer/Mill," or equivalent apparatus. Allow the vial to pre-cool under liquid nitrogen for 5 minutes, then mix at maximum frequency for 6 minutes. Dilute 0.040 g of this mixture with 3.960 g of boric acid, using the "Freezer/Mill" to insure sample homogeneity (Standard I) (arsenic = 100 ppm). Mix 0.120 g of Standard I with 3.880 g of the magnesium stearate reference sample, again using the "Freezer/Mill" technique (Standard II) (arsenic = 3 ppm). Place about 5 g of Standard II into an aluminum sample cup and compress at 40,000 psi for 10 minutes (Working Standard).

- cont'd -

~~0530~~

0831

Raw Material - MAGNESIUM STEARATE

Sample Preparation

Place about 5 g of sample into an aluminum sample cup and compress at 40,000 psi for 10 minutes.

Instrument and Conditions (An equivalent instrument and appropriate operating conditions may be used.)

Instrument	GE XRD-6 X-ray Spectrometer
Generator	50 KV, 50 MA
Tube Target	Molybdenum
Optics	Lithium fluoride crystal; 0.02" x 3.5" Soller slit; Air atmosphere
Detector	Scintillation counter at plateau; Pulse Height Selector adjusted for maximum As K_α intensity; Base = 5V, ΔE = 4V
Scaler	100 second count
Goniometer	Combined As K_α, Pb K_α peak and $\pm$ 1.0° 2θ

Procedure

Place the Working Standard pellet into the sample chamber of the X-ray spectrometer and irradiate according to the above Instrument Conditions. Record the counts at each prescribed 2θ angle. Follow the same procedure for the sample pellet.

Calculation

$$C_s - \left[\frac{(C_2 + C_3)}{2}\right] = \text{sample net count}$$

where:

C_s = sample count at As K_α peak

C_2 = sample background at As K_α peak -1.0° 2θ

C_3 = sample background at As K_α peak +1.0° 2θ

- cont'd -

Calculate the net counts of the standard and sample pellets. If the net count of the sample is less than the net count of the standard, the sample is within both arsenic and lead specification limits. If the net count of the sample is greater than the net count of the standard, the sample contains more than 3 ppm arsenic, or more than 5 ppm lead, or a combination of the two, and an analysis for lead by atomic absorption spectrophotometry is required. If more than 10 ppm lead is found by atomic absorption analysis, the sample exceeds the lead specification limit. If no lead is found, the sample exceeds the arsenic specification limit. If less than 10 ppm lead is found, prepare a standard pellet containing an amount of lead equal to that found by atomic absorption spectrophotometry, and determine the net count for this pellet by X-ray fluorescence under the Instrument Conditions described above. Subtract the net count for this lead standard pellet from the combined arsenic-lead net count of the sample pellet. If this remainder is less than the net count for the 3 ppm arsenic standard pellet, the sample is within both the arsenic and lead specification limits.

Lead

Atomic Absorption Spectrophotometry (if necessary)

Reagents

Nitric Acid: Reagent grade

Sulfuric Acid: Reagent grade

Perchloric Acid: Reagent grade

Ammonium Hydroxide: Reagent grade

Methyl Isobutyl Ketone: (referred to as MIBK): Fisher Scientific or suitable equivalent.

Ammonium Pyrrolidine Dithiocarbamate (referred to as APDC): 1-Pyrrolidine-carbodithioic acid ammonium salt, reagent grade. Prepare a 5% aqueous solution of this material.

Lead Reference Solution: Certified Atomic Absorption Standard, 1000 ppm, Fisher Scientific Company, Cat. No. SO-L-21, or suitable equivalent. From this solution prepare a Standard Solution which contains 1 mcg Pb/ml.

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QUALITY CONTROL DEPARTMENT

Raw Material - MAGNESIUM STEARATE

~~0535~~ 0833

Instrument and Conditions (An equivalent instrument with appropriate operating conditions may be used.)

Instrument	Perkin-Elmer Model 303 Atomic Absorption Spectrophotometer
Tube	Lead
Wavelength	2170 Å
Fuel	Air-Acetylene
Flame	Oxidizing
Current	10 ma
Burner	Techtron AB51
Slit	#4

Standard Preparation

Prepare standard lead solutions by pipetting 4.0, 8.0, and 12.0 ml of Standard Solution (equivalent to 4 ppm, 8 ppm, and 12 ppm Pb respectively) into 125-ml separators and add 30 ml of water to each. Prepare a 0 ppm solution by placing 30 ml of water into a fourth separator.

Sample Preparation

Accurately weigh 1.00 g of sample into a 100-ml long-necked Kjeldahl flask. Add 10 ml of nitric acid, 3 ml of perchloric acid, and 3 ml of sulfuric acid, and slowly heat to boiling. After the contents are charred, add 5 ml of nitric acid and continue heating until the mixture is clear and colorless. Cool, add water to dissolve the magnesium salt, and transfer into a 125-ml separator. Rinse the flask with two 10-ml portions of water, combining the rinse solutions in the 125-ml separator.

Procedure

Treat the standard solutions and the sample solution in the same manner. Adjust the pH of the solutions to 2.8 using ammonium hydroxide and hydrochloric acid, and then dilute with water to 50 ml. Add 1.0 ml of 5% APDC and shake well. Add 8.0 ml of MIBK, shake thoroughly, and allow to stand for 10 - 20 minutes. Transfer the MIBK layer into a 10-ml centrifuge tube, and centrifuge for 10 minutes. Using the instrument conditions described above, measure the lead absorption of the MIBK layer.

Calculation

Prepare a working curve by plotting the absorbance values of the standards against the concentrations in ppm. Determine the concentration of lead in the sample directly from this curve.

Alternative Procedures

Lead

According to USP XVIII, page 374.

Arsenic

According to FCC I, page 408.

44.0 Assay: Magnesium Oxide

Accurately weigh about 1 g of sample into a 100-ml beaker, and add, from a buret, 50.0 ml of 0.1N sulfuric acid. Boil for about 10 minutes, or until the fatty acid layer is clear, adding water, if necessary, to maintain the original volume. Cool and, using a suitable filter, filter into a 250-ml conical flask. Wash the beaker and filter thoroughly with water until the washing is not acid to litmus paper, combining the washes in the 250-ml conical flask. Titrate the excess sulfuric acid with 0.1N sodium hydroxide, using methyl orange T.S. Perform a blank determination by adding, from a buret, 50.0 ml of 0.1N sulfuric acid into a 250-ml conical flask. Titrate with 0.1N sodium hydroxide, using methyl orange T.S. Each ml of 0.1N sulfuric acid is equivalent to 2.015 mg of magnesium oxide.

Calculation

$$\frac{(\text{ml blank titr.} - \text{ml spl. titr.}) \times \text{N NaOH} \times 0.02015 \times 100}{\text{weight of sample (g)}} = \% \text{ magnesium oxide}$$

60.0 Microbiological Purity

According to USP XVIII, page 845, for E. coli, Salmonella, Pseudomonas aeruginosa, and Staphylococcus aureus.

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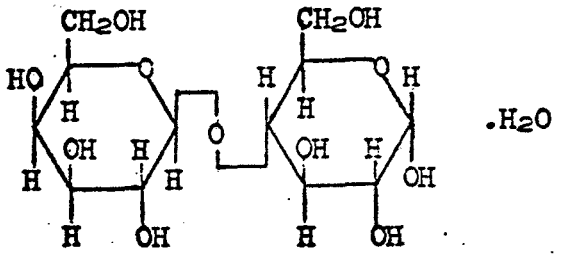
QUALITY CONTROL DEPARTMENT

0835

Raw Material - LACTOSE, HYDROUS



$C_{12}H_{22}O_{11}.H_2O$ Mol. Wt. 360.32

Specifications

Test No.

	01.0	Appearance	White to creamy white, hard crystalli masses, or powder
	03.0	Odor	None.
	05.0	Solution Test	Clear
	06.0	Color of Solution	Maximum APHA 100
	06.1	Odor of Solution	Odorless
	07.1	Reaction of Solution	Neutral to litmus
	15.0	Identity Test	Positive
*	17.1	Bulk Density	0.85 - 0.95 g/ml
	19.0	Specific Rotation (dry basis)	+54.8° to +55.5°
	26.0	Loss on Drying	Maximum 5.5%
	27.0	Residue on Ignition	Maximum 0.1%
	30.0	Heavy Metals	Maximum 5 p.p.m.
	37.0	Other Sugars	Passes test
	49.0	Sieve Test: US Std Sieves	
*	49.1	On No. 60	Maximum 1%
*	49.2	On No. 100	Maximum 15%
*	49.3	Through No. 200	55 - 70%
		Microbiological Purity	
	60.0	Salmonella	Negative
	60.1	E. Coli	Negative

* This specification may vary according to end use.

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~~0558~~

Raw Material - LACTOSE, HYDROUS

0836

Directions for Testing

05.0 Solution Test

Dissolve 3 g of sample in 10 ml of boiling water: the solution shall be clear. (Use this solution for Tests 06.0, 06.1, and 07.1.)

15.0 Identity Test

According to USP XVIII, page 358, or revision thereof.

17.1 Bulk Density

Pass about 100 ml of sample through a No. 20 sieve, and collect the material that passes through on a large sheet of glassine paper. Do not settle or compress the sifted material in any way. Carefully transfer, by sliding and not by pouring, about 50 ml of the sifted material into a tared 100-ml graduated cylinder. Place the cylinder on the Tapping Machine and let it tap for exactly 3 minutes. Carefully level the meniscus and observe the volume. Reweigh the cylinder to determine the weight of the sample.

Calculation

$$\frac{\text{wt. of sample (g)}}{\text{volume of sample (ml)}} = \text{Bulk Density in g/ml}$$

19.0 Specific Rotation

According to USP XVIII, page 358, or revision thereof.

26.0 Loss on Drying

According to USP XVIII, page 358, or revision thereof.

27.0 Residue on Ignition

According to USP XVIII, page 901, or revision thereof.

30.0 Heavy Metals

According to USP XVIII, page 358, or revision thereof.

37.0 Other Sugars

According to USP XVIII, page 358, or revision thereof.

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QUALITY CONTROL DEPARTMENT

~~1529~~

0837

Raw Material - LACTOSE, HYDROUS

49.0 Sieve Test: US Std. Sieves

According to USP XVIII, page 940, or revision thereof, as described under "Powder Fineness," using 50 g of sample, and No. 60, 100, and 200 US Standard Sieves. 3 individual requirements

60.0 and 60.1
Salmonella and E. Coli

According to APhA "Recommended Methods for Microbiological Examinatic of Foods" and/or according to the methods outlined in the "Bacteriological Analytical Manual" of the U.S. Department of Health, Education and Welfare Food and Drug Administration.

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~~25401~~

0838

Raw Material - GELATIN, TYPE A, 100 Mesh
(Porkskin Gelatin)

This raw material is tested and shall meet all U.S.P. tests as defined in U.S.P. XVII, pages 263-264, or revision thereof.

In addition, this compound shall meet the following specification:

Sieve Test (U.S. Standard Sieve)	Less than 5% on No. 100

pa

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QUALITY CONTROL DEPARTMENT

Raw Material - STARCH, Direct Compression Grade*
STA-RX 1500

[redacted] 0839

Specifications

Test No.		
01.0	Appearance	White, fine granular powder
03.0	Odor	None
05.0	Solubility in Cold Water	7.0 - 22.0%
13.1	pH	4.5 - 7.0
15.0	Identity Test A	Positive
15.1	Identity Test B	Positive
26.0	Loss on Drying	Maximum 14.0%
27.0	Residue on Ignition	Maximum 0.5%
31.0	Iron	Maximum 10 p.p.m.
37.0	Oxidizing Substances	None detected
37.1	Sulfur Dioxide	Maximum 80 p.p.m.
49.0	Sieve Test: US Std Sieves	
49.1	Through No. 40	Minimum 99%
49.2	Through No. 100	Minimum 90%
49.3	Through No. 200	Minimum 60%
60.0	Microbial Limit	Meets USP requirements

*USP XVIII

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F 4430*

Raw Material - STARCH, Direct Compression Grade
STA-RX 1500

0342

0840

Directions for Testing

05.0 Solubility in Cold Water

Accurately weigh about 2 g of sample into a 200-ml volumetric flask. Add about 100 ml of water which has been adjusted to 25°C, shake vigorously until sample is suspended completely, and dilute to volume with water. Stopper, and shake for 1 hour at 25°C. Filter through Whatman #12 paper, or suitable equivalent, refiltering the first portion of the filtrate. Pipet 50.0 ml of the filtrate into a tared evaporating dish, and evaporate to dryness on a steam bath. Dry for 1 hour in a vacuum oven at 100°C. Cool, and reweigh.

Calculation

$$\frac{\text{Wt. of residue (g)} \times 4 \times 100}{\text{Wt. of sample (g)}} = \% \text{ solubility}$$

13.1 pH

Weigh 20.0 g of sample into a 250-ml beaker, and add 100 ml of water. Agitate continuously at a moderate rate for 5 minutes, using a magnetic stirrer or suitable equivalent. Immediately determine the pH of the slurry, using a suitable pH meter. (Save for Test 15.1.)

15.0 Identity Test A

Prepare a smooth mixture of 1 g of sample and 2 ml of cold water. Stir this mixture into a 50-ml beaker containing 15 ml of boiling water, boil for 2 minutes, and cool: the product is a translucent, whitish jelly.

15.1 Identity Test B

To 5 ml of the slurry from Test 13.1 add 1 ml of iodine T.S.: a purplish-blue to deep blue color results.

26.0 Loss on Drying

Dry about 1 g of sample, accurately weighed, in an oven at 120°C for 4 hours.

27.0 Residue on Ignition

According to USP XVIII, page 901, or revision thereof.

Raw Material - STARCH, Direct Compression Grade
STA-RX 1500

31.0 Iron

Reagents

Standard Iron Stock Solution: Prepared according to USP XVIII, page 956, or revision thereof, as described under "Iron in Reagents." This solution contains 0.10 mg iron/ml.

Standard Iron Solution: Dilute 5.0 ml of Standard Iron Stock Solution to 100 ml with water. One ml of this solution contains 0.005 mg of iron, equivalent to 10 p.p.m. in a 0.5 g sample.

Procedure

(Note: Rinse all glassware with dilute hydrochloric acid (1 in 5) before proceeding.)

Weigh 500 mg of sample into a 50-ml, glass-stoppered conical flask. Add 20 ml of dilute hydrochloric acid (1 in 5), insert the stopper, and shake vigorously for 5 minutes. Filter the suspension through Whatman #40 filter paper, or suitable equivalent, into a Nessler tube, wash with a few ml of water, and dilute with water to 50 ml. Simultaneously prepare a control solution by filtering 20 ml of dilute hydrochloric acid (1 in 5) into a second Nessler tube. To this tube add 1 ml of Standard Iron Solution, and dilute with water to 50 ml. To each tube add about 40 mg of ammonium persulfate crystals, and 3 ml of ammonium thiocyanate T.S., and mix: any red color produced in the sample solution is not darker than that of the control solution (10 p.p.m.).

37.0 Oxidizing Substances

Weigh 5 g of sample into a 50-ml beaker. Add 10 ml of water, and 1 ml of acetic acid, and stir until a homogeneous suspension is obtained. Add 0.5 ml of saturated solution of potassium iodide, mix, and allow to stand for 5 minutes: no blue, brown, or purple color is observed.

37.1 Sulfur Dioxide

(Note: Fill a 500-ml flask with water, and use this water throughout the procedure.)

Weigh 20 g of sample into a 400-ml beaker. Add 200 ml of water, and mix until a smooth suspension is obtained. Filter through Whatman #40 filter paper, or suitable equivalent, which had previously been washed with water. Place 100 ml of the clear filtrate into a 250-ml conical flask. Titrate with 0.01N iodine to the first permanent blue color, using starch-type indicator. Perform a blank determination on 100 ml of water, and subtract this titration from the sample titration: the net titration shall not exceed 2.7 ml (80 p.p.m.).

Raw Material - STARCH, Direct Compression Grade
STA-RX 1500

0842

49.0 Sieve Test: US Std. Sieves

According to USP XVIII, page 940, or revision thereof, as described under "Powder Fineness," using 50 g of sample and No. 40, 100, and 200 U.S. Standard Sieves.

60.0 Microbial Limit

The sample meets the requirements of the tests for absence of Salmonella and Escherichia coli under "Microbial Limit Tests," USP XVIII, page 846, or revision thereof.

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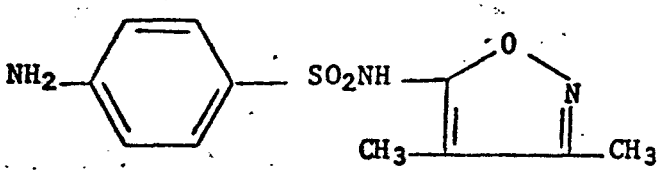
~~0545~~

QUALITY CONTROL DEPARTMENT

0843

Material - SULFISOXAZOLE*
(N^1-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide)

Effective Date: March 24, 1972



$C_{11}H_{13}N_3O_3S$ Mol. Wt. 267.31

Specifications**

Test No.		
01.0	Appearance	Crystalline powder
02.0	Color	White to slightly yellowish
03.0	Odor	Odorless
05.0	10% Solution in Alcohol	Clear
05.1	3.33% Solution in 10% Hydrochloric Acid	Complete and clear
06.0	Color of 3.33% Solution in 10% Hydrochloric Acid	Maximum APHA #80
07.0	pH of 1% Suspension in Water	4.0 - 6.0
15.0	Identity Test A	Positive
15.1	Identity Test B	Positive
15.2	Identity Test C	Positive
24.0	Melting Range	194 - 199°C
26.0	Loss on Drying	Maximum 0.5%
27.0	Residue on Ignition	Maximum 0.1%
30.0	Heavy Metals	Maximum 20 ppm
30.2	Selenium	Maximum 10 ppm
34.0	Chlorides (as Cl)	Less than 100 ppm
44.0	Assay (dry basis)	99.0 - 101.0%
50.0	Ampul Solution Test (For ampul type)	Maximum APHA #150

*USP XVIII

**See following pages for Directions for Testing.

A-2200

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F 4490

Material - SULFISOXAZOLE
(N^1-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide)

0844

Directions for Testing

05.0 10% Solution in Alcohol

Dissolve 500 mg of sample in sufficient boiling USP alcohol to make 5 ml of solution.

05.1 3.33% Solution in 10% Hydrochloric Acid

Dissolve 0.5 g of sample in sufficient 10% hydrochloric acid to make 15 ml of solution. Save this solution for Test 06.0.

06.0 Color of 3.33% Solution in 10% Hydrochloric Acid

Compare the color of the solution from Test 05.0 with APHA Color Standards.

07.0 pH of 1% Suspension in Water

Mix 200 mg of sample with sufficient water to make 20 ml of suspension. Shake for 3-5 minutes, filter and measure the pH of the filtrate at 25°C with a suitable pH meter.

15.0 Identity Test A

According to USP XVIII, page 825, as described under Spectrophotometry.

The infrared absorption spectrum of a potassium bromide dispersion of sample, at a concentration of about 1 mg/300 mg, agrees qualitatively with that of a similar preparation of a sulfisoxazole reference standard.

15.1 Identity Test B

Ultraviolet Absorption

Reagents

0.2M Potassium Phosphate: Dissolve 27.218 g of potassium phosphate, monobasic (KH_2PO_4), in sufficient water to make 1 liter of solution.

0.2M Sodium Hydroxide

0.1N Sodium Hydroxide

pH 7.5 Phosphate Buffer: Place 250 ml of 0.2M potassium phosphate solution into a 1-liter volumetric flask. Add 204 ml of 0.2M sodium hydroxide and dilute to volume with water. Measure the pH and adjust, if necessary.

- cont'd -

Material - SULFISOXAZOLE
(N^1-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide)

0845

Procedure

Weigh accurately about 100 mg of sample into a 100-ml volumetric flask and dissolve in 10 ml of 0.1N sodium hydroxide. Dilute to volume with pH 7.5 phosphate buffer (Sample Solution I). Dilute 10.0 ml of Sample Solution I to 100 ml with pH 7.5 phosphate buffer (Sample Solution II). Dilute 10.0 ml of Sample Solution II to 100-ml with pH 7.5 phosphate buffer (Sample Solution III). Concomitantly measure the absorbance of Sample Solution III and of a similarly prepared solution of a sulfisoxazole reference standard with a suitable spectrophotometer against pH 7.5 phosphate buffer in the reference cell. Sample Solution III exhibits a maximum (at 253 ± 2 nm) and a minimum (at 222 ± 2 nm) at the same wavelengths as the sulfisoxazole reference standard solution.

15.2 Identity Test C

Dissolve about 10 mg of sample in 2 ml of diluted hydrochloric acid, heating carefully. Cool for 5 minutes in an ice bath, add 3 drops of 1% sodium nitrite solution and dilute to 4 ml with water: the solution turns yellow. Add 1 ml of a 10% sodium hydroxide solution containing 10 mg of betanaphthol: an orange-red precipitate forms.

24.0 Melting Range

According to Class Ia, USP XVIII, page 935. Report to the nearest whole degree.

26.0 Loss on Drying

Weigh accurately about 1 g of sample and dry at 105°C for 2 hours.

27.0 Residue on Ignition

According to USP XVIII, page 901. Save the residue for Test 30.0.

30.0 Heavy Metals

According to Method II, USP XVIII, page 897, using the residue from Test 27.0.

30.2 Selenium

According to USP XVIII, page 901, the Test Preparation being made with 200 mg of sample.

or alternatively:

Material - SULFISOXAZOLE
(N^1-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide)

454B

0846

X-Ray Fluorescence Method

Standard Preparation

Mix intimately, in a Spex "Freezer-Mixer", or suitable equivalent, a portion of a sulfisoxazole reference standard, which contains less than 3 ppm of selenium, with an amount of selenium dioxide equivalent to a concentration of 10,000 ppm. Prepare a pellet by pressing, on a Mylar film base, approximately 4 g of this mixture in a die at 50,000 psi for 10 minutes. Remove the Mylar film from the pressed pellet (Alignment Standard).

Also prepare a standard pellet containing 10 ppm of selenium by appropriate dilution of the 10,000 ppm mixture with a sulfisoxazole reference standard.

Sample Preparation

Prepare a pellet of the sample, using a quantity of sample equivalent to the amount of the sulfisoxazole reference standard used for the standard preparation. Save this sample pellet for Test 34.0.

Instrument and Conditions (An equivalent instrument and appropriate operating conditions may be used.)

Instrument	**General Electric XRD-6 Spectrometer**
Generator	**50 KV and 50 mA (full wave rectified)**
Tube Target	**Molybdenum**
Optics	**Lithium fluoride crystal; Soller slit = 0.02" x 3.5"; Air atmosphere**
Detector	**Scintillation Counter at plateau; Pulse Height Selector adjusted for maximum SeKα intensity; Base 5V; ΔE = 3V**
Scale	**20 second count**
Goniometer	**SeKα peak and background at ± 1.0° 2θ**

Material - SULFISOXAZOLE
(N^1-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide)

0847

Procedure

Align the analyzing crystal of the instrument with the 10,000 ppm Alignment Standard. Measure and record the intensity of emission of the sample pellet and the 10 ppm standard pellet on the surfaces which were adjacent to the Mylar film.

Calculation

$$C_s - [(C_2 + C_3)/2] = \text{sample net count}$$

where:

C_s = sample count at SeKα peak

C_2 = sample background at SeKα -1.0°2θ

C_3 = sample background at SeKα +1.0°2θ

The sample net count should be less than or equal to the net count of the 10 ppm standard pellet calculated in the same manner.

34.0 Chlorides (as Cl)

Standard Preparation

Prepare a 100 ppm chlorine mixture by mixing intimately, in a Spex "Freezer Mixer", or suitable equivalent, a portion of a sulfisoxazole reference standard, which shows no characteristic chlorine radiation, with reagent grade sodium chloride. Prepare a pellet by pressing approximately 4 g of this mixture in a die at 50,000 psi for 10 minutes.

Sample Preparation

Use the sample pellet prepared for Test 30.2.

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QUALITY CONTROL DEPARTMENT

Material - SULFISOXAZOLE
(N^1-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide)

0848

Instrument and Conditions (An equivalent instrument and appropriate operating conditions may be used.)

Instrument	General Electric XRD-6 Spectrometer
Generator	50 KV and 50 mA (full wave rectified)
Optics	PET analyzing crystal; Soller Slit = 0.02" x 3.5"; Helium atmosphere
Detector	Flow proportion counter at plateau; Pulse Height Selector adjusted for maximum Cl K_α intensity Base 5V; ΔE = 3V Chromium K_α - Window out
Scaler	100 second count at Cl K_α 1st order peak; 10 second count at the Cr K_α second order peak
Goniometer	ClK_α^1 peak and $\pm$ 1.0° 2θ
	CrK_α^2 peak and $\pm$ 1.0° 2θ

Procedure

Place the pellet in the sample holder of the XRD-6 Spectrometer and measure the intensity of the characteristic fluorescence produced by chlorine and the intensity of the primary chromium second order line reflected by the pellet with the background intensity of each line.

Calculation

A. Corrected Intensity = peak intensity - average background intensity

B. Relative Intensity = $\dfrac{\text{corrected intensity for chlorine } K_\alpha^1}{\text{corrected intensity for chromium } K_\alpha^2}$

The relative intensity of the sample pellet should be less than the relative intensity of the standard pellet containing 100 ppm chlorine.

Material - SULFISOXAZOLE
(N^1-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide)

0849

1551

44.0 Assay (dry basis)

Weigh accurately about 800 mg of sample into a 250-ml conical flask. Add 50 ml of dimethylformamide, shake thoroughly to dissolve the solid, add 5 drops of a 1% solution of thymol blue in dimethylformamide, and titrate with 0.1N lithium methoxide to a blue end-point (avoid excess swirling). Perform a blank titration and make any necessary correction. Each ml of 0.1N lithium methoxide is equivalent to 26.73 mg of sulfisoxazole.

Calculation

$$\frac{\text{ml LiOMe} \times \text{N LiOMe} \times 0.2673 \times 100}{\text{Sample Wt. (g)}} = \text{percent sulfisoxazole}$$

Also report on as is basis.

50.0 Ampul Solution Test

Dissolve 4.0 g of sample in 5.6 ml of water, add 1.57 g of diethanolamine (colorless, distilled), and shake for 10 minutes. Filter and compare the color of the filtrate with APHA Color Standards.

ROCHE LABORATORIES

DIVISION OF HOFFMANN-LA ROCHE INC. • NUTLEY, NEW JERSEY 07110

Mr. Minor L. Kelso
Chief
Medical Services
Department of Human Resources
State Capital Complex
Carson City, Nevada

Dear Mr. Kelso:

I am pleased to send you the proceedings of a recent Excerpta Medica Colloquium, "The Scientific Evaluation of Drug Equivalency".*

The colloquium generated considerable controversy concerning the importance of positively establishing through adequate evidence the equivalency between drug products bearing the same generic name before permitting their interchangeability. These proceedings are of particular relevance today in light of the Health, Education and Welfare Department's recently published regulations regarding the implementation of a Maximum Allowable Cost (MAC) program for drug products reimbursed through federally financed programs.

We at Roche believe that the patient's right to safe, effective, quality assured drug products will be violated should the MAC program be implemented in accordance with the regulations published in the November 15 and November 27 Federal Register. In our opinion, the greatest potential danger to the patient arises from the scientifically invalid premise underlying the drug product equivalency criteria established by the proposed regulations:

- equivalency among drug products within a generic (multisource) category will be assumed unless proven otherwise.

*The mention of any pharmaceutical product in the enclosed colloquium proceedings does not imply any recommendations for such products. Manufacturers' product information should be consulted for specific information.

Many examples of inequivalency have been cited in the literature and documented by scientific experts, which we believe clearly demonstrate that therapeutic equivalency cannot be assumed among chemically equivalent products. In light of the uncertainties in this area, in our judgment, equivalency must be proven, not assumed. We further believe that proof of equivalency must be demonstrated on the basis of adequate objective scientific standards. There is no room for a subjective or nonscientific determination of equivalency when this issue bears so directly on patient health care.

Under the proposed MAC program, physician and pharmacist prerogatives in drug product selection will be severely restricted and will be based essentially on cost considerations. In addition, this program would impose a significant administrative burden upon the existing State Medical Assistance Programs since by regulatory mandate, they would have to be drastically altered in order to comply with the proposed scheme.

We urge all concerned parties, especially professional members of the health care community, to express their views on this far-reaching proposal which could seriously affect the quality of drug products utilized by this nation's disadvantaged and elderly ill.

All comments should be sent to:

Hearing Clerk
Food and Drug Administration
Room 4-65
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20852

Sincerely,

Gerald D. Lore

Gerald D. Lore
Group Manager
Institutional Planning

0852

Morris and Loring Drug
Fallon, Nevada 89406
February 10, 1975

James S. Dwight, Jr., Administrator
Social and Rehabilitation Service
Department of Health, Education, and Welfare
P. O. Box 2382
Washington, D.C. 20013

Re: Proposed Reimbursement of Drug Cost; Federal Register, Volume 39, No. 230, dated 11-27-74

Dear Mr. Dwight:

The Proposed Reimbursement of Drug Cost is found to be unsatisfactory for various reasons.

Pharmacists would be forced to keep a double inventory of specified multiple-source drugs, one for the general public, and one for the second class citizens, i.e., Medicaid recipients. This is both costly for the pharmacist and paradoxical to the goal of Title XIX of the Social Security Act, which is to bring the Welfare recipient into the mainstream of medical care. Welfare recipients would be administered the cheapest available generic drugs with no assurance of quality.

An inordinate degree of medical-legal liability would be imposed on a pharmacist obliged to change the physician's prescription from a brand name drug to a so-called "generic equivalent," selected because it is the cheapest available.

It must also be pointed out that it is imperative that many drugs NOT be selected on the basis of cost only, because of the demonstrated lack of equivalent bioavailability. Examples of such drugs are digoxin, prednisone, and diphenylhydantoin.

If rules are established which list types of drugs by price and state that reimbursement will not be made for any brand of that type of drug costing more, then it must be mandatory that the drugs on that list truly meet USP standards. The bioavailability data must be on the material currently being sold and used, not that obtained from various lots and batches chosen at random.

Another problem arises if the pharmacist is unable to obtain the brand of drug specified by the Pharmaceutical Reimbursement Board. He might then be forced to dispense a brand whose cost exceeds the Maximum Allowable Cost. In that case he would be financially penalized through no fault of his own.

The proposed regulations would increase record keeping requirements and the pharmacist would be forced to endure periodic harassment by auditors. Pharmacists are not enthusiastic at the prospect of additional bureaucratic red tape.

It would also appear that the proposed regulation would necessarily result in increased cost of administration of the Medicaid program. As a taxpayer, I feel that before the proposed regulations are given serious consideration, a realistic cost analysis should be performed to determine whether increased administrative costs outweigh any projected savings to the Medicaid program attributable to the establishment of maximum allowable cost regulations.

It is my opinion that, as compared to the present policy of the Nevada Medicaid program, the proposed regulation is unwieldy, inefficient, uneconomical, and regulatory. I strongly oppose adoption of the regulation and urge your reconsideration.

Sincerely,

George R. Tucker, R.Ph., Chairman
Pharmaceutical Committee
Nevada Medical Care Advisory Group

GRT:dd

0854

February 11, 1975

James S. Dwight, Jr., Administrator
Social and Rehabilitation Service
Department of Health, Education, and Welfare
P. O. Box 2382
Washington, D.C. 20013

Re: Proposed Reimbursement of Drug Cost; Federal Register, Volume 39, No. 230, dated 11-27-74

Dear Mr. Dwight:

The proposed reimbursement of drug cost was discussed at recent meetings of the Physicians' Committee and the Pharmacy Committee of the Nevada Medical Care Advisory Group. There was unanimous agreement that the proposed rules present many difficulties, including increased administrative costs, medical-legal liability, and possible reduction in quality of care.

The requirement that actual acquisition cost be used to determine payment would require State agencies to obtain considerable additional auditing staff to insure that participant providers in the program bill charges based on actual acquisition cost. This additional auditing burden is also inherent in the 25% incentive payment allowance for drugs purchased below maximum allowable cost. It is our opinion that these additional administrative costs would more than offset any projected savings to the Medicaid program attributable to the establishment of maximum allowable costs.

In referring to drug costs, current regulations specify "cost as determined by the State." Nevada presently reimburses pharmacy providers for prescribed drugs covered under the program on the basis of Average Wholesale Price (A.W.P.), as established by Red Book or Blue Book data, plus a dispensing fee. The dispensing fee is uniform and applies to all participating providers of out-patient pharmacy services. The established fee is considered a reasonable fee for service which still results in an average prescription price less than that paid by the general public. Competition between pharmacies serves effectively to maintain reasonable prescription prices to the general public.

The policy of basing cost on A.W.P. plus a unfform dispensing fee allows for rapid automated claim processing, and avoids the expense of periodically auditing each pharmacy to check acquisition cost and determine and update a respective dispensing fee.

Concern has also been expressed by both the Physicians' Committee and the Pharmacy Committee of the Medical Care Advisory Group, regarding the medical-legal liabilities inherent in the proposed rules. Although the proposed rules state that a physician may certify in writing that only a specific brand of drug can be tolerated by, or is effective for a particular patient, the manner of certification is as yet undefined. Many physicians are concerned that they would be forced into the position of prescribing medicine for which there is no assurance of quality. The proposed rules would also place the pharmacist into the position of having to alter the physician's prescription, thus imposing potential medical-legal liabilities upon pharmacists.

The stated purpose of Title XIX of the Social Security Act is to bring the Welfare recipient into the mainstream of medical care. It appears now, however, that emphasis is being swung the other way. Welfare recipients will be administered the cheapest available generic drugs with little assurance of biological equivalency.

It is the opinion of the Nevada Medicaid program that the M.A.C. and actual acquisition cost proposal is too costly to implement and enforce. The potential savings appear to be far less than the administrative costs, while the quality of care appears to be diminished.

We protest most strongly adoption of this proposal and urge your reconsideration.

Sincerely,

Minor L. Kelso, Chief
Medical Care Services

Steven P. Bradford, Pharm.D.,
Pharmaceutical Consultant

MLK:SPB:dd

cc: Roger S. Trounday, Director, Nevada State Department of Human Resources
George E. Miller, Nevada State Welfare Administrator
Members of Physicians' Committee, Nevada Medical Care Advisory Group
Members of Pharmaceutical Committee, Nevada Medical Care Advisory Group
Nevada State Board of Pharmacy

ABBOTT'S BIOCHROMATIC ANALYZER ON RECALL LIST FOR 2nd TIME

as a *Class I Recall* because, according to the FDA list, (see below) 260 Model ABA-100s "infrequently eliminate or otherwise misprint the first digit involving a four-digit answer on end-point determinations." Model ABA-100 of the diagnostic was initially listed as a *Class I Recall Aug. 28* because of "incorrect instructions for use and product non-linearity" ("The Pink Sheet" Sept. 2, p. T&G-6). That problem was corrected. However, 260 of the original 770 ABS-100s which were modified at the time, are the subject of the current "recall." "It's the same machine – the same recall number – but only the ABA-100s that were modified are affected by this new recall," Michael French, Acting Recall Coordinator at FDA's L.A. District Office told "The Pink Sheet." Abbott's Nov. 14 letter to customers noted: "Because the error occurs very infrequently, a repeat run will most likely be acceptable. A card stating. . .instructions (error determination) to be posted on your ABA-100 is enclosed for your convenience." Machines are not physically being recalled.

FDA RECALLS AND COURT ACTIONS . . . . ISSUED DEC. 25, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALLS				
[1] Biochromatic Analyzer Model ABA-100	All	Abbott	Footnote	11/14
CLASS II RECALLS				
[2] Sodium Edecrin I.V.	All w/suffix 'S'	MS&D	Subpotency	Ltr 11/27
[3] Theelin Aqueous Suspension	All	P-D	Crystallization	Ltr 12/13
[4] Medic Brand aspirin tabs & Carroll Brand "Nods" geletin caps	40895 & 410009	Internatl. & Carroll (Internatl. Div.)	X-contamination w/ methyl testosterone	Ltr 11/14
[5] IMI Infant Care Centers Model 2300 prior to 6/71 & Model 4000 prior to 9/72	All	Becton, Dickinson	Side panels become unlatched & collapse	Ltr 11/22
[6] Physiological Irrigating sol.	G4K042	McGaw	Fusarium, penicillin & mucor contamination	Visits 11/26
CLASS III RECALLS				
[7] Xylocaine HCl 1.5% hyperbaric aqueous sol.	PL0173	Astra	Variance in pH	Phone 12/3 & ltr 12/4
[8] Elixir Terpin Hydrate & Elixir Terpin Hydrate w/Codeine	Footnote	Carroll	Precipitation	Ltr 11/19

[1] Initially listed on FDA's Aug. 28 Recall List. Modified devices will infrequently eliminate or misprint the first digit involving a four-digit answer on end print determinations. Natl. & internatl. distribution. Approx. 260 devices remain on market. [2] Natl. & internatl. distribution. Approx. 6,400 units remain on market. [3] Natl. distribution to MDs & hosps. Approx. 30,000 10 ml. & 5,000 5 ml. vials remain on market. [4] Distribution to retail pharmacies & super market chains in Eastern 2/3 of US. [5] Natl. distribution to hosps. Approx. 1,000 Model 2300 series & 2-300 Model 4,000 series remain on market. [6] Distribution to Eastern US. [7] Distribution limited to 19 MDs, not publicly marketed. [8] Lot numbers: Elixir Terpin Hydrate – 40174; Elixir Terpin Hydrate w/Codeine 2, 16 oz. & 1 gal. - 40542 and Elixir Terpin Hydrat w/Codeine 4 oz. btls. - 40624. Distribution to whslrs. & chain or retail pharmacies in Eastern 2/3 of US.

EDITORS' NOTE: Above tabulation is prepared from a weekly list made public by FDA's Office of Asst. Commissioner for Public Affairs. Re-arrangement of information supplied by FDA chiefly involved expansion of footnotes to shorten tabulation. Though listed by FDA, DESI recalls – undertaken to implement FDA findings, based on NAS/NRD efficacy review – are not included in "The Pink Sheet" tabulation. FDA's recall procedure now has three categories: *Class I*, for emergency, life-threatening recalls; *Class II*, a "priority" situation that is possibly or potentially life-threatening; Class III, a "routine" situation with little or no threat to life. Editors of "The Pink Sheet" appreciate hearing from any company that would like to provide additional information of any recall listed in these weekly tabulations.

EXPANDED MALLINCKRODT RECALL AFFECTS APPROXIMATELY 300,000 VIALS

of six diagnostic products: Conray, Conray 400, Angio-Conray, Vascoray, Pyelokon-R, and Cysto-Conray. Original Class I Recall of 3240 units of Conray IV solution appeared on FDA's Dec. Recall List ("The Pink Sheet" Dec. 9, T&G-7) after two vials were found to be non-sterile, one containing a mold growth. Three other vials inspected at the same time were found to be sterile, according to FDA sources.

¶ Second recall came after discovery of ten additional non-sterile vials including units of Conray 400 and Vascoray as well as Conray. All 50 ml. vials of Conray 400, Angio Conray, Vascoray, Pyelokon-R and Cysto-Conray are covered by the recall. Eight different lots were affected by the action, FDA noted; direct contact was made by the firm to each user.

Mallinckrodt attributed the problem to slight chips in the lips of the vials, which in some cases, after packaging and autoclaving, developed into hairline cracks allowing contamination to take place. The company noted that 600,000 vials had be reinspected before the decision to recall the 300,000 units was made. Notification to users, through a "Dear Dr." letter dated Dec. 17, stated that the situation "is very serious" and "may be life-threatening." All products involved in the recalls were produced at the company's St. Louis plant.

FDA RECALLS AND COURT ACTIONS. . . . ISSUED DEC. 26, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALLS				
[1] Conray, Conray 400, Angio Conray, Vascoray, Pyelokon & Cysto-Conray	All - Footnote	Mallinckrodt	Non-sterile	Ltr 12/17
CLASS II RECALLS				
[2] McGaw 3.3% Sorbital urologic irrigating sol.	G4J167	McGaw	Nigrosporin mold contamination	Visits 12/11
[3] Ames Blood Analyzer Dial Faces	All defective faces	Ames	Mislabeling & incorrect notching	Ltrs 10/17
[4] Bennett Monitoring Spirometer & Spirometer alarm	2642, 5460	Bennett Respiration Products	Footnote	Ltr 11/18
CLASS III RECALLS				
[5] Neuromod Transcutaneous Nerve Stimulator	Footnote	Medtronic	Potentially faulty amplitude potentiator	Ltr 11/6
SEIZURE ACTION FILED				
[6] Hair Food w/Vitamins A & D, Hair Food Pressing Conditioner & Non-Alkaline Hair Food Shampoo		Esirig	False & misleading labeling	12/5

[1] All lots recalled except: Conray - BLR-E, BPX-B, BRX-A, BRX-B, BRX-D, BRX-E, BSL-A, BSL-B, BSL-C, BSL-E, BSR-B, BSR-C, BSR-D, BSR-X & BSR-G. Conray 400 - BPY-D, BPY-E, BRT-B, BTG-B, BTG-C, BTG-D, BTG-E, BTG-G, BTL-A, BTL-B, BTL-D, BTL-E, BTL-G, BTN-C, BTN-D, BTN-E & BTN-G. Angio Conray - BSG-A, BSG-B, BSG-C, BSG-D, BSG-E & BSG-G. Vascoray - BMA-G, BPP-A, BPP-B, BPP-C, BPP-D & BPP-G. Natl. & internatl. distribution. Approx. 200,000 vials of all products remain on market. Direct contact was made to each user. [2] Natl. distribution to warehouses. [3] Letters instructed consignees to check all dial faces against illustrations provided and to notify co. if any defective dials were found. Natl. distribution to MDs and to Africa, Far East, Europe, Japan, Latin America, Canada & Caribbean. Approx. 20,000 faces remain on market. [4] Reason: Failure of devices to alarm of a machine malfunction under the condition of disconnection of certain tubing between a respirator machine and the spirometer unit. Natl. & internatl. distribution to hosps. [5] Lot numbers: All devices shipped between 9/11 & 11/4. Natl. distribution. Approx. 95 devices remain on market. [6] US District Court, North Calif.

FDA RECALLS AND COURT ACTIONS.....ISSUED JAN. 1, 1975

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] A-Gent SGPT In-Vitro Diagnostic Test 3 ml.	Footnote	Abbott ✓	Loss of chemical stability [& 18]	Phone 11/15, Ltr 11/18
[2] Dexamethasone .75 mg. tabs	Control # 8279	Danbury	Contamination w/ methyl testosterone	Ltr 12/21
[3] Disposable Plastic 3-way Stopcock device	All beginning w/H4 & H3S	Pharmaseal	Footnote	Ltr 11/23
Suby's Solution G Urinary Calculi Solvent	G4K023	McGaw	Mold contamination	Visit 12/17
[4] DC Defibrillator Catalog #A3220C, model #46-203270GIC	91304	GE	Sync test switch malfunction	Corrective prog. 10/14
CLASS III RECALLS				
[5] Hepvironim liver inj., 30 cc.	22138	Bel-Mar	Subpotent in Vitamin B-12	Phone 12/22
[6] Walgreens Cod Liver Oil, Mint Flavored & Plain	Footnote	Walgreen	Error in label dosage recommendation	Ltr 10/29
[7] Liver IM inj., 30 cc.	22013	Bel-Mar	Subpotent in Vitamin B-12	Phone 12/3 & 4
[8] Aggregated Albumin in kits	99.4 - 146	Medi-Physics	Label bears 190 day expiration instead of 180	Phone, ltrs, visits beg. 12/9
[9] Code 1676 Stilbestrol Pearls Synthetic Estrogen	All	R.P. Scherer	No ANDA	Ltr 11/26
[10] Liver inj. 10 & 30 cc.	Footnote	Bel-Mar	Subpotent in Vitamin B-12	Phone 12/16
SEIZURE ACTIONS FILED				
[11] Zorane		Lederle ✓	Misleading drug advertising	12/19
[12] Elcar Model 90A Air Purifier		Service Ideas	Misleading labeling & dangerous to health	12/20

[1] Lot numbers: 160A274X, 160A274H, 160274AA, 160274BB. Natl. distribution & to Canada. Approx. 250 vials remain on market. [2] Also distributed by: Deacon, Bioline, Sherry, Interstate, Wolins, United Research, Henry Schein & Rugby. Natl. distribution. Approx. 7,100 tabs remain on market. [3] Reason: Ill-fitting luer ports may cause leaks or disconnections from an IV appartus and pinhole leaks or disconnections in the well of the stopcock handle; may cause leakage of fluid or non-sterile air to be sucked into an IV administration set-up during use. World-wide distribution. Approx. 1 to 2 mil. remain on market. [4] All devices have been repaired. Distribution to hosps. [5] Also labeled: Liberon, Henry Schein; Liver, Iron & Vitamins, Sherry; Liver, Iron & Vitamins, Spencer-Mead & Liver, Iron & Vitamins w/B-12, Hilco. Distribution to NY, NJ, Pa., & Calif. Approx. 400 vials remain on market. [6] Lot numbers: mint flavored - 0153C64 & 0154C64. Plain - B822U64. Imported by Arista. Natl. distribution Approx. 10,000 units remain on market. [7] Also labeled for Wolins. Approx. 300 vials remain on market. [8] Natl. distribution. Approx. 130 kits remain on market. [9] Natl. distribution & to Canada. [10] Lot numbers: 21706 & 22104 under Rugby, Prime, Henry Schein & Lannett. 21710, 22010, 22011 & 22168 under Rugby, C.O. Truxton, Henry Schein, Hilco, Spencer-Mead & Sherry: 21689, 21741, 21995, 22059, 22063, 22064, 22065, 22076, 22090, 22163, 22164, & 22182 under Rugby, Wolins, Spencer-Mead, Sherry, Prime, Federal, Bel-Air & Henry Schein. Natl. distribution including Puerto Rico. Approx. 2500/30cc. & 250/10 cc. vials remain on market. [11] US District Court, South NY. [12] US District Court, Minn.

EDITORS' NOTE: Above tabulations are prepared from weekly lists made public by FDA's Office of Asst. Commissioner for Public Affairs. Re-arrangement of information supplied by FDA chiefly involved expansion of footnotes to shorten tabulation. Though listed by FDA, DESI recalls -- undertaken to implement FDA findings, based on NAS/NRC efficacy review -- are not included in "The Pink Sheet" tabulation. FDA's recall procedure now has three categories: *Class I*, for emergency, life-threatening recalls; *Class II*, a "priority" situation that is possibly or potentially life-threatening; Class III, a "routine" situation with little or no threat to life. Editors of "The Pink Sheet" appreciate hearing from any company that would like to provide additional information of any recall listed in these weekly tabulations.

T&G **R.P. SCHERER CORP. NOT RESPONSIBLE FOR RECALLING** "Code 1617 Stilbestrol ... included under Class III ... lation of FDA's Weekly Recall List issued Jan. 1, 1975 ("The Pink Sheet" Jan. 6, T&G-7). As is widely ... in the industry, Scherer is a contract mfr. and doesn't market drug products under its own label.

Scherer made the recalled vet drug for Cutter's Haver-Lockhart Labs, Shawnee ... Kan., whose Bayvet Corp. subsidiary was responsible for the recall, based on ... FDA's allegation that the product was marketed without an approved New ... Animal Drug Application.

FDA RECALLS AND COURT ACTIONS..... ISSUED JAN. 8, 1975

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
McGaw 1,000 ml. Normal Saline	G4K048 & G4K050	McGaw	Leaking containers	Visit 12/20
[1] Digital Devices Model 560	All devices	Digital Devices	Unnecessary radiation exposure	Footnote
[2] S.S. White Panorex Panoramic Dental X-Ray machine	Footnote	Pennwalt's S.S. White Dental Products	Unnecessary radiation exposure	Footnote
Dantrium 25 mg. caps	Control #809941	Eaton	Non-content uniformity	Ltr 12/14
[3] Maalox magnesia & Alumina oral suspension	15545	William H. Rorer	Bacterial contamination	Ltr 12/18
CLASS III RECALLS				
[4] Thiamine HCl inj.	21591	Bel-Mar	Possible mold contamination	Phone 12/2
[5] Mineral Oil Cathartics	All	Cremagol	Viable yeast contamination	Ltr 12/4
[6] Travenol Code No. 2C001 Standard Administration Set	Footnote	Travenol	Footnote	Ltr 12/6
[7] Triple Isolated Precision Physiological Pressure Transducer	All serial nos.	Bell & Howell	Footnote	Phone, Ltrs 12/2
SEIZURE ACTIONS FILED				
[8] Gervimone - V caps		C.M. Bundy	No ANDA	12/20
[9] Solarama Board		Rubiat	Misleading labeling	12/30

[1] Corrective action program initiated 11/6. [2] Lot numbers: All units manufactured on or before 8/1. Corrective action program initiated 12/13. Natl. distribution. [3] Distribution to South NY, East Ohio, W. Va., Northeast Ky., Ind. & NC. [4] Distribution to 2 drug mail order houses. Approx. 50/100 cc. vials remain on market. [5] Recall includes Plain Cremagol, Phenolphthalein in Cremagol & Cascara in Cremagol. [6] Lot numbers: J04L7, J04L8, J04L9, J04N9, J04P1, J04R2, J04R9, J04S1, J04P3, J04P5, J04P7, J04R0, J04R4, J04R5, J04R6 & J04R7. Distribution to hosps. & clinics in East US & possibly Puerto Rico. Reason: Tubing not concentric & does not collapse normally when clamp is closed. May not occlude properly. [7] Reason: When device is steam autoclaved, the plastic parts deform. Labeling indicates steam autoclaving as an acceptable method of sterilization. Natl. & internatl. distribution. Approx. 170 units remain on market. [8] US District Court, North Ohio. [9] US District Court, Central Calif.

EDITORS' NOTE: Above tabulation is prepared from a weekly list made public by FDA's Office of Asst. Commissioner for Public Affairs. Re-arrangement of information supplied by FDA chiefly involved expansion of footnotes to shorten tabulation. Though listed by FDA, DESI recalls – undertaken to implement FDA findings, based on NAS/NRC efficacy review – are not included in "The Pink Sheet" tabulation. FDA's recall procedure now has three categories: *Class I*, for emergency, life-threatening recalls; *Class II*, a "priority" situation that is possibly or potentially life-threatening; Class III, a "routine" situation with little or no threat to life. Editors of "The Pink Sheet" appreciate hearing from any company that would like to provide additional information of any recall listed in these weekly tabulations.

T&G **AIR-SHIELDS' VENTIMETER VENTILATOR *CLASS II* DEVICE RECALL** -- due to a potential misconnection of the ventilator-gas machine hose, applies only to those units manufactured by the Narco subsidiary prior to Jan. 1, 1973. Air-Shields initially discovered the potential misconnection problem in Nov. 1972 and made an engineering change which was incorporated in production, according to Air-Shields Quality Assurance Director Hal Sumner. "At that same time we sent a field service bulletin to all our dealers and salesmen telling them about the problem and informing them we would supply new adapters to anyone that requested them," Sumner said. FDA discovered that the problem still existed with devices manufactured prior to Jan. 1, 1973 through an article in the March/April 1974 issue of *Anesthesia and Analgesia*, in which three W.Va. MDs reported a case of "severe pneumothorax" resulting from a hose misconnection. FDA's Recall List notes "approximately 2,250 devices are in use"; company maintains 1,218 remain to be modified within U.S.

FDA RECALLS AND COURT ACTIONS.... ISSUED JAN. 15, 1975

Name, Form & Labeler [Numbers refer to footnotes]	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Sodium Diphenylhydantoin	983194	Kasar	Label mix-up	Phone 12/31, 1/2, Ltrs 1/8
[2] Centrifichem Test for Quantitative Determination of Serum Urea Nitrogen	D 4201	Union Carbide	Footnote	Phone 11/4
[3] Isolette Ventimeter Ventilator	Footnote	Air-Shields	Misconnection of hoses to wrong ports	Footnote
[4] Ceiling Crane XD1801	All units	Philips Medical Systems	Faulty installation	Memo 10/25
[5] Beckman Instruments Model VSM-100, vital signs moniter	All serial nos.	Beckman Instruments	Footnote	Footnote
CLASS III RECALLS				
[6] Lyo B-C Forte w/B-12	16885	MS&D	Label mix-up	Phone 12/16
[7] Prodryl caps	22169	Progress	Footnote	Phone, ltr 12/2
[8] Temaril-P tabs	Footnote	Norden	Subpotent	Ltr 11/15

[1] Distribution to state & county hosps. and distribution centers in Conn., Ill., Minn., Calif. & Ariz. [2] Natl. & internatl. distribution. Approx. 985 kits remain on market. [3] Lot numbers: All units manufactured before 1/1/73, including serial numbers 25164 - 25303. All numbers with prefixes FB, MB, DB, JB, BB, GB, NB, EU, KU, CU, HU, AU, FU, MU, DU, JU, BU, GU, NU, EM, KM, CM, AM, FM, MM, DM, JM, BM, GM or NM. Corrective action program begun 12/16 by letter advising that field reps will inspect devices and replace bag connector pipe with one containing a pin insert. Natl. distribution. Approx. 2,250 devices in use. [4] Devices not physically recalled. Distribution to hosps. & radiology offices nationwide. [5] Reason: Mislabeled – Failure to warn users of restrictions of use in that electrodes cannot be connected to catheters or other devices indwelling or implanted in the body and terminating in the vicinity of the heart. Corrective action begun 11/11 by letter, 2 adhesive labels and return cards. Natl. and internatl. distribution. Approx. 420 devices remain on market. [6] Distribution to hosps. in Atlanta, Kansas City, Minneapolis, Philadelphia and Memphis. [7] Reason: Label error – the face panel of the label states 25 mg. diphenhydramine HCl, while side panel states 50 mg. Product is 25 mg. strength. Manufactured by Rachelle. Distribution in Calif. [8] Lot numbers: C750 (11/10/72), C522 (8/8/72), C486 (6/20/72) & C392 (6/7/72). Natl. distribution.

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FDA RECALLS AND COURT ACTIONS . . . ISSUED JAN. 22, 1975

Name, Form & Labeler [Numbers refer to footnotes]	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALLS				
[1] Abboject Pediatric Sodium Bicarbonate Injection U.S.P.	42-783-DK	Abbott	Footnote	Phone 1/3, Ltr 1/7
CLASS II RECALLS				
[2] Sterile Thrombin N.P. 1,000 Units Derived from Bovine Sources	645 CP	Upjohn	Subpotency	Ltr 12/18
CLASS III RECALLS				
[3] Acetaminphen Tabs	11986 & 11987	Wolins Pharmacal	Misbranded	Ltr 1/7
[4] Butabarbital Sodium Elixir	B-79	Bowman Pharmaceuticals	Subpotency	Phone 12/20
[5] Hoyster Tabs	TK7463	C.M. Bundy	Footnote	Ltr 1/7
[6] Liver, Iron & Vitamins with B-12 Veterinary Injectable	21741	Bel-Mar Labs	Subpotency	12/6
[7] Magnesium Sulfate Injection U.S.P. 50%	7652, 7656, 7661	Chemrich Labs	Footnote	Phone & Ltr 1/8
[8] OTC Multiple Vitamin Tabs	5278	The Pill Mill	Subpotency	Ltr 1/10
[9] Pedahist Tabs	540974SG	Dooner Labs	Footnote	Phone 1/2-7, Ltr 1/6
SEIZURE ACTIONS FILED				
[10] Dent's Toothache Drops Treatment & Dent's Toothache Gum		C.S. Dent	Adulteration	1/10

[1] Single dose vial labeled in part, "10 ml. Abboject/Pediatric/Sodium Bicarbonate Injection, U.S.P. 8.4%/10 meq." Natl. distribution to 116 hospitals with approx. 2,200 units still on market. Reason: Packaging mix-up - stray vial labeled as "10 ml. Abboject Epinephrine 1:10,000 (0.1 mg./ml.)" found in box containing recalled product. [2] Natl. distribution to hospitals with firm estimating that approx. 500 vials remain on market. Rx biological contains 1,000 units thrombin/vial. [3] Manufactured by D. Graham in white plastic bottles of 1,000 tabs each, labeled in part "Wolins Sansprin. Each tablet contains acetaminophen 5 mg." Label should read 5 grains/tab. Natl. distribution. [4] Packaged in gallon and pint glass bottles. Distribution to MDs and hospitals in Ohio. [5] Dietary supplement, 48 tabs/bottle packed in one dozen cartons, 7 dozen cartons/case. Distribution to whslrs. in Ohio, northern Ky., eastern Ind., southern Mich., western Pa. Reason: Product deficient in Vitamin A & Iron, over in potassium & magnesium. [6] Product in 100 cc multiple glass vials labeled as "Distributed by Tamco Professional Equine Product" & "Liver Injection Equivalent to 10 megm. Cyanocobalamin per cc." Firm estimates that approx. 25/100 cc vials remain on market. [7] Distributed by Robinson Labs in 30 cc multiple dose vials. Reason: Particulate matter in all lots; one lot (7656) superpotent. [8] Distributed by The Chrisman Co., in bottles of 100 tabs labeled "Daily Vitamins." Distribution to Mich., Ill., & Ohio with firm estimating that approx. 135,000 tabs remain on market. [9] Antihistamine decongestant manufactured by D. Graham Labs. In starter dose, physicians sample, 6 tabs/vial, 144 vials/carton with labels reading "Each Green Tablet." Distribution in eastern US to 12 states from New England to Fla. with firm estimating that approx. 3,200 vials remain on market. Reason: Product formulation was changed resulting in white tabs instead of green. Old labels were not destroyed. [10] Products contained D&C Red No. 17 which is unsafe for internal use. US District Court, Southern Ohio.

C-O-R-R-E-C-T-I-O-N: Bell & Howell transducer device was *Class III* Recall and not *Class II* as carried in "The Pink Sheet" Jan. 13, p. T&G-7.

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FDA RECALLS AND COURT ACTIONS . . . ISSUED JAN. 29, 1975

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Medi-Pak Soft-N-Gentle lotion	Footnote	Red-Products	Contaminated w/ pseudomonas bacteria	Ltrs 11/14, 12/18
[2] Irrigation sols.	All lots beg. w/G&M	McGaw	Mold contamination	Mailgram 1/13
[3] Pentids & Veetids	Footnote	Squibb	Subpotency	Ltr 1/17
[4] Akineton tabs	13500253	Knoll	Footnote	Ltr 1/14
[5] Proserum 25 Normal Serum Albumin	174-077	Dow	Fever & chills in recipients	Phone & ltr 12/3
CLASS III RECALLS				
[6] Orabex-TF tabs	B-112	Pharmed	Cracked & broken tabs	Visit 11/15
[7] Formula 239 Analgesic Balm	4217	G&W	Footnote	Phone 11/5
[8] Phos-Cal caps w/Vitamin D & Iron	4F475	McKesson	Footnote	Teletype 1/21
SEIZURE ACTIONS FILED				
[9] Skin-Cote Waterless Hand Cleaner		Handy	Packaged in margerine or lard containers	1/16

[1] Lot numbers: All except ADP, ADB, ADT, ADV, ADW & ADX. Natl. Distribution to hospitals. Approx. 250 gals. remain on market.

[2] Products include: Distilled water in irrigating container, 3.3% Sorbital Solution, Resectisol 5% Hannitol, Normal saline in irrigating container, 5% dextrose in distilled water, .45% sodium chloride in irrigating container, Ringers solution in irrigating container, .225% sodium chloride in irrigating container, lactated ringers in irrigating container, silver nitrate solution mixing kit, 33% sorbital solution urologic irrigating fluid concentrate, 15% Glycine in distilled water urologic irrigating fluid concentrate, 1.5% Glycine solution urologic irrigating solution, .25% acetic acid in irrigating container, and saline solution kit. Natl. distribution w/shipments to Puerto Rico & Canal Zone. Approx. 1.3 mil. bottles remain on market.

[3] Lot numbers: Pentids - 4B544, 4B547, 4C463, 4C464, 4B460, 4B527, 4E595, 4D535, 4B543, 4B600, 4C462, 4C517, 4C456, 4D444, 4D457, 4D488, 4D521, 4D549, 4D571, 4D002, 4D642, 4E447, 4E449, 4E464, 4E475, 4E483, 4E523, 4B641, 4B560, 4E572, 4E575, 4E596, 4B622, 4G450, 4G481, 4G571, & 4G629. Veetids -- 4B536, 4B539, 4B585, 4C460, 4C457, 4C461, 4C493, 4D536, 4C459, 4D600, 4E448, 4E539, 4E508, 4E590, 4F445, 4G501, 4G446, 4H489 & 4H539. Natl. & internatl. distribution. Approx.490,000 units remain on market.

[4] Reason: Due to an error in mailing of MD samples, product was mailed to expectant mothers. Distribution to Northwestern NY.

[5] Natl. distribution. None of the product remains on market.

[6] Manufactured by Mallard. Distribution to Tenn., WVa. & Va.

[7] Manufactured by Ambix, Reason: Tubes of rectal ointment were mislabeled as analgesic balm. Distribution to pharmacies in DC; Hartford, Conn.; St. Petersburg, Fla.; Indianapolis, Indiana; Kansas, Mo. & Long Beach. Calif.

[8] Manufactured by Scherer. Reason: Product contains 400 I.U. of Vitamin D while label states 66 I.U. Natl. distribution.

[9] U.S. District Court, West Wash.

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0863

conducted to see if the insert has any effect on the patient. Chairman Fowler responded that he felt a "trial balloon" could be helpful, not just to test the insert, but also to improve it. However, he declared, he was unwilling to await the work of other cmtes. on patient inserts, because such inaction could postpone the project indefinitely.

The cmte. has already discussed the need for including patient inserts with all hypertensive drugs and believes the inserts would promote patient compliance with taking medication, while pointing out some of the major side effects of different antihypertensive drugs. Belton noted the cmte.'s agreement re placement of adverse effects on a sheet to be included with all hypertensive drugs, because the patient is often undergoing concurrent heart drug treatments.

FDA RECALLS AND COURT ACTIONS..... ISSUED FEB. 4, 1975

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Estrone suspension	4A007	D-M	Some units labeled Promethazine HCl inj.	1/27
[2] Oxytetracycline HCl caps	23806	Rondex	Unsatisfactory bio-availability	Ltr 1/22
CLASS III RECALLS				
[3] Allorganic Trace Minerals	413	Standard Process	Deficient in B-12	Sales bulletin 1/13
[4] Quinudune Sulfate tabs	Batch control #12225	Phoenix	Footnote	Phone 1/17, Ltr 1/24
[5] Daily Multivitamin Supplement	7455-1, -2	ICN	Subpotent in Vitamin A	Ltr 12/23
SEIZURE ACTIONS FILED				
[6] Super-T liquid supplement		Bio-Dyne	Deficient in folic acid & Vitamin B-12	12/5

[1] Manufactured for Rugby. [2] Distributed by: Rondex, Purepac, B.R. Mitchell, Bioline, Cooper, Geneva, Henry Schein & United Research. [3] Natl. distribution. [4] Manufactured for Wolins & Unite Research, Natl. distribution. [5] Approx. 175,000 tabs remain on market. [6] US District Court, Neb.

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T&G **DIGITOXIN PEDIATRIC GUIDELINE LABELING AWAITING *FED. REGISTER*ING** will contain "textbook" dosage levels, BuDrugs Cardio-Renal Div.'s John Harter, MD, reported to Cardiovascular-Renal Drug Advisory Cmte. Feb. 7. Recommended total pediatric digitalizing dosages, Harter said are: .022 mg./Kg for infants up to two weeks old; .45 mg./Kg. for two weeks to two years; .04-.03 mg./Kg. for two to five years; .025 mg./Kg. for five to 12 years. Based on a recent reading of the labels from 50 digitoxin preparations, Harter said he had found only one label – for an injectable form – identical with FDA's proposed pediatric dosages. Thirty-three labels, he noted, had no pediatric dosage guidelines. Cmte.

0864

(T&G) **NO RECALL ON FDA's LIST ISSUED FEB. 12** reports an action taken later than Jan. 27 – two-and-a-half weeks prior to issuance of FDA's weekly document. All recalls were *Class III* – routine, little or no threat to life. Earliest recall on list was Bristol-Myers Dec. 20 instructions to salesmen to pick up 7,500 bottles of plastic-packed "Body-On-Tap" shampoo in Colo., Kan., Ohio & Wyo. because of bacterial contamination. Latest was Jan. 27 phone recall by McGaw Labs to hospitals in five states of 300 units of Normal Saline, mislabeled as Distilled Water Irrigating Solution. Two recalls by Internal Drugs, Smyrna, Tenn., involved contamination with methyltestosorone during repackaging.

FDA RECALLS AND COURT ACTIONS ... ISSUED FEB. 12, 1975

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS III RECALLS				
[1] Prophenamine Expectorant with Codeine	40786	Carroll	Subpotent	Ltr 1/17
[2] Normal Saline	A4K152	McGaw Labs	Normal saline labeled as distilled water irrigating sol.	Phone 1/27
[3] "Body on Tap" hair shampoo	4C04, 4C05, 4C06	B-M ✓	Bacterial contamination	Salesman pick up 12/20
[4] Stamyl	580LE, 580LE	Winthrop Products ✓	Footnote	Salesman pick up 1/16, Ltr. 1/17
[5] Butamin Tabs	C005	Mallard	Subpotent	Ltr 1/7
[6] Thiamine HCl Tabs	40606	Internatl. Drugs	Footnote	Ltr. 1/17
[7] Calcium Lactate Tabs	40313	Internatl. Drugs	Footnote	Ltr. 1/17
SEIZURE ACTIONS FILED				
[8] Myotonachol Tabs		Glenwood Labs	Adulteration – product contaminated with insect filth	2/3

[1] Distribution in eastern 2/3 of US. Approx. 100 gallon btls. remain on market. [2] Distribution to hospitals in Alaska, Ariz., Calif., Mont., & Utah between 9/4/74 and 1/23/75. Approx. 300 units remain on market. [3] Packed in 4 oz. and 8 oz. plastic bottles. Distribution to Colo., Kan., Ohio, & Wyo. Approx. 7,500 btls. remain on market. [4] OTC tab in strip paks of 167 strips of 6 tabs in hospital shelf carton. Reason: Shelf cartons lack following mandatory labeling: "Stamyl Marca Pegistrada Para: Complementer la Seerecon Insufficiente de Enzimas Pancreaticas Cada Tableta Contiene: Pancreaticas Cada Tableta Contiene: Pancreatina a Concentraeion Tres Veces Major Oue la Indicada en al MF 175 mg.: Hemicelulesa 50 mg., Extracto de Bilis de Buey 25 mg." Distribution to hospitals in Puerto Rico. Approx. none remain on market. [5] Sodium butabarbital, 30 mg., packed in botls. of 100 tabs. Distribution to Ill., Mich., Ind., Iowa, Mo., Pa., & NY. Approx. 7,000 tabs remain on market. [6] Distributed by Carroll Chemical Co. Manufactured by Stanley Drug. Repacked by Internatl. Drugs. 100 mg. tabs in bottles of 1,000 distributed to Ala., Fla., La., Mass., Miss., NH, NJ, NC, Tenn., Va., DC, & one foreign country: Approx. 15 botls. remain on market. Reason: Trace contamination with methyltestosterone during repackaging. [7] Distributed by Carroll Chemical Co. Manufactured by Private Formulations, Repacked by Internatl. Drugs in botls. of 100. Distribution to eastern 2/3 of US/one shipment to Bermuda. Approx. 500 btls. remain on market. Reason: Trace contamination with methyltestosterone during repackaging. [8] US District Court, Minn.

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OTC DENTAL CUSHIONS/RELINERS/REPAIR KITS ARE "CRUTCHES," AND "should be illegal" because

of the "fantastic amount of damage a layman can do in the interrelationship between the mandible and maxilla," NJ Prosthodontics Dept. Head Paul Vinton, DMD, declared at Feb. 26 OTC Dental Advisory Panel meeting. Also present were Block Drug's Kenneth Kasses, PhD, and Murray Rosenthal for a discussion of Block's study-protocol on denture adhesive efficacy. The study will include the testing of four different products on 32 subjects with poorly-fitting dentures.

¶ Most denture wearers are "in the geriatric age group," Vinton observed, and older people have a harder time developing new musculatory patterns necessary for denture wear. Vinton praised "any device that can help in this transition," but was concerned that patients use adhesives as "a crutch. . .often using dentures beyond the time when they ought to." He suggested that the panel's proposed adhesive labeling be changed from "help provide confidence for new denture wearers" to "an aid to adjustment of a physical mass."

FDA RECALLS AND COURT ACTIONS.....ISSUED FEB. 26, 1975

Name, Form & Labeler [Numbers refer to footnotes]	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALL				
[1] Tincture of Benzoin Compound	41387	Consolidated Midland	Part of lot mislabeled as Iodine Tincture	Phone 1/31
CLASS III RECALLS				
[2] Soma tabs	4H1001	Wallace	Mold contamination	Telegram 2/5
[3] Rauwolfie Serpentina	30570	Cord	Subpotent	Letter 2/10
[4] Calactron S.C. tabs	33248	Ferndale	Subpotent	Letter 1/30
[5] Blue Cross Omnitabs Multiple Vitamin tabs	4G22, 3J20B	Halsey	Subpotent in Vitamin B12	Phone 2/10
[6] High Potency Multiple Vitamin tabs	4D24	Halsey	Subpotent in Vitamin B12	Phone 2/10
SEIZURE ACTIONS FILED				
[7] Amygdalin sol.		John A. Richardson	No NDA	2/10
[8] Pro-Vitamin & Amygdalin sol.		John A. Richardson	No NDA	2/6
[9] 3-P Gest-Plus Decongestant caps		Alpha	Subpotent	2/14

[1] Manufactured by Natl. Pharmaceutical. Distribution to W.Va. None remain on market. [2] Natl. distribution. [3] Distribution to Ind., Iowa, Mich., Ohio, Pa., Tenn. & Wis. Approx. 5,000 tabs remain on market. [4] Distribution to Fla., Ind., Mich. & Ohio. Approx. 20,000 tabs remain on market. [5] Distributed by Blue Cross. Distribution to NY & Puerto Rico. Approx. 470 bottles remain on market. [6] Distributed by Salida, Stanley Pharmacy, Moore Drug Exchange, Adler Pharmacy & Locurto's Pharmacy. Distribution to NY & Puerto Rico. Approx. 470 bottles remain on market. [7] U.S. District Court, Ore. [8] U.S. District Court, East Wash. [9] U.S. District Court, Mo.

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CANADA RECALLS 7 COSMETIC PRODUCTS, following discovery of several types of bacterial contamination, including pseudomonas. Six of the products were exported to Canada from U.S. by Natural Organics. They include: *Avocado Moisturizing Lotion; Fresh Cucumber Cleansing Lotion; Miracle Rejuvenator; Derm-ADE Nutritional Skin Crem; Glycerine-Rose Water Rejuvinating Lotion;* and *Protein Enzyme Night Cream* – all in 4 oz. sizes. The seventh product, Wheat Germ Beauty Balm, is exported from the U.K. by Charles Perry. Despite the absence of adverse effect reports, the recall was "advertised" on Canadian radio and TV.

¶ "What took place in Canada was unnecessary," a Natural Organics spokesman said. He criticized the Canadian action for "scaring people" and noted that his company would have been glat to cooperate with the govt., but added: "We never knew until a week after it happened." Although Natural Organics only distributes and does not market the products, it sent samples to an independent lab. The results showed no pathogenic bacteria, the company said. FDA is now in the process of testing the same products sold in the U.S. Historically, Canadian cosmetic recalls have occurred on a "very seldom" basis, however, a govt. official told "The Pink Sheet," that recalls are expected to increase in the future, following "pending passage" of cosmetic regs.

FDA REPORT OF RECALLS ..... ISSUED FEB. 19, 1975

Name, Form & Labeler	Lot No.	Mfr. or Distributor	Reason	Recall Depth
CLASS II RECALL				
[1] Blusalase liquid enzyme preparation	Footnote	Endo ✓	Subpotent	Phone 12/20 & Ltrs. 12/30
CLASS III RECALLS				
[2] Histatussin - A.C. cough syrup	H 145, H 126, G 998	Lasar	Footnote	Visits 1/28
[3] Doctate 300 caps	Footnote	Heyer	Leaking caps	Ltr 1/30
[4] Octocaine HCl 2%	X8248	Novocol	Footnote	Phone 2/6 & Ltrs. 2/7
SEIZURE ACTIONS FILED				
[5] Surgi Scrub		Ray Cross Medical Div., Gard Research	Contains hexachlorophene, no NDA	1/7
[6] Amygdalin inj. & yellow tabs		John A. Richardson	No NDA	2/6
[7] Zirobee, Bee-Tops, B12 & Bee-Tops w/Pangamie acid		Zirin	Held under unsanitary conditions, strengths differ from label	2/4

[1] Lot numbers: BO0964, BO0968B, BO096C, DE061A, DE061B, BE061C, ED0544, ED054B, ED054C, EO152A, EO152B, EO152C, FJJ58A, HJJ58P, HJJ60A, FJJ82A, FJJ83A, HA043A, HA043B, HA043C, HC072A, HC072B & HFJJ7C. Natl. distribution & to 29 foreign countries. [2] Reason: Label declares prophenpyridamine maleate is an active ingredient when it is not present. Distribution to 3 pharmacies in Va. Approx. 100/4 oz. & 2/16 oz. btls. remain on market. [3] Manufactured by R.P. Scherer. Repacked by Heyer. Natl. distribution, primarily in Fla., Ind., Ky., Mich., NC, Ohio, SC & Tenn. Lot numbers: (mfrs.) 58073, 55453, 51695, (repacker) 7301 644, 7207 608, & 7110 451. [4] Reason: Indiv. 1.8 cc. cartridges properly labeled as Lidocaine HCl 2% w&Epinephrine 1:50,000. Outer packaging mislabeled as Lidocaine HCl 2% w/ Epinephrine 1:100,000. Distribution to 7 consignees in Ala., Minn., NJ. NY, Ore. & Pa. Approx. 61 tins remain on market. [5] US District Court, North Ill. [6] US District Court, Minn. [7] US District Court, South Fla.

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FDA's CORPORATE-EXEC-LIABILITY THEORY NEARING SUPREME COURT via argument on case involving

the conviction by a federal court jury in Baltimore of John R. Park, president of a nationwide food chain, Acme Markets, Inc., on charges filed by FDA alleging rodent infestation and other unsanitary conditions in an Acme warehouse. As *corporate* defendant, Acme pleaded guilty to each count in a five-count indictment, but Park went to trial, was found guilty by the jury, and was fined $250. The U.S. 4th Circuit Court reversed the conviction on appeal. The govt., however, turned to the highest court, contending that the 4th Circuit's ***wrongful action*** standard significantly weakens the criteria for top corporate executive responsibility, established by the U.S. Supreme Court in a 1943 decision *(Dotterweich)*. "The govt.'s policy," its brief said, "is to prosecute only those individuals in a position and who have an opportunity to prevent or correct violations, but fail to do so."

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SORBO SORBITOL SOLUTION CLASS I RECALL DUE TO *FORMALDEHYDE* mixup; FDA via late Friday,

March 7 press release, announced re the Amend Drug & Chemical *and* Ruger Chemical product: "FDA today notified approximately 50 consignees – including MDs, hospitals, pharmacies and food, drug and cosmetic mfrs., not to use one lot (C712314) of more than 500 gallons of sorbitol solution. . . .Both firms, which share the same premises and manufacturing equipment, are carrying out a voluntary recall."

The agency reported: "On March 5, 1975 the chief pharmacist at V-A Hospital at Houston, Texas reported to FDA that a patient given an enema with the solution was burned and was still bleeding three days after administration of the enema on March 3. So far this is the only injury reported; there have been no deaths. Use of a full pint formulation of formalin (formaldehyde) orally or as an enema can be fatal." (Not included in list below)

FDA RECALLS AND COURT ACTIONS. . . . . ISSUED MAR. 5, 1975

Name, Form & Labeler [Numbers refer to footnotes]	Lot No.	Mfr. or Distributor	Reason	Date
CLASS III RECALL				
[1] Aminophylline	32924, 33246, 33493	Cord	Subpotent	Letter 2/19
SEIZURE ACTIONS FILED				
[2] 100 caps Pro-Vitamin B-15 & 20 Amber Glass Ampules Amygdalin		John A. Richardson	No NDA	2/7
[3] Calcium-Phosphorous w/Vitamin D Wafers		Vegetrates	Lacks adequate directions for safe use	1/31
[4] B-Covet animal inj.		Western Serum	Subpotent in B12	1/23

[1] Distribution to Calif., Ill., Ind., Mass., Mich., NY, Ohio & Pa. Approx. 500,000 tabs remain on market.
[2] U.S. District Court, East Wisc. [3] U.S. District Court, Central Calif. [4] U.S. District Court, Ariz.

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0868

C.E.B. PRODUCTS -- FTC CONSENT ORDER: "WARNING: 'DARK-EYES' can cause severe pain to the eye for a substantial period of time," is "specific disclosure" agreed to by C.E.B. Products in FTC consent order dealing with all advertising and packaging for the Chicago mfr.'s Dark-Eyes Lash and Brow Tint. C.E.B. can avoid the disclaimer, under terms of the FTC order, if *FDA* were to okay a "color additive" petition for the product, probability of which appears to be remote in light of FDA's own legal maneuvers ("The Pink Sheet" July 22, p. T&G-6). Dark-Eyes case has been cited by FTC in budget justifications for several years in effect to convince congressional appropriations cmtes. of activity in cosmetic investigations ("The Pink Sheet" April 16, 1973, p. T&G-6).

¶ On Dec. 11, FTC announced compliance was so urgent that unless C.E.B. *immediately* displayed the warning on all point-of-purchase displays, agency will go through with a "consent" preliminary injunction in federal court. C.E.B. signed the agreement with FTC on Sept. 23; informed FTC Dark-Eyes ads had been stopped; and all remaining packages at retail/whsle. levels were being recalled ("The Pink Sheet" Oct. 14, p. T&G-10). Complaint was based on TV commercials going back to 1971, and alleged TV demonstrations of the application process detracted from effectiveness of precautions in the directions for use.

FDA RECALLS AND COURT ACTIONS . . . . ISSUED DEC. 11, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Treadmill Model E-10C	Serial nos. 1-855	Del Mar Engineering	Defective circuity of electronic component	Footnote
CLASS III RECALLS				
[2] Coccidioidomycosis Immune Diffusion Test Kit	7200K005A1	Travenol	Mix-up of reactive components	Letter 10/15
[3] Pediatric Diptheria, Tetanus Toxoids & Pertussis Vaccine	0566CE, 0839DB	Merrell-National	Resuspension difficult, syringe needle clogs	Letter 11/6
SEIZURE ACTIONS FILED				
[4] Devra Harris Exquisite Nails		House of Barri	Methyl methacrylate monomer	11/26
[5] Long Nails		C.E.B.	Methyl methacrylate monomer	9/9

All Rx. [1] Firm issued copy of Service Information Report #1070 dated 2/22/74 to all consigness. Report consisted of warning statement to be added to Operations Manual for device. Natl. and internatl. distribution. [2] Kit contains agar plates, coccidioidin antigen, positive & negative control material & pippets. Natl. distribution to labs and lab supply houses. Few remain on market. [3] Packaged in cartons of 5 prefilled syringes. Natl. distribution to MDs, whslrs., hosps. & retail pharmacies. Approx. 220 cartons remain on market. [4] US District Court, North Calif. [5] US District Court, Kansas.

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FDA RECALLS AND COURT ACTIONS . . . . . ISSUED DEC. 4, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALL				
[1] Conray sterile sol., 50 ml.	BCC-E	Mallinckrodt	Non-sterility	Letters 11/14 11/23
CLASS II RECALLS				
[2] Aspirin tabs, 5 gr.	Footnote	Otis Clapp & Son	Non-USP disintegration	Letter 11/14
[3] Wellcome Peripheral Nerve Stimulator	All	B-W	Causes burns	Letter 5/3
[4] Ultra Flo II Dialyzer	Footnote	Travenol	No high filtration	Letter 9/27
[5] Large vol. parenterals	None	Travenol	No warnings	11/18
[6] Enteric Sodium Salicylate tabs	Footnote	Kirkman	Non-USP disintegration	Letter 11/5
[7] Aspirin-Free & Saloxium Analgesic tabs ["The Pink Sheet" Nov. 25, T&G-6]	All	Whitehall	No ANDA	
CLASS III RECALLS				
[8] Cortisone Acetate	10348	Medwick	Subpotent	Letter 11/14
Prednisone tabs, 1 mg.	10138	Alpha Pharm.	Non-USP content uniformity & potency	Phone 9/25
[9] Diphenhydramine HCl Elixir	33032	Cord	Precipitation	Phone 10/16
[10] Glynazan Expectorant	Footnote	First Texas	Subpotent	Letter 11/15
SEIZURE ACTION				
[11] Dialyzed Iron		Schuyler	No ANDA	11/25

All Rx. [1] Distribution limited to 29 accounts in N.J., N.Y., Pa., R.I., Conn., Md., Mass., Tenn. & Tex. Direct contact to each user. [2] Distributed under following labels: Otis Clapp Safety Pack, Buffington Quality Aspirin & Aidpak. Lot numbers: A387, C7, C76, C5126, E987, E9876. Natl. distribution to medical supply houses & first aid supply distributors. [3] Firm issued caution letter stating product for use only with needle electrodes applied under skin surface. Natl. distribution. [4] Lot numbers: ZC68W2-W9, ZC69A0-A6, ZC69A8-A9, ZC69P1 & all lots distributed in last 6 mos. "Dear MD" letter states coils are only capable of standard ultrafiltration, weight loss should be monitored, & new product brochure is forthcoming. Product itself is not recalled. Natl. and internatl. distribution. Approx. 100 cases (6 coil/case) remain on market. [5] Includes all lots packaged in viaflex containers which do not bear warning that bag should be checked for leaks prior to use. Natl. distribution to hosps. & clinics. [6] Lot numbers: 10220A, 10220B & 03234A. [7] Includes Aspirin Arthritis Pain Formula Analgesic tabs & Saloxium Analgesic/Anti-Inflammatory tabs. Distribution: "Aspirin-Free" natl.; "Saloxium" test-marketed in Boston, Dayton, Houston, Seattle. [8] Natl. distribution to whslrs. & VA hosps. [9] Distributors: Tutag, Geneva Generics, General Surgical Supply, Lampert, Skelton's, Veratex Corp., Pharm. Corp. & Harnel. [10] Lot numbers: 7031444 & 7083314. Distributed to South Central & Southeastern U.S. [11] Filed in U.S. District Court, Southern District of Ill.

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● C-O-R-R-E-C-T-I-O-N: In "The Pink Sheet" Dec. 2, weekly FDA recall table correctly listed Wyeth's Purodigin as digitoxin. But text of Wyeth's recall letter – and headline on it – substituted digoxin for digitoxin. Same error also on cover-page T&G index.

T&G A RECALL IS A *RECALL* EVEN WHEN ON-THE-SPOT LABEL CHANGES are involved in lieu of actual necessity to remove product from market, according to most recent *revision* of FDA's Guide To Recall Procedures. Definition in latest Sept. 1973 version states: "A mfr.'s *correction of products in the field (field correction)* or removal of products from the market which present a threat or a potential threat to consumer safety and well-being, involve product adulteration, cause gross fraud or deception of consumers, or are materially misleading causing consumer injury or damage, and which are subject to legal action under FDA's existing compliance policy are bases for determination that such operation is a *recall.*"

FDA RECALLS AND COURT ACTIONS . . . ISSUED NOV. 27, 1974

Name, Form & Labeler [Numbers refer to footnotes]	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALLS				
[1] Purodigin crystalline digitoxin .05, .1, .15 & .2 mg.	All	Wyeth	Incorrect infant dosage on insert	Footnote
CLASS II RECALLS				
[2] Search-Cyte Reagent Blood Cells	CEL-1-400	Dade Div., AmHospSup	Loss of stability	Letter 10/11
[3] Progesterone	10761	Medwick	Non-homogeneous	Phone 10/16
[4] Isuprel HCl	Footnote	Winthrop	Shelf carton mix-up	Letter 11/8
CLASS III RECALLS				
[5] Caffeine caps	221010	Adco	Wrong lot number	Letter 10/4
[6] Caffeine caps	8200	Adco	Mislabeling	Letter 10/4
[7] F Aerolate elixir	7140, 7145	Felming & Co.	Sub-potent	Footnote
SEIZURE ACTIONS FILED				
[8] Liver, Iron & Vitamins		Bel-Mar	Low potency Vitamin B-12	10/22
[9] Angelion D-1, medical device		Angelion of America	Labeling in Japanese	11/8
[10] Long Nails		C.E.B.	Methyl methacrylate monomer	11/12
[11] Rohist D. Chlorpheniramine Maleate Timed Release caps		Alpha Pharmacal	Sub-potent	11/12

[1] Product itself is not being recalled. Dear Dr. letters went to all MDs & letters w/replacement inserts went to all pharmacists & whslrs., 11/21. Insert was printed 9/20/72 & included in all units since 12/12/72. Natl. distribution. Approx. 50,000 package units remain on market. [2] Natl. distribution to clinical labs. [3] Manufactured for Wolins. Only 1 shipment made. [4] Undetermined quantity of Isuprel 1-100 shelf cases were used in shipment of Isuprel 1-200 units. Lot numbers: S156LD, S159LD, S182LD, S064LH, S157LJ & S187LJ. Product not being recalled. Letter notified pharmacists, hosps. & whslrs. of possible mislabeled shelf cases & requested they be examined and any mislabeled cases destroyed. Natl. distribution & to Puerto Rico & Chile. Approx. 6,000 shelf cases remain on market. [5] Manufactured by Zenith. Distribution to Ohio & Indiana. Approx. 5,000 caps remain on market. [6] Manufactured by Camall. Label shows strength as 200 mg. Actual strength is 100 mg. Distribution to Mich. & Ohio. Approx. 5,000 caps remain on market. [7] Manufactured by Na-Spra. Recalled by letter for lot 7145 & phone for 7140. Natl. distribution to pharmacies & clinics. [8] US District Court, East NY. [9] US District Court, Central Calif. [10] US District Court, Ariz.

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T&G **PURE AIR PRODUCTS' OZONE GENERATOR DEVICES VIOLATE FDA LAW** because labeling falsely "represents and suggests that the articles are adequate and effective for deodorizing, sterilizing, and purifying the air, will kill bacteria, fungi, viruses, and regenerate oxygen in the air. . .is more indispensable than any other electro domestic appliance," FDA Newark district office informed the company. Products named by FDA as not complying were: Roel Air Purifier; Domus Home Model; Ozo-Auto; and Mountain Aire. In addition, labeling "fails to bear adequate directions for use for the purposes for which it is intended," FDA charged.

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FDA RECALLS AND COURT ACTIONS. . . . ISSUED NOV. 20, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALLS				
[1] Pacemakers	Footnote	Biotronik Sales	Footnote	Footnote
CLASS III RECALLS				
[2] Liver inj. for IM use	21705	Bel-Mar	Sub-potency	Phone 10/25
[3] H-I-L-20 & Bafil Rx topical lotions	30914, 31730	Cord	Hydrocortisone sub-potency	Phone 10/2
[4] Gammacorten dexamethasone tabs	37-0136	Ciba	Non-USP content uniformity	Phone 11/6
[5] Phenobarbital Sodium 1/2 & 1 gr., rectal suppositories	3284-3, 3284-5	G & W	Sub-potency	Phone 11/4
[6] Phenobarbital liquid	DE006	Pharmacare	Sub-potency	Letter 11/6
[7] FD&C Red No. 2 & 3	Z 2519, Z 0805	Allied Chemical	Label mix-up	Phone 9/12
SEIZURE ACTION FILED				
[8] Betadine Surgical Scrub		Murry Grossman, MD (shipper); Central Veterinary Supply Co. (dealer)	Product adulterated by fire	11/15

[1] Recall includes: IRP-44, R-Wave Triggered Demand (all serial nos. up to 72171); IDP-44, Wave Inhibited Demand (up to 57168); IP-44, Fixed Rate (up to 15043); IP-45, High Output Fixed Rate (up to 4651); IVP-54, P-Wave Triggered (up to 41216). Natl. distribution, 5/72 - 4/73. Biotronik GmbH (mfr.) notified 33 U.S. MDs of problem (tissue necrosis, inflammation, reddening at implantation site, & premature battery depletion). At FDA request, all known U.S. users (293 MDs) were advised by letter, 10/17, of potential problems & symptoms of malfunction. Firm recommended increased monitoring of patients with these models, approx. 1,050 still implanted. No reported deaths. [2] Approx. 1,000 30 cc. & 500 10 cc. vials remain on market. [3] Approx. 3,500 btls. remain on market. [4] Natl. distribution primarily to VA hosps. Approx. 1,000 btls. remain on market. [5] Natl. distribution. [6] Natl. distribution to whslrs. Approx. 50 cases remain on market. [7] Manufactured by Color Com Co. Relabeled & distributed by Benbow Chemical Packaging. Recall involves two shipments to W-L. None used. [8] U.S. District Court, Mass.

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FDA RECALLS AND COURT ACTIONS . . . ISSUED NOV. 13, 1974

Name, Form & Labeler [Numbers refer to footnotes]	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Ultra Vie eye shadow (OTC)	"Y"	Luzier, Clairol div.	Mold contamination	Letters 9/20, 10/15
[2] Diphenhydramine HCl caps, 25 mg.	4018	J.W.S. Delavau	Non-USP content uniformity	Letter 10/17
[3] Phenobarbital elixir	30-808-AF, 33-502-AF	Abbott	Overfill of containers	10/21
[4] Ardet Orix 60/10 dental X-ray machines	Footnote	Professional Equipment	Unnecessary radiation exposure	9/26
CLASS III RECALLS				
[5] Enteric-coated aspirin tabs	4209007, 4209019 & 4209131	Barr	Non-USP disintegration	Letter 10/24
[6] Fischerquartz ceiling lamp, model 87	Individual serial no.	Stanley Physical Therapy Equipment	Rx device distributed to unlicensed practitioners	Letter 10/18

[1] Natl. distribution. Approx. 1,125 units remain on market. [2] Distribution to 2 distributors in NY & Pa. None remains on market. [3] Distribution to hosps. [4] Lot numbers: All units imported into US. Distribution to hosps. [5] Distribution to VA marketing centers in Ill. & Calif. & to an NY whslr. [6] Manufactured by Stanley Physical Therapy Equipment & Supply.

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T&G **IOWA PHARMACY COLLEGE "DRUG MANUFACTURING FIRM"** cited by FDA in Oct. 25 letter pointing out at least eleven violations of FD&C Act in the college's "semi-commercial" production of parenteral and solid-dosage Rx drugs. Recent investigations of the college production operation – which serves as an educational lab for students on manufacture and quality control of drugs as well as a commercial venture for the college – uncovered "serious violations of the FD&C Act," according to FDA's warning. Jerry Vince, FDA Region VII director of compliance, noted, while none of the college pharmaceuticals had been found in retail pharmacies, they had been located in several hospitals not connected with the university. "Some samples were not only commercially marketed, but there were even interstate shipments of antibiotics and other Rx drugs," the FDAer noted.

¶ The College of Pharmacy responded to FDA's complaints Nov. 4 in a four-page letter assuring that specific violations were being corrected. John Lach, Iowa director of pharmaceutical services, indicated in addition to a violation-by-violation correction of problems cited by FDA, the university has decided to discontinue distribution of antibiotics to off-campus outlets, and would not ship the products again without applying for certification. Among violations mentioned by FDA were: failure to maintain appropriate records on components; failure to retain reserve samples of active ingredients; the appearance of discrepancies between the quantities of labels issued and used; failure of labeling to bear adequate directions and warnings; and failure to include on package labels the full name and place of business of the mfr., packer, or distributor.

District Office told mfr. – Cincinnati Sub-Zero Products. Product further violates FDA law, the agency declared, because: "Labeling fails to bear adequate directions for use (weight control) and adequate directions for use cannot be written for the layman, nor can directions for use of the device be furnished under which practitioners can use it safely for weight control."

FDA RECALLS AND COURT ACTIONS .... ISSUED NOV. 6, 1974

Name, Form & Labeler [Numbers refer to footnotes]	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Digoxin tabs, .25 mg., unit dose blister packs	337-406	Lederle	Some double-filled blisters	
[2] Ohio Anesthesia Ventilator	Footnote	Ohio Medical Products	Manufacturing error	"Medical Device Alert Letter" 9/11
[3] Long Nails Nail Lengthener	All	C.E.B.	Methyl methacrylate monomer	
[4] Red Blood Cells Unit	S 961	Ortho Diagnostics	Hemolysis of red blood cells	Letters 9/21, 10/3
[5] Baby shampoo	Footnote	Council	Samples revealed pseudomonas aeruginosa	Phone 10/18, letter 10/21
[6] Silicone oil lubricant	All	Medtronic	Possible non-sterility	Letter 8/28
[7] Dark Eyes Lash & Brow Tint	All	C.E.B.	Contains silver nitrate	
CLASS III RECALLS				
[8] Syntocinon nasal spray	025 U 3396	Sandoz	Packaging error	Letters 10/18-19
SEIZURE ACTION FILED				
[9] Long Nails Nail Lengthener		C.E.B.	Methyl methacrylate monomer	10/23

[1] Natl. distribution to hosps. & nursing homes on 11/8/72. Maximum of 50 1,000 unit cartons remain on market. [2] Faulty assembly of ventilator flow rate valve, causing the ventilator bellows to stop cycling, resulting in failure to provide sufficient reservoir for ventilation of gases. Faulty assembly of the gas evacuator vent valve, allowing escape of anesthesia support gases intended for inhalation by the patient. Lot numbers: AAEA0001-00476 and AAEB0001-01125. Natl. distribution beginning 1/73. Approx. 800 units still in use. [3] Natl. distribution from 1968 to 5/74. No estimation of amount remaining on market. [4] Natl. distribution to hosps. & blood banks, 9/16-9/20. Very little remains on market. [5] Lot numbers: 4855, 4857, 4964, 4968, 4970 & 5014. Distribution to retail & whsle. outlets in Minn., Wis., Ky., Ga., SC, Wash., Mich., Tex. & Kan. Approx. 1,833 cases distributed. Half remains on market. [6] Manufactured by Dow Corning. One tube included with each of Medtronic's pacemakers, service & lead adapter kits packed before 8/15. Letter instructed MDs to remove & destroy tubes. Natl. distribution & to Can., Eur., Middle East, Africa & Mediterranean countries. Approx. 300 units in distribution channels. [7] Natl. distribution. Firm unable to estimate amount remaining on market. [8] Natl. distribution to whslrs. & hosps.; 4/16-10/16. Approx. 3,000 btls. remain on market. [9] U.S. District Court, Md.

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T&C ULTRAVIOLET *DENTAL DEVICE* PRODUCT USE INFORMATION SHOULD "be made avail to all probable

FDA Bureau of Radiological Health's (BuRad) Radiation Bio-Effects and Epidemiology Advisory Cmte. mended at Oct. 29-30 meeting. Cmte. expressed concern *re* possible injury to mouth lining, gum and lip resulting from use of ultraviolet devices. Cmte. also urged that "the present momentum in research on ul sonic bio-effects and in development of standards be carried forward." An additional resolution specific requested a study to "derive some baseline information on the use of ultrasound during pregnancy." It v announced that the World Health Organization has invited BuRad to be internatl. collaboration center fo ionizing radiation. A BuRad draft report on dangerous levels of *near ultraviolet* was made public at the m

FDA RECALLS AND COURT ACTIONS.... ISSUED OCT. 30, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALLS				
[1] Liquid Lytren Oral Electrolyte Sol. for Beneflex 32 oz. cans (OTC)	All	M-J	Bacterial contamination	Telegram 10/24
CLASS II RECALLS				
[2] Digoxin tabs	Footnote	Daylin	Fails USP dissolution	Letter 10/8
[3] Cholorpherine Compound (OTC)	3306	Delavau	Misbranded	Phone 9/16
[4] Aortic Perfusion Cannual Straight & Angled	Footnote	Div. Sherwood Med. SMI	Non-sterility	Letter 9/19
[5] Thermo Blood Reservoir	Footnote	Med Science Electronics	Defective units	Letter 9/13
[6] Synthetic Disc	Footnote	Rhoades Rubber	Defective units	Letter 9/17
CLASS III RECALLS				
[7] 15 Allergenic Extracts	Footnote	Pharmacia Labs	No effective IND application or license	Letter 9/26
SEIZURE ACTIONS FILED				
[8] Ana Hep Vet		Seney & Co.	No ANDA	10/10
[9] Injectable Muscle Antispasmatic – Ethaverine Hydrochloride		Wittney & Co.	No ANDA	10/18

All Rx unless marked OTC. [1] Recall extended to include all lots. Dist. in U.S. only to hospitals. [2] Mfr., American Pharm. Daylin, responsible for recall. Lots: Daylin – 701773; Am. Pharm. – 17484. Dist. to MDs, pharmacies and hospitals in So. Calif. [3] Label claims two "highly effective antihistamines." Product actually contains two antacids. Dist. to N.J., Pa. & Del. Estimated 8,000 tabs on market. [4] Lots: 418084, 418099, 418319, 418164. Sterility guaranteed only if package is unopened; seals on these lots were broken. Natl. dist. to hosps. & MDs. [5] No lot number used. Manufactured by Polystan Surg., Denmark. Water leaks from heating element into blood reservoir. [6] No lot number used. Disc being recalled in models 705, 707, 711, 713, 789, 790, 791, 792, 796, 798, 910, 911, 1005 – if models were sold on or after June 1974. [7] Lots: B3N029, B3M023, B3M011, B3M027, B3M012, B3M026, B3N028, B3N031, B3N034, B3N036, B3N037, B3P043, B4B048, B3M019 and B3M021. Dist. to NY, Ohio, Minn., Ga., Mich. & Calif. [8] U.S. District Court, Colo. [9] U.S. District Court, Colo.

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changes in the pacemakers' rate for battery failure or, if they elected, to replace the pacemaker entirely, FDAers noted. Reportedly, four patients with the pacemakers implanted have died, but "the firm said the pacemakers (*per se*) had nothing to do with it," an FDAer added. The deaths are being investigated by FDA as part of its overall probe into the matter. Cordis asserts that the age of the patients combined with their need for pacemakers in the first place indicates the deaths were not unnatural. "There is no real substantiation," a Cordis spokesman maintained. FDA reported the problem was caused by a leaky sealing in the units which allowed moisture to get in. When the leaks were found during testing, they were resealed but the moisture remained trapped inside, causing short circuits and depletion in the batteries. (See story, p. 16).

FDA REPORT OF RECALLS ..... ISSUED OCT. 23, 1974

Name, Form & Labeler	Lot No.	Mfr. or Distributor	Reason	Recall Depth
CLASS I RECALLS				
[1] Liquid Lytren Oral Electrolyte sol. (OTC)	SAD-17A - M	M-J	Bacterial contamination	Letter 9/24 Footnote
CLASS II RECALLS				
[2] Septi-Phene presurgical soap	Footnote	Pan Western Trading	Label mix-up	Phone 9/12
[3] Cardiac pacemakers	None	Cordis	Premature battery depletion	Visits 10/73 - 3/74
[4] Methenamine Mundelate tabs	24155	Richlyn	Non-USP disintegration	Letter 9/23
[5] Kelvin Tetracine tabs	76271	Kelvin	Repacked without certification	Letter 10/8
[6] QID Pen V-K	715943N	Mylan	Label mix-up	Letter 10/4
CLASS III RECALLS				
[7] Menolyn tabs	17219-1273, 17219-472	Leed-Dixon	Non-USP content uniformity	Letter 10/15
SEIZURE ACTIONS FILED				
[8] Long Nails		C.E.B.	Methyl methacrylate monomer	9/25
[9] Daily Multivitamins with iron		Pacific Pharmaceutical	Less D. Calcium Pantothenate than stated on label	9/23
[10] Beauty Line Bust Developer		Beauty Line Plan	Labeled effective for developing bust	10/3
[11] Iron Dextran Glycocide & Dexamethasone		Schuyler	No ANDA	9/30

(1) 10/11 after recall was classed as I, M-J telegraphed all US recipients. Distributed to hosps. in US and hosps. & pharmacists in Puerto Rico. FDA issued press release in Puerto Rico, 10/18. Very little remains in hosps. [2] Lot numbers: 328, 424, 569, 741 & 760. Distribution to South Calif. [3] Models recalled: Omni-Stanicor 162C, Omni-Ectocor 163A, Omni-Atricor 164 & Omni-Ventricor 167A. Natl. & foreign distribution. Firm identified 283 suspect units. [4] Distributed by Spencer Mead, Wolins & Robinson to NY, Pa., Calif. & Costa Rica. Aprox. 18,000 tabs remain on market. [5] Manufactured by ICN. Less than 10 btls. remain on market. [6] Some btls. contain 125 mg./5 ml. instead of the labeled 250 mg./5 ml. [7] Recalled by Arcum. [8] US District Court, Ariz. [9] US District Court, Ariz. [10] US District Court, Central Calif. [11] US District Court, South Ill.

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FDA RECALLS AND COURT ACTIONS . . . ISSUED OCT. 16, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Potassium Phosphate vials	BV12L7	Travenol	Mislabeling	Registered letter 10/1
[2] Trilute T-3 Reagent & Bulk kits	Footnote	Ames	Contains excessive free iodine	Telegram 9/4 9/16
[3] Digitoxin .1 mg.	10731	Westerfield	Non-USP content uniformity	Letter 9/26
[4] Whole blood unit	Donor # 2112574103	Antibodies	Misbranded	Phone, telegram 10/4
[5] Long Nails Nail Lengthener kit (OTC)	All	C.E.B.	Methyl methacrylate monomer	"Action Bulletin" letters 7/12
[6] List No. 6714 Hepatitis Associated Antibody	Footnote	Abbott	Label mix-up	Phone, telex 6/19; letters 6/21, 6/25
CLASS III RECALLS				
[7] Surgical Scrub sol (OTC)	S 035 LJ	Winthrop	Sub-potent	Letter 9/25
[8] Magna Medics Suction tray	All	Windsor Nuclear	Non-sterility due to defective packaging	Phone 9/12-17 Letter 9/17
[9] T.D. Cold timed release caps (OTC)	30927	Cord	Footnote	Letter 8/29
COMPLAINTS FOR INJUNCTION FILED				
[10] Veterinary drugs		I.D. Russell	No ANDAs, non-GMP	9/26
SEIZURE ACTIONS FILED				
[11] Long Nails (OTC)		C.E.B. Products	Methyl methacrylate monomer	10/7
[12] Edwards Myo Flex device		Harold J. Wilson, MD	Misbranded	10/3

All ℞ unless marked OTC. [1] Potassium phosphate vials packed in cartons labeled postasium chloride. Distribution to Pa., Mo., Ohio., Va., Mich., Ill., Tenn., Fla., NY, Tex., NM, La., Kan., Okla., SD, NJ & D.C. Approx. 1,500 units remain on market. [2] Manufactured by Ames-Yissum, Israel. Lot numbers: reagent kit – 0096064 through 0120074; bulk kit – 0107064, 0108064, 010964, 0113064, 0114064 and 0115064. Natl. distribution. Approx. 4,000 Trilute T-3 Kits and 200 Trilute Bulk Kits remain on market. [3] Distribution to MDs in Ohio, Ky., Mich., Ind., Ill., and Wisc. [4] Distribution to one account in Texas. [5] Recalled by Dart Drug Corp. Approx. 3,300 kits remain on market. [6] Some vials of HAA (List 8344) were labeled for list number 8809. Distribution was natl. and internatl. None remain on market. [7] Manufactured by West Chemical Products. [8] Recalled by Magna Medics Div. of Superior Surgical Manufacturing. [9] Distribution to Ill., Mich., NY, and Ohio. Approx. 77,000 caps remain on market. [10] U.S. District Court, West. Mo. [11] U.S. District Court, Middle Fla. [12] U.S. District Court, So. Fla. FDA C-O-R-R-E-C-T-I-O-N: *"two pieces of ancillary equipment used with the FO-8800 American Cystoscope Makers Marici Fiber Optics Flexible Bronchoscope, appearing on Recall List 8/28/74* ("The Pink Sheet" Sept. 2, p. T&G-6). *Reason should read: T-031-5 - Y Connector Tube - defective units (plastic flashing obstructing air flow); and T-032-5 - Plastic Endotrachael Tube - Size of endotrachael tubes used in conjunction with the bronchoscope restricts air flow."*

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mix-ups are the most commonly occurring reason for removal from the marketplace... FDA will continue to emphasize the responsibility of top management in the GMP process, Byers indicated. He read to the group a section from a draft GMP reg for Large Volume Parenterals (LVP) which is now being prepared by the Compliance Office. The purpose of the section is to "nail down responsibility," Byers declared.

¶ "Management shall periodically review and record the status of all manufacturing and control operations," the draft LVP GMP states. "This shall be accomplished through establishing a written quality assurance program. The program shall involve top echelon personnel and may provide for the participation of qualified independent outside experts," it continues.

Besides being able to detect conditions which might adversely effect the quality of a product, the program must also assure that "corrective actions where called for are taken." It must also provide for periodic inspections either by qualified in-house or outside experts with a "report prepared and supplied to top management."

¶ Byers also reported that FDA will be placing increasing emphasis on the design of manufacturing and controls processes and the steps taken to assure that they are adequate prior to the initiation of productions. "In order to assure products of uniform quality, purity and performance, it is essential that such process be defined with a great deal of specificity and that the adequacy of each step of such a process be challenged to determine its adequacy," Byers declared.

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FDA REPORT OF RECALLS ..... ISSUED OCT. 9, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] CPD Whole Blood	Donor Nos. C17380-C17442	Community Blood Bank, Marion County, Ind.	Wrong expiration date	Letter 8/7
[2] Cosmetic fingernail preparation kit (OTC)	All	Lori's Patti Nail Supply	Methyl methacrylate monomer	Letter 10/1
[3] Silastic Mammary Prothesis & Gel-Filled Testicular Implant	All lots	Dow Corning	Non-sterility due to defective packaging	Telegram 8/26
[4] Anti-S Serum	S-17	Spectra Biologicals	Label mix-up	Phone & letter 8/23

("The Pink Sheet" Oct. 7, p. T&G-6)

All Rx unless marked OTC. [1] Distribution to local hospitals. None remain on market. [2] Manufactured by Kerr. Distribution to Calif., Ill., Tex., NJ, Ga., Nev., Wash. & Mont. [3] Distribution was natl. & internatl. Products held pending relabeling & sterilization instructions from salesmen. [4] Distribution to Ger., Greece, D.C., Neb., Ky., Ill., Iowa, Ohio, Utah, Ore. & Calif.

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FDA RECALLS AND COURT ACTIONS. . . . . ISSUED OCT. 2, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALL				
[1] Allergan/Lubricating Astringent Decongestant Prefrin-Z Liquifilm Opthalmic Solution	See footnote	Allergan Pharm. *[See "The Pink Sheet" Sept. 16, p. T&G-9 for story on recall]*	Footnote	8/28 & 9/19 Letter & Press Release
CLASS II RECALLS				
[2] Nesacaine CE 2% inj.	R-275 - 277	Taylor Pharm.	Discoloration	Phone 9/10
[3] Digoxin tabs	2C17484	American Pharm.	Fails USP dissolution	Phone 9/24
[4] Fenwall Double Elutra-Pack Unit, Code 4R2400	All	Travenol	Footnote	Visits & letter 8/27
[5] Various Serums, Vaccines & Biological-Diagnostic Tests	Footnote	McK&R (distributor)	Held in Canton, Ohio whlse. branch without refrigeration	Phone 8/26
CLASS III RECALLS				
[6] Gramulin T Pre-filled Syringes	157021B	Dow Chem.	Needle burrs	Telegram 7/24
[7] Promethazine HCl inj.	Footnote	Central Pharm.	Crystallization	Phone & letter 9/18
SEIZURE ACTIONS FILED				
[8] Long Nails (OTC)		C.E.B. Products	Methyl methacrylate	8/28
[9] Long Nails (OTC)		C.E.B. Products	Methyl methacrylate	9/12
[10] Low Cal Sweetner		Dykem Co., St. Louis	Calcium cyclamate	9/17

All Rx unless marked OTC. [1] Number of Ophthetic (Rx) 15 cc. btles. have been erroneously packaged in Prefrin-Z (OTC) unit cartons. Natl. and internatl. distribution. Lot numbers: J0707, J1421, J1461, J1671, K0149, K0739 K0740, K0867, K0877, K1328 and K1468. [2] Distributed and recalled by Pennwalt. Nationwide distribution. [3] Distributed and recalled by Reyman Drug, Balto. Distributed only to Balto. area. [4] Reason: Leak in seal of injector and seal body allowing aspiration of air into unit and potential bacterial contamination of washed blood. Estimated 5,000 units on the market. Natl. and internatl. distribution. [5] Products: (a) Immune Serum Globulin, Dow, Lots 172 & 365; (b) Ortho Anti-Human Chorionic Slide test for Pregnancy, Ortho, Lots R9L425 or 9L425; V-563 Staphylococcus Vaccine, Eli Lilly, Lots 7KL53A. Distributed to Ohio & WVa. Estimated none remains on market. Recalled by McK&R. [6] Natl. distribution. 800 syringes remain on market. [7] Lot numbers: KCC, KDM and KGP. Product is also packaged under private labels: (a) "Anergan 25," O'Neal, Jones & Feldman (St. Louis), Lots KCC and KDM; (b) "Phenerject 25," Mayrand (Greensboro, NC), Lot KGP; (c) "Prorex - 25," Hynex-Key (Memphis), Lot KDM. Natl. distribution. [8] U.S. District Court, Eastern Ky. [9] U.S. District Court, Southern Fla. [10] U.S. District Court, Southern Mo.

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T&G FDA *CLARIFIES* LISTING OF ZYLOPRIM & IMURAN RECALLS -- *"all"* lots, *Class II*, issued Sept. 18 ("The Pink Sheet" Sept. 23, p. T&G-4). As a matter of fact, *no recall* was involved (see story, "The Pink Sheet" Sept. 30, p. T&G-7). Based on what is understood to have been a representation from Burroughs Wellcome's Washington counsel to FDA, following *NOTE* was included in FDA's Recall List issued Oct. 2:

on this basis, B-W telephoned all its field representatives to check stocks in possession of all whslrs., chain warehouses, retail pharmacists, hospitals and V-A depots; this was followed up with an Aug. 28 letter to field representatives reiterating instructions.

¶ On the same day (Aug. 28), B-W sent a letter to all whsle. pharmaceutical buyers asking them to "check immediately all Imuran and Zyloprim stocks to verify stocks of *carrier outers* and correct placement of all shelf stocks of these products." Since B-W has a "whslr. only" policy, this letter was directed to the key control point in its distribution system. Two days later (Aug. 30), a letter was sent to all retail pharmacies asking that they check stocks to be certain that "carrier outers" contain the product indicated.

¶ In essence, there was no *recall* at all, in the general meaning of the word. The nationwide survey, plus a check of the stocks in B-W's own inventories, produced only about 10 *carrier outers* that carried the name of the wrong drug. In its Aug. 28 letter to field representatives, B-W said: "We are notifying FDA of this action and furnishing them copies of the instructions to the sales staff, the whslrs., and pharmacists." More than two weeks later, the situation was recorded on FDA's weekly list as an "all lots" *Class II recall.*

FDA RECALLS AND COURT ACTIONS . . . ISSUED SEPT. 25, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALL				
Ped-Pod Pediatric Oral Dispenser	0354	MPL Solopak	Over dose potential	Visits 5/6
[1] Long Nails Nail Lengthener Kit	All	Footnote	Contains methyl methacrylate monomer	Letter 7/24
[2] Modulung - Teflo, total body perfusion disposable membrane oxygenator	All	Travenol	Footnote	Mail-O-Gram 7/25; letter 7/26
CLASS II RECALL				
[3] Concentrated Potassium Chloride inj.	G4C064A	McGaw	Particulate matter	Visits 7/2
Moorman's Rid-Ezy Medicated cattle feed	8140, 8300	Moorman	Misbranding	Visits 4/1
[4] Tetra-Ria T-4 Kit	40202A	Medical Systems	Mislabeling	Phone
[5] Magna Medics Connect-Trol	All	Magna Medics	Nonsterile	Nonsterile
SEIZURE ACTION FILED				
[6] Long Nails		C.E.B.	Contains methyl methacrylate monomer	9/5

[1] Manufactured by C.E.B. Recalled by Peoples Drug. Distributed by Dark Eyes. Distribution to 10 eastern states. [2] Reason: Shunts found in gas side of some units which can result in elevated carbon dioxide levels of blood. Natl. and internatl. distribution. Recall consists of a labeling corrective action. [3] Natl. distribution. Aprox. 19,000 vials remain on market. [4] Manufactured by Industrial Nuclear. Distribution to Mich., NM, Calif., Tex., & Ala. None remains on market. [5] Manufactured by Windsor Nuclear. Aprox. 20 cases remain on market. [6] US District Court, Northern Calif. 3 actions filed.

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FDA RECALLS AND COURT ACTIONS . . . ISSUED SEPT. 18, 1974

Name, Form & Labeler	Lot No.	Mfr. or Distributor	Reason	Recall Depth
CLASS II RECALL				
[1] Long Nails Nail-Lengthener Kit	All	Footnote	Contains methyl methacrylate monomer	Bulletin 8/23
[2] Travenol or Sarns battery operated blood pump	Footnote	Sarns	Electronic failure in motor speed control switch	Phone & ltr. 8/30
[3] Zyloprim Brand Allopurinol & Imuran Brand Azathioprine	All	Burroughs-Wellcome	Label mix-up	Footnote
[4] Various sutures & teflon pledgets	Footnote	Deknatel	Lack of assurance of sterility	Night ltr 8/19
CLASS III RECALL				
[5] Gordon's Econo-Pak Multi-Vitamin Chewable tabs (OTC)	127353	Freshman	Label mix-up	Phone 8/10
[6] Sleep Caps (OTC)	All	Michigan Pharmacal	Footnote	Letter 8/20
[7] Red S/C tabs	9963	Phoenix	Subpotent in chlor-pheniramine	Phone 8/2
[8] Solution Purified Insulin	Footnote	Arnar Stone	Subpotent	Letter 8/2
[9] Aminophylline tabs	9586	Heun/Norwood	Non USP disintegration	Phone 9/4
SEIZURE ACTION FILED				
[10] Long Nails		C.E.B.	Contains methyl methacrylate monomer	9/11
[11] Long Nails		C.E.B.	Contains methyl methacrylate monomer	9/5
[12] Long Nails		C.E.B.	Contains methyl methacrylate monomer	9/5
[13] Zymaferm & Silogen veterinary Drugs		BZD Livestock	No NADA adulteration	9/3
[14] Veterinary drugs		A.M. Dodge	Products sold w/out Rx, adulteration	9/3

[1] Recalled by Woolworth. Manufactured by C.E.B. Distributed by Dark Eyes. Distribution to NYC area. [2] Lot number: Model 5M6202 - 1162, 1174-1234, & 1500-1502. Model 5M253 - 1021-1029 & 1030-1032. Devices are not returned but on site corrections are being made. Model 5M6202 distributed to US & Canada. Model 5M6253 was internationally distributed. [3] Whslrs. notified by salesmen's visits & 8/28 letters. Retailers and hosps. notified by 8/30 letters. 300,000 btls. of Zyloprim & 40,000 btls. of Imuran remain on market. [4] Lot numbers: sterilization runs 34023 & 34024; needle products coded 834023 & 834024. Natl. & internatl. distribution. [5] Distribution to 1 consignee in Ind. [6] Products were misbranded, methapyrilene HCl caps repacked in btls., labeled as containing methapyrilene HCl & scopolamine aminoxide hydrobromide. Manufactured by Cord. Distribution to Mich. w/some natl. distribution. Approx. 800 36-cap btls. remain on market. [7] None remain on market. [8] Manufactured by Taylor Pharmacal. Lot numbers: 00201, 00401, 00601, 00801, 01001, 01202, 10201, 10401, 10601, 10701, 10801, 10901, 11001, 11101, 20401, 20601, 20801, & 21001. [9] Approx. 70 1,000-tab btls., 220 500-tab btls. remain on market. [10] US District Court, Southern Ind. [11] US District Court, Eastern Mo. [12] US District Court, Neb. [13] US District Court, Neb. [14] US District Court, Neb.

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T&G **ALLERGAN *PREFRIN-Z* "ALL-LOT" RECALL** announced Fri., Sept. 13 via FDA *Public Warning* release: "FDA today announced the recall of Prefrin-Z, an eye drop product sold OTC to consumers. The product is being recalled by the mfr., Allergan, because of some the Prefrin-Z cartons were incorrectly filled with bottles of Ophthetic, a potent eye drop product used by MDs as an anesthetic. Ophthetic, in rare instances, may cause serious allergic reactions resulting in severe eye damage. FDA advised consumers who may have purchased the product to check the label on the bottle and return any labeled 'Ophthetic' to the store were purchased. Bottles labeled as 'Prefrin-Z' may continue to be used. Allergan estimates that approximately 100 bottles are involved in the label mix-up."

Allergan President Gavin Herbert told "The Pink Sheet" that the firm had sent out a warning letter "10 to 14 days ago," and he did not understand why FDA waited until Sept. 13 in the afternoon to issue a release. He also said that the OTC is a low-volume drug, selling only about 5,000 units a month. The company was first alerted to the packaging mix-up when one unit was discovered mis-boxed in the Allergan plant. One hundred more boxes were subsequently discovered to be mis-boxed.

FDA RECALLS AND COURT ACTIONS . . . . ISSUED SEPT. 11, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] D-Alpha-E topical ointment	111462	Wilson & Wolfer	Bacterial contamination	Letter 8/2
[2] Otalgine otic drops	M72-12925	Purdue Frederick	Subpotent in neomycin	Letter 8/16
[3] Sculptured Nails kit	All	Jan Rodgers (repacker)	Contains methyl methacrylate monomer	Letter 7/21
[4] Brush-on Fingernail kit	None used	Maji-Nail	Contains methyl methacrylate monomer	Letter 8/27
[5] Evacuated blood collection tubes w/ sodium oxalate sol. .5 & .7 ml.	Footnote	Abbott	Erratic prothrombin times	Letter 7/15 Phone 8/8-8/12
SEIZURE ACTIONS FILED				
[6] Long Nails		C.E.B. Products	Contains methyl methacrylate monomer	8/29
[7] Long Nails		C.E.B. Products	Contains methyl methacrylate monomer	8/28 8/26
[8] Chuiform Toukuwan, arthritis, rheumatism medication		Nan Lien	Footnote	8/28
[9] Prophylactics		M&M Rubber	Product contains holes	8/27
[10] Sanorex tabs & booklet		Sandoz	Misbranded	8/29

[1] Natl. distribution. 20 jars remain on market. [2] Manufactured by Bard Pharmaceuticals. Natl. distribution. [3] Manufactured by L.D. Caulk. Approx. 45 kits remain on market. [4] All btls. under recall regardless of net contents statement. [5] Manufactured by Concept Industries. Lot numbers: 538-3-100, -101 & -102. 738-3-100, -101 & -102. [6] U.S. District Court, Western NY. [7] U.S. District Courts, Middle & Western Tenn. [8] Product has no NDA and is dangerous to health when used in dosage or duration prescribed. Label fails to list active ingredients. [9] U.S. District Court, Kansas. [10] Booklet contains statements & representations which are inconsistent with labeling. Labeling fails to bear adequate directions for use.

EDITORS' NOTE: *FDA's Aug. 21 Recall List ("The Pink Sheet" Aug. 26) failed to note that Basic Bee C & Balanced-50 Super B Complex were manufactured and mislabeled by Basic Organics.*

T&G C.E.B.'s *LONG NAILS* BEING SUBJECTED TO MULTIPLE-SEIZURE TACTIC; the methyl methacrylate monomer-containing product will be seized via on-going campaign in various parts of the country, following the mail-out of 50 "alert" letters from FDA Rockville headquarters, according to an FDA legal staffer. As of Sept. 5, recent seizures included: southern and northern Ohio, northern and western Texas – in addition to three listed in *FDA Recalls and Court Actions* for Sept. 4 (see below). FDA Dallas District Office has reportedly put in filings for other seizures in Texas (3) and Arizona (1).

¶ FDA has succeeded in obtaining "voluntary," Class II – priority. . .possibly or potentially life-threatening or hazardous – recalls from mfrs./distributors of other methyl methacrylate monomer-containing products. Chicago Federal Judge Bernard Decker June 28 "ruled that a product of this nature is adulterated. . .therefore, (FDA) is instituting regulatory action against" such products, Associate Com. for Compliance Sam D. Fine wrote Lang Dental, mfr. of Smartee Instant Nail Kit ("The Pink Sheet" Aug. 19, p. T&G-6). A Texas FDAer attributed the recall of Viva's Nail Liquid (raw materials manufactured by Lang Dental) to his district office's "sweeping investigation made as a result of the C.E.B." Chicago decision.("The Pink Sheet" Sept. 2 – FDA recall listing – p. T&G-6). Judge Decker, on July 12, ruled against FDA's request that the court order a recall.

FDA RECALLS AND COURT ACTIONS. . . . . ISSUED SEPT. 4, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Sculptured Nail & Lash Kits	All	See footnote	Adulteration	Letter 8/8
[2] Heidbrink Series DM5000 Cabinet Kinet-O-Meter Anesthesia Machine	See footnote	Ohio Medical Products	See footnote	Letter 6/25
SEIZURE ACTIONS FILED				
[3] Prophylactics		M&M Rubber Co.	Adulteration – product contains holes	8/26
[4] Long Nails		C.E.B. Products	Adulteration	8/20
[5] Long Nails		C.E.B. Products	Adulteration	8/23
[6] Long Nails		C.E.B. Products	Adulteration	8/27
[7] Calcium Lactate		Humko Sheffied Chem. Co.	Misbranded	8/28

[1] Product manufactured by Harry J. Bosworth Co., and Esschem Co., and repacked and recalled by Mona's Sculptured Nails and Lashes. Unlabeled liquid in kit contains methyl methacrylate. [2] Recall covers all devices with the "Model" No. in the DM5000 series, manufactured between 1968 and Aug. 31, 1971. Recall involves a modification procedure only. "Medical Device Alert" letters were mailed June 25, 1974 notifying consignees of the modification program, which consists of replacement of a slip-on cap by a threaded nipple. Distribution in U.S., Canada and overseas. Recall due to malfunction in the oxygen piping system causing oxygen to flow into the cabinet of the device instead of being delivered to the patient. [3] U.S. District Court, Kansas. [4] U.S. District Court, Southern District, Texas. Product contains methyl methacrylate monomer – a harmful substance. [5] U.S. District Court, Eastern Mich. [6] U.S. District Court, Northern Ind. [7] U.S. District Court, N.J. Labeling is false and misleading and fails to bear the name and place of business of the mfr.

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FDA RECALLS AND COURT ACTIONS . . . . ISSUED AUG. 28, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS I RECALL				
[1] Bichromatic Analyzer, models ABA-100 & ABA-50	All units	Abbott	Non-linonlinearity	Footnote
CLASS II RECALLS				
[2] Apresoline HCl, IV or IM	All	Ciba	Particulate matter	Letter 8/7
[3] Nitrofurantoin caps, 50 & 100 mg.	All	Bolar	No NDA	Phone 8/9 Letter 8/12
[4] Devilbiss Model No. 65 Ultrasonic Nebulizer	Footnote	Devilbiss	Electronic hazard	Footnote
[5] Allergenic Extract	38405FD	Center	Bacterial contamination, subpotency	Letter 8/6
[6] Nail Liquid	All	Viva	Contains methyl methacrylate monomer	Letter 7/24
[7] In-Vitro Diagnostic Culture Plate Products		Clifford Biologicals	Microbiological contamination	Letter 8/8
[8] White Plastic Y-connecter Tube & Plastic Endotracheal Tubes	None	American Cystoscope	Defective units	Letter 7/5
CLASS III RECALL				
[9] Webbs Isopropyl Alcohol, 16 oz.	None	Webbpak	Contains mineral oil residue	Letter 9/19

[1] Mailgram & letter (6/27) for ABA-100. Phone (7/29 & 7/31) & letter (7/31) for ABA-50. Natl. distribution and to Australia, Japan, Mexico, Canada & W. Europe. 770 ABA-100s & 100 ABA-50s were distributed. [2] Natl. distribution & to Canada. [3] Distributors: Rugby, Pharmocon, Spencer-Mead, H.L. Moore, Vangard, Gen-King, Bioline, Henry Schein, Richie, & Sherry. Distribution to Eastern U.S. 500,000 caps remain on market. [4] Lot numbers: Models with serial numbers 30,000 to 33,696 manufactured between 12/72 and 12/21/73. Corrective action started by visits, 5/23. Natl. distribution & to foreign consignees. 1,650 units remain to be modified. [5] Distribution to MDs, researchers & hosps. in Mich., Minn., Mo., N.Y., Ohio, Pa., Tex., Va., D.C., Italy, Columbia & Switzerland. [6] Raw materials manufactured by Lang Dental. [7] 73 agar types recalled. Distribution to hosps., clinical labs & MDs in Mass., R.I. & N.H. 1,500 plates remain on market. [8] Y-connecter tubes mfr.: Prototype Plastic. Endotracheal tubes mfr.: Natl. Catheter. Natl. & internatl. distribution to MDs & hosps. [9] Distribution to Birmingham, Ala.

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T&G **ABBOTT ANALYZER RECALL RATED *CLASS I* BECAUSE OF DEATH** allegedly caused by misreporting of glucose level on the instrument, according to FDAers. An error in the instruction manual told users to set the read-out dial in such a way that the decimal point was misplaced, resulting in the first digit of the glucose reading being dropped, govt. spokesmen explained. The patient who died at Ft. Leavenworth Army Hospital, Mo. reportedly had an extremely high glucose level, but the reading on the machine indicated a very low level. A misdiagnosis resulted and dextrose was administered as treatment and the patient

T&G **FINAL ORDER BANNING VINYL CHLORIDE PROPELLANT** in all cosmetic and drug aerosol products published in Aug. 26 *Federal Register*, effective after 30 days. Proposal was originally published for comment April 22 ("The Pink Sheet" April 22, p. T&G-9). However, only three comments were received – from the American Academy of Pediatrics, a municiple consumer affairs unit and an unspecified individual – and all were in favor of the proposed reg.

¶ Second part of proposal, governing polyvinyl chloride (PVC) in devices and food and cosmetic containers, has been held up pending further comments. Specifically requested by *Federal Register* notice is data concerning "extent of usage of PVC containers, the rates of extration of vinyl chloride (VC) monomer from these containers and other matters that will pertain to the safety of these containers." Notice also adds that supplementary submissions received by FDA "are being compiled and reviewed to determine whether additional action by the Commissioner is needed to protect the public health."

FDA RECALLS AND COURT ACTIONS.... ISSUED AUG. 21, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Digitoxin tabs, .2 mg.	87271	Westerfield	Non-USP content uniformity requirements	Letter 8/9
[2] Reserpine tabs, 1 mg.	3J216	McKesson	Non-USP potency & content uniformity tests	Information Bulletin & visit 7/25
SEIZURE ACTIONS FILED				
[3] Long Nails		C.E.B.	Contains methyl methacrylate monomer	8/9
[4] Basic-Bee-C & Balanced-50 Super-B-Complex		Generix	Footnote	7/30

All Rx. [1] Distribution to Ohio, Ind. & Ill. Approx. 4,500 tabs remain on market. [2] Natl. distribution. [3] U.S. District Court, Western Tex. [4] Labels contain false & misleading statements. Vitamin B-12 & folic acid were in part omitted or abstracted. Co-r-r-e-c-t-i-o-n: Vitamin B-12, recalled Aug. 14, was repacked and recalled by Indianapolis Pharmacal, not by mfr. Banner Gelatin.

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T&G **BANNER GELATIN PRODUCTS**, Chatsworth, Calif., had no connection with "Vitamin B-12" *Class II* recall reported by FDA in its weekly summary, issued Aug. 14 ("The Pink Sheet" Aug. 19, p. T&G-7, second entry in weekly tabulation based on FDA's report). In the tabulation, Banner Gelatin is listed in the column headed "Mfr. or Distributor." The FDA Aug. 14 report designated Banner as the mfr. of the Vitamin capsules that were sold to Indianapolis Pharmacal Co., Indianapolis, Ind., which repacked them and was responsible for the recall. In the repacking, two 100-capsule bottles apparently were mislabeled as Vitamin B-12 tablets, 50 mcgm.

duction into interstate commerce and all labeling accompanying said prohibited devices, heretofore introduced or delivered for introduction into interstate commerce, to be returned to the possession of the defendant by providing notice in writing to each person having possession of any of said devices advising such persons to return all such devices and labeling at defendant's expense. . ."

FDA RECALLS AND COURT ACTIONS . . . . ISSUED AUG. 14, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALL				
[1] No. 822E 100 Sensitivity Discs Gentamicin 10 mcg.	2835	Pfizer	Mislabeling	Letter 7/30
[2] Vitamin B-12 (OTC)	37406	Banner Gelatin	Mislabeling	Visit & phone 6/11
[3] Promapar tabs 50 & 100 mg.	PG338A PG339A	P-D	Labeling mix-up	Phone 8/1 Letter 8/2
[4] Horse Antihuman Thymocyte Gamma Blobulin, 50 mg. (IND)	Footnote	Upjohn	Leaking vials	Telegram 6/24
[5] Smartee Instant Nail kit (OTC)	All	Lang Dental	Contains methyl methacrylate monomer	Letter 8/1
CLASS III RECALL				
Eye Make-up Remover (OTC)	All	Rozelle	Contains Blue No. 1	Phone 7/18
SEIZURE ACTIONS FILED				
[6] Various Drugs		Sewell Enterprises	Adulteration	8/5
[7] Phisohex & minibath kits (OTC)		Delta	Misbranded	7/30

All Rx unless marked OTC. [1] Natl. distribution & to Canada. 1,600 cartridges remain on market. [2] Distribution to 10 pharmacies & 1 hosp. None remain on market. Two btls. of Vitamins B labeled B-12. [3] Natl. distribution. [4] Natl. distribution from 7/24 to 6/21. 1,000 vials remain on market. Lot numbers: 13B-13, 14, 15, 16, 17, 18 & 20. [5] Repacked & recalled by Cameo Cosmetics. Natl. distribution. 6,000 units remain on market. [6] US District Court, Southern Fla. Labeling fails to bear adequate directions for use. New drug without an approved application.

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T&G **ALLERGENIC EXTRACTS' ADVISORY CMTE.'s INTEREST IN VISITING A MFR.**, presumably to see how products are actually manufactured, has endorsement from FDA Com. Schmidt, Panel Chairman Paul M. Seebohm told Aug. 16 meeting of the group assisting BuBio in relatively uncharted regulatory area. However, Seebohm explained, the FDA commissioner stressed that the advisory panel must first be invited by a mfr., and its visit must not be considered as an official advisory cmte. function. Also, he reported, FDA wants it made clear that the visit would be solely for educational purposes, and not for review of either manufacturing processes of products.

¶ BuBio's Dr. Harold Baer told panel regulatory problem areas include: Raw materials' control; pollen identification, purity, potency, safety, stability re dating periods, and lengthy lists of extracts. He said he didn't know where dating periods originated, but they appear in regs as far back as 1915.

0886

T&G

KIDNEY DIALYSIS MARKET TO QUADRUPLE IN NEXT 10 YEARS; over that period of time, "100 mil. worth of equipment will be needed just for the new patients that are starting on home dialysis," according to a new Frost & Sullivan study. The report projects an expected "rapid expansion in home dialysis and treatment in limited care centers, while hospitals will incur a reduction in this workload," Frost & Sullivan noted. "The study also finds a great variation by location in the cost of treating a patient."

FDA RECALLS AND COURT ACTIONS..... ISSUED AUG. 7, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] Normal serum albumin, 25% sol.	17921	Abbott	Labeling error	Letter 7/25
[2] Tuberculin purified protein derivative	12094-1	Connaught	Incorrect expiration date	Letter 7/23
[3] Several reagent products	Footnote	Hycel	Noneffective	Letter 6/24
[4] CP101 Blood Agar 5%	Footnote	Clifford Biologicals	Bacterial contamination	Phone 7/5
[5] Lidocaine HCl inj. ½ & 2%; procaine HCl 2%	Footnote	Invenex	Glass particles	Letter 7/25
[6] Philips Scopomatic 71 Spot Film device XD3453		Philips Medical Systems	Unnecessary radiation exposure	
CLASS III RECALL				
[7] H-I-L-20 Lotion ½% PH6	30240	Cord	Subpotent	Letter 7/23
INJUNCTION COMPLAINT FILED				
[8] Source & human blood plasma		Footnote	Footnote	7/30
SEIZURE ACTION FILED				
[9] Sodium acid pydrophosphate		Nonpareil Processing	Adulteration	7/11
[10] Thermoscribe II device		Murdoch Engineering	Misbranded	7/15

All R. [1] Natl. distribution to 9 hosps. & 1 blood bank. Approx. 230 vials remain on market. [2] Importer and distributor was Ormont. Recalled by Ormont. Natl. distribution. 5,000 vials remain on market. [3] Products for in-vitro diagnostic testing: **Acid Phosphatase Color Reagent, CPK Phosphorus Reagent, Phosphorus Reagent, CPK Set, and Acid Phosphatase Set.** Lot numbers: **580 ml. btles.** – 1087A1, 1275A1, 1280A1, 1294A1 & 1348A1; **1,890 ml. btles.** – 1087B1, 1275A1, 1280A1, 1294A1 & 1348A1. Natl. distribution and to 7 foreign accounts. [4] Lot numbers: 111693 with suffixes A, B, C, F & G; 11694 with suffixes A-G and 111717. Distribution to New England hosps. [5] Lot numbers: Lidocaine HCl ½% – 207-7341; Lidocaine HCl 2% – 202-7646B; Procaine HCl – 92-7350. [6] Units located in hosps. & medical facilities nationwide. Corrective program begun 2/28. [7] Recalled by S.J. Tutag. Natl. distribution. Approx. 1,000 btls. remain on market. [8] U.S. District Court, Southern Fla. Charge: Delivery for introduction into interstate commerce of adulterated, misbranded and falsely labeled drugs and biological products. Consolidated Pharmaceuticals, Benasil Corp., Tampa Plasma Center & Ocean Plasma Center. All companies have same president and VPs. [9] U.S. District Court, Colo. Product held in rodent contaminated bags. [10] U.S. District Court, Western NY. Product fails to bear adequate directions for use.

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0887

MYLAN ERTHROMYCIN RECALLS: MORGANTOWN PLANT *"not the source"*

– "contrary to impressions and hearsay which may have resulted from a series of notices published in F.D.C. Pink Sheet ("F-D-C" REPORTS – "The Pink Sheet") and elsewhere," the company declared in July 25 memo sent to customers. "All of the tablets were recalled ("The Pink Sheet" June 24, p. T&G-5; June 17, p. T&G-7; May 6, p. T&G-6) for penicillin contamination in bulk erythromycin material supplied by Cipan (Portugal) and Pierrel S.P.A. (Italy)," Mylan said. In a covering letter to "The Pink Sheet," Mylan President Jerome N. Lehman said: "...FDA has moved to tighten allowable limits of penicillin to a zero level. Mylan unfortunately has been the first up to bat on this subject." The "notices" published in "The Pink Sheet" were based on FDA's official weekly listings.

"The recall itself was noteworthy to the extent that new methodology was used to detect the penicillin contamination in previously certified batches, thereby retroactively cancelling previous FDA Certifications which had indicated 'No Detectable Penicillin'," Mylan noted.

¶ Since the first of the year, according to FDAers, the agency has been using new, more sensitive tests to detect penicillin contamination. A revised version of FDA's manual "Procedures for Detecting and Measuring Penicillin Contamination in Drugs" is now at the printers. FDAers apparently believe a zero tolerance level should be used for penicillin contamination of erythromycin on the basis of a "health hazard" decision, because the drug is indicated for use in patients hypersensitive to penicillin. The FDA recall list of May 1 did not specify the source of the contamination for the Mylan product. The reason stated for the recall was "Penicillin contamination." Subsequent lists, however, reported the reason for the recalls as "Penicillin contamination of bulk powder raw material."

FDA RECALLS AND COURT ACTIONS.....ISSUED JULY 31, 1974

Name, Form & Labeler (Numbers refer to footnotes)	Lot No.	Mfr. or Distributor	Reason	Date
CLASS II RECALLS				
[1] 9 Southern Grass Allpyral Allergenic Extract	60903NZ	Miles	Product improperly compounded	Phone 5/30
[2] Lyophilized Blood Culture Antisera	All	Difco	Non-specific reactions	Letter 6/17
[3] Non-absorbable sutures	34023	Deknatel	Non-sterile	Visit 7/18
CLASS III RECALL				
[4] Acotus cough syrup, 1 gal., 4 & 12 oz.	All	Whorton Pharmacal	Misbranding	Letter 6/22
SEIZURE ACTION FILED				
[5] Digitoxin tabs		Generic Drug	Adulteration	7/22

All Rx unless marked OTC. [1] Recalled by Dome. Distribution to Atlanta & Sacramento. None remains on market. [2] Includes salmonella O antiserum, group B, pactors 4 & 5; salmonella O antiserum, pactor 8; salmonella O antiserum, group E, pactors 1, 3, 10, 15, 19 & 34; and Salmonella VI antiserum. Natl. & Canadian distribution. [3] Natl. & Italian distribution. [4] Distribution to Ala. Little remains on market. [5] U.S. District Court, Western Mich. Product fails content uniformity requirements.

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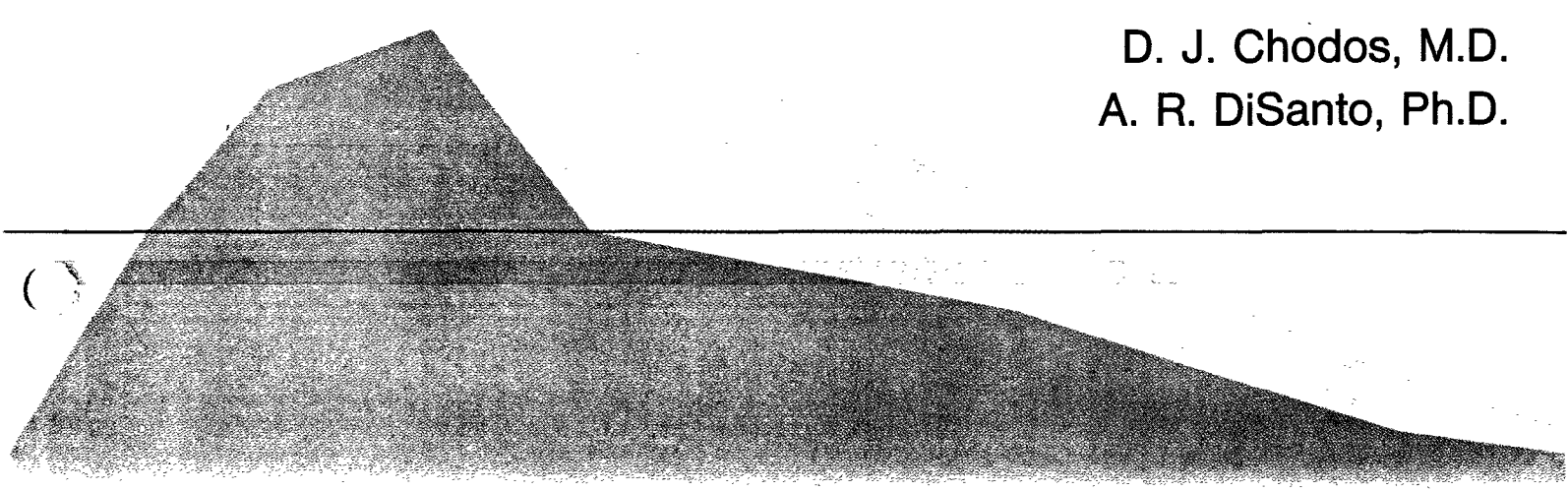
BASICS OF BIOAVAILABILITY

D. J. Chodos, M.D.
A. R. DiSanto, Ph.D.



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