COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETIETH CONGRESS

FIRST AND SECOND SESSIONS

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 6

NOVEMBER 29, 1967; FEBRUARY 6, 8, 27, 28, AND 29, 1968

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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, NOVEMBER 29, 1967

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

The subcommittee met, pursuant to recess, at 10:05 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Hatfield.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The meeting of the subcommittee will come to order.

The committee welcomes these witnesses representing the Pharmaceutical Manufacturers Association. I understand the first witness will be Dr. Leslie Lueck; the second witness, Dr. Slesser; the third witness, Dr. Scheele; the fourth witness, Dr. Van Riper; and the fifth witness, Mr. Blazey.[1]

Dr. Lueck, the committee welcomes your appearance today.

Did you submit to the committee a biographical sketch?

STATEMENT OF LESLIE M. LUECK, PH. D., DIRECTOR OF QUALITY CONTROL, PARKE, DAVIS & CO., DETROIT, MICH.; ACCOMPANIED BY LLOYD N. CUTLER, SPECIAL COUNSEL, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, D.C.

Dr. LUECK. Yes, I did—a brief one.

Mr. CUTLER. It is at the beginning of Dr. Lueck's statement, Mr. Chairman.

Senator NELSON. Dr. Lueck, we welcome your appearance today. The committee is aware of your distinguished record, including your association with the great State of Wisconsin and its university.

You may present your testimony in any way you see fit. I assume you have no objection if we have questions during the presentation of your statement.

Dr. LUECK. No, sir; I do not.

Senator NELSON. The full statement will be printed in the record. If at any stage you feel it would expedite matters to extemporize in

[1] Dr. Lueck, Dr. Slesser, Dr. Scheele, Dr. Van Riper, and Mr. Blazey were originally scheduled for appearance with Mr. C. Joseph Stetler, president, Pharmaceutical Manufacturers Association, hearing date, November 16, 1967, Competitive Problems in the Drug Industry, part 4.

order to summarize some material, you may do that, or you may read it in toto, however you see fit.

Dr. LUECK. Thank you, Mr. Chairman.

With your permission, may I suggest that the first statement that was submitted on November 6 for presentation on November 16 be included in the record, and that we go on to the supplemental statement, which was submitted to your staff on the 13th of November and is labeled the supplemental statement.

Senator NELSON. You are asking that the original statement be printed in full in the record?

Dr. LUECK. Yes, sir.

Senator NELSON. And you do not intend to comment or read anything from the original statement?

Dr. LUECK. No, sir; I am prepared to respond to any questions the chairman might have, however, on that statement.

Senator NELSON. All right, then, we will probably have some questions on the original statement, but we will let you proceed with the second statement and we can always jump back to the original statement.[1]

Dr. LUECK. Thank you, Mr. Chairman.

Then proceeding with the supplemental statement, it is relatively short and I think I may just read it for the record.

In my prepared statement of November 16, 1967, to your subcommittee, I indicated that Parke, Davis & Co. had initiated a study to compare a product originated by the company with several products containing the same active ingredient now available from other firms by nonproprietary and brand names. Sufficient information has now been gathered to make the findings of these studies meaningful to the subcommittee. The technical information in this statement has been filed with the Food and Drug Administration.

This report contains information derived from comparing several companies' chloramphenicol capsules with Chloromycetin capsules, Parke, Davis & Co.'s brand of chloramphenicol. The products studied are currently in commercial distribution in the United States and, therefore, are available for use on a physician's prescription.

Chloramphenicol, an antibiotic drug, is the result of the research and development efforts of Parke, Davis. Chloramphenicol, under the Parke, Davis trade name, Chloromycetin, was first made available to the medical profession in 1949.

In February of 1967, chloramphenicol capsules, from companies other than Parke, Davis, became available in the United States for commercial distribution. Shortly thereafter, it was called to our attention that at least one of the competitive drugs did not disperse in water to the same degree as Chloromycetin, Parke, Davis.

The above information suggested that it was advisable to carry out laboratory studies to compare some of the competitive chloramphenicol capsules with the Parke, Davis product. To conduct these studies, Chloromycetin capsules, Parke, Davis, several other companies' chloramphenicol capsules were obtained from retail pharmacy stocks. The materials tested were, therefore, available and ready to be used on a physician's prescription in the treatment of disease.

[1] The complete prepared statement and attachments submitted by Dr. Lueck for presentation on Nov. 16, 1967, begins at p. 2225, infra.

It should be noted that the drug chloramphenicol and all its product forms are subject to a batch-by-batch certification pursuant to the antibiotic regulations of the Food and Drug Administration. Therefore, the capsules studied in this report, which were all in commercial distribution, should have passed all the requirements contained in the antibiotic regulations, and the Food and Drug Administration should have certified that all those requirements were met.

On each of the samples mentioned above, certain laboratory tests contained in the U.S. Pharmacopeia and the antibiotic regulations were performed by Parke, Davis. None of the materials was found to be deficient in meeting the standards of those tests. However, as was mentioned in our earlier statement to the subcommittee, a reputable manufacturer frequently does more testing and has more expertise than is required to meet the minimum standards. This is certainly true for Chlormycetin, Parke, Davis.

It should be emphasized that Parke, Davis has defined the quality level of its Chloromycetin product in terms of clinically demonstrated efficacy. In fact, in 1964, before the Food and Drug Administration would certify batches of Chloromycetin manufactured by a new synthetic process, they required Parke, Davis to produce not only animal data supporting safety, but also blood level and clinical efficacy data in human subjects. Studies were performed to obtain this information and it was supplied to the Food and Drug Administration.

Laboratory tests and standards in addition to those required by FDA and the USP were developed by Parke, Davis to maintain this built-in quality in each batch of Chloromycetin that is produced. To mention just one of the additional tests, Parke, Davis explored a dissolution rate test on batches of chloramphenicol capsules. This test was performed on each sample of the chloramphenicol capsules obtained from the pharmacies.

Dissolution rate is a test performed in the laboratory to measure the length of time required for the dosage form, such as a capsule, to release the drug. The test was carried out using an official U.S. Pharmacopeia test solution, simulated gastric juice. The dissolution rate test is believed by experts to be a valuable tool to ascertain whether the manufacturing process produces a product which is readily absorbed into the bloodstream from the gastrointestinal tract of the patient. Indeed, this is one of the tests required in the procurement of chloramphenicol capsules by the Defense Supply Agency (DSA).

This point we think is very important in oral antibiotic therapy because without early and rapid absorption, the drug cannot be expected to reach the disease site sufficiently rapidly and in high enough concentrations to carry out its therapeutic action.

The results of the dissolution rate test are summarized in chart 1, which is attached, Mr. Chairman, to the supplemental statement.[1]

It is seen from the chart that none of the competitive chloramphenicol capsules dissolved in simulated gastric juice as quickly or at the same rate as Chloromycetin, Parke, Davis. The Parke, Davis standards for dissolution rate, which have been adopted by the Defense Supply Agency, are as follows: The capsules shall release not less

[1] Charts 1 to 13 attached to Dr. Lueck's supplemental statement begin at p. 2151, infra.

than 85-percent chloramphenicol in 10 minutes, not less than 93 percent in 20 minutes, and not less than 98 percent in 30 minutes. None of the other chloramphenicol products which we tested met these standards.

Because the dissolution rate test is a laboratory test, in vitro and not in man, it alone cannot be considered to be sufficient to establish whether there was a lack of efficacy for these chloramphenicol products. A question of efficacy can only be answered with established clinical data. Consequently, we applied to the Food and Drug Administration for permission to conduct clinical studies on these same products to ascertain if human subjects would absorb the drug in a manner that could be correlated with the results of the dissolution rate test.

The Food and Drug Administration granted Parke, Davis permission to proceed with these clinical studies. The studies thus approved were to be conducted on normal human subjects, each of whom was to receive a single 500-mg. dose of one of the chloramphenicol. The tests of (1) the blood plasma levels of chloramphenicol and (2) the urinary excretion rate of chloramphenicol were to be determined for each subject.

The first clinical study, designated on the charts as "Study 1," was carried out on five normal subjects who received FDA-certified Chloromycetin capsules and on five normal subjects who received presumably an FDA-certified sample of product A. Both samples, as previously stated, were obtained from a retail pharmacy.

Chart 2 shows the results of the blood plasma level tests.

Senator NELSON. Do we have the names of the other companies in the sample comparative tests?

Dr. LUECK. No, you do not, Mr. Chairman. The names and the lot numbers have been turned into the Food and Drug Administration.

Senator NELSON. Do you object to giving the committee the names of the other companies?

Mr. CUTLER. Mr. Chairman, Parke, Davis would certainly prefer not to furnish those names to the committee. But they have been furnished, together with all of the protocols and results of the tests, to the Food and Drug Administration. So they would be available to you, I assume, on a confidential basis, from the Food and Drug Administration.

Senator NELSON. Is there any reason why information of this kind should be confidential?

Mr. CUTLER. Well, these are very serious charges addressed to the other drugs, Mr. Chairman, and Parke, Davis would prefer not to be naming the makers of the other products. It has turned its evidence over to the Food and Drug Administration. The Food and Drug Administration will presumably seek to verify the results found by Parke, Davis and take whatever action it deems to be appropriate.

Senator NELSON. Do any of the companies involved, without naming them, produce brand-name products?

Dr. LUECK. Yes, sir.

Senator NELSON. How many of them?

Dr. LUECK. I think it would be divulging the companies' names if I went any further than my statement.

Senator NELSON. Why would that divulge their names?

Dr. LUECK. Because I think they could decipher which products we had tested if I continued any further along that questioning. There are brand-name products.

Senator NELSON. Are any of them companies that produce only generic drugs?

Dr. LUECK. Yes, sir.

Senator NELSON. These are going to be public anyway.

Dr. LUECK. Yes. Both types of products, both brand names and generic, are represented in the study.

Senator NELSON. Are any of the brand-name companies that produce an inadequate chloramphenicol tablet members of the Pharmaceutical Manufacturers Association?

Mr. CUTLER. I do not believe any of them are, Senator Nelson.

Dr. LUECK. To respond to that, I think one member is an associate member.

Is that right?

Mr. CUTLER. I don't know the answer to that, sir, but we will find out and let you know.

Senator NELSON. Well, all right, go ahead. It will become public at some stage, anyway.

Dr. LUECK. Thank you, Mr. Chairman.

Continuing on page 5, a plasma-level test consists of measuring the amount of the drug present in the blood at a given time. The plasma level of an antibiotic is considered by experts to be a measure of the amount of drug that has been absorbed by the bloodstream and, is therefore, indicative of the amount available for eliciting a therapeutic response. It is important to note that physicians require that an oral antibiotic product give as high and as rapid a blood level as possible per given dose. This is because quick absorption of the antibiotic into the bloodstream is necessary in order that the drug may be immediately transmitted to the site of the infection.

As can be seen from chart 2, the blood plasma levels of chloramphenicol for the two products, Chloromycetin and product A, are markedly different. To illustrate the significance of this difference, please note the following statement appearing in the labeling—package insert—of both products:

> Chloramphenicol administered orally is absorbed rapidly from the intestinal tract, producing detectable concentrations in blood within one-half hour after administration and peak concentration in from one to three hours. Peak blood concentration is roughly proportional to the dose.

It can readily be seen that product A is not absorbed as rapidly as Chloromycetin nor is the peak concentration in the blood as high as that found with Chloromycetin.

The second test conducted in this study was the urinary excretion rate of chloramphenicol. The test was performed on the same subjects taking part in the blood-plasma-level test.

The excretion rate of a drug is determined by measuring the amount of the drug in a sample of urine taken at various time intervals after administration of the product. It is pointed out that before a drug can be present in the urine, it must be absorbed from the gastrointestinal tract into the bloodstream of the patient, and thence partially metabolized and found in the urine. This test, therefore, ascertains how much

of the drug has been assimilated in the body to combat the infection being treated.

As can be seen from chart 4, the urinary excretion rate data corresponds very closely to the blood-level data. Thus the product A chloramphenicol was excreted at a much lower rate than Chloromycetin, Parke, Davis.

Particular note should be made of the fact that after 24 hours only 46 percent of the total chloramphenicol administered as product A could be accounted for by the urinary excretion rate test. This is in sharp contrast to Chloromycetin, Parke, Davis, where 76.4 percent of the drug was excreted in the same period of time. This point is especially significant because the Food and Drug Administration approved labeling for both products contains the statement that:

> Seventy to 90 percent of a single oral dose of 50 mg. of chloramphenicol is excreted in 24 hours in the urine of human subjects, with 5 to 10 percent as free chloramphenicol and the remainder as microbiologically inactive metabolites, principally the conjugate with glucuronic acid.

Thus, in this test, product A was not excreted in the urine in the 70- to 90-percent range mentioned in the official labeling, see chart 4.

The analytical procedures used in performing the blood-plasma level tests and the urinary excretion rate test for chloramphenicol were developed by Parke, Davis. These procedures were published by Parke, Davis scientists and, of course, are available to anyone who wishes to use them. The plasma and urine samples were analyzed by the colorimetric procedure—Glazko, et al., Arch. Biochem. 23:411, 1949, modified as described in Antibiotics Agents and Chemotherapy—1966, page 655.

A second study, designated in the charts as Study II, was conducted in precisely the same manner as described in Study I. Study II was done to verify the results obtained in Study I. The results of the blood plasma level test conducted in Study II can be seen in charts 5 and 6. The results of the urinary excretion rate test in Study II can be seen in chart 8. It can be observed from the charts that the blood plasma level tests and the urinary excretion rate tests of Study I and Study II are consistent.

In addition to colorimetric or chemical test for chloramphenicol in the blood, a microbioligical assay was also carried out in Study II.

Senator NELSON. May I interrupt, Doctor?

There has been a scheduled rollcall, so we will recess for 10 minutes.

(Short recess.)

Senator NELSON. The hearing will come to order.

Dr. Lueck, you were where when we interrupted you?

Dr. LUECK. Mr. Chairman, I was on page 7 of the supplemental statement, the second full paragraph, starting on the second sentence of that paragraph.

Senator NELSON. Fine, Doctor, proceed.

Dr. LUECK. The microbiological assay is important because it is a direct measurement of only the microbiologically active chloramphenicol, and does not pick up any of the inactive metabolites which are measured by the chemical determination. This test, which was performed on the same blood samples previously used for the chemical test, is an actual measurement of the ability of the drug to inhibit

growth of a test microorganism. As can be seen from chart 6, product A demonstrated less inhibition of the microorganism, as measured in terms of micrograms of chloramphenicol per milliliter of blood sample tested, than did the Chloromycetin, Parke, Davis.

At this point, it was evident that a significant difference did, indeed, exist between product A capsules and Chloromycetin capsules, Parke, Davis.

The final clinical study, designated on the charts as Study III, was initiated to compare additional chloramphenicol capsule products with Chloromycetin, Parke, Davis. This study was performed in a manner identical to that described in Study I and Study II above. However, to improve the statistical significance of the study, 10 normal subjects were used per product in Study III.

Samples of Chloromycetin capsules, Parke, Davis, and product A different batches, were again obtained from pharmacy stocks on the open market. Also, samples of product B and C, in commercial distribution by two other companies, were obtained as above. Chart 9—and, Mr. Chairman, chart 9, for your convenience, is displayed over on your left. Number 5 you can see that product A and particularly product C showed very different dissolution rates as compared to Chloromycetin, the product depicted on the left.

Senator NELSON. Did product A meet FDA standards?

Dr. LUECK. Yes, sir; so far as we know, all of the products tested in these studies met the requirements of the antibiotic regulations or the laboratory tests of the antibiotic regulations.

Senator NELSON. Is this a case where the FDA set the standard and USP adopted it?

Dr. LUECK. No, sir.

Senator NELSON. Does the USP have a different standard from FDA?

Dr. LUECK. No, sir; in this case, this is a certifiable antibiotic and the standards that prevail are the ones included in the Federal regulations on the antibiotic regulations. They supersede the USP.

Senator NELSON. That is what I said, the USP simply accepts the FDA standards.

Dr. LUECK. Yes.

Senator NELSON. This is not a case, then, of the USP establishing a standard itself?

Dr. LUECK. No, sir.

Senator NELSON. When did the patient expire on Chloromycetin?

Dr. LUECK. The patent expired October 1966.

Senator NELSON. October 1966?

Dr. LUECK. Yes, sir.

Senator NELSON. Did any representatives of Parke, Davis participate with the FDA in setting the standards to be met?

Dr. LUECK. Yes, sir; initially, when Chloromycetin was approved for marketing, the standards were established on the basis of information submitted by Parke, Davis & Co., to the Food and Drug Administration. They, through the years, have been improved and changed, but standards were set largely on Parke, Davis information, corroborated by the Food and Drug Administration.

Senator NELSON. At the time the patient expired and the FDA set

the standards, did any representative of Parke, Davis participate with the FDA in establishing these standards?

Dr. LUECK. No, sir; they did not change at that time.

Senator NELSON. What do you mean?

Dr. LUECK. There was no change in standards at the time the patent expired.

Senator NELSON. In other words, the FDA accepted the standards that had been established at the time the New Drug Application was approved for Chloromycetin?

Dr. LUECK. Yes, sir; Mr. Chairman.

Senator NELSON. What year was that, about 1949?

Dr. LUECK. 1949, but I wish to point out again that those standards have changed through the years and improved since 1949.

Senator NELSON. And did FDA adopt the improved standards?

Dr. LUECK. Yes.

Senator NELSON. And was your company aware that the standards adopted by FDA would not produce a product that measured up to Parke, Davis' Chloromycetin?

Dr. LUECK. No, sir. At that time we were not in any position to render that judgment at all, except to say, Mr. Chairman, that it has been our policy for many years that one can't rely on laboratory tests to ascertain therapeutic efficacy. This is the case in question, I think, of extreme interest to you and your subcommittee, whether laboratory testing alone can suffice to guarantee clinical effectiveness. In all cases, it certainly can't.

Senator NELSON. I do not think anybody disagrees with the proposition that two drugs which meet USP standards do not always produce equivalent therapeutic results. I do not think anybody before our committee has asserted that it would in all cases. What is at issue here is that there are exceptions. Is that not the case? And out of these rare exceptions, the manufacturers like to make the rule.

Dr. LUECK. I do not know if these exceptions are rare exceptions, Mr. Chairman. Exceptions come to our attention and they have come to my attention in Parke, Davis & Co. When we are in the process of researching a new compound, we have seen differences that we can create in the laboratory and we are cognizant of those differences. I do not know if these exceptions are rare.

Senator NELSON. Well, the assertion by Dr. Miller of USP is that it is rare. The assertion by Dr. Feldmann, of the National Formulary, your classmate at the University of Wisconsin, is that they are rare. The assertion of Dr. Modell, a very distinguished pharmacologist and M.D., is that they are rare. The assertion by many witnesses before this committee who are highly distinguished doctors, researchers, and professors, is that they are rare. Dr. Miller's assertion is that there are perhaps 15 or 18 cases known in all of the United States, versus all the drugs on the market where a drug meets USP standards and does not produce therapeutically equivalent results. And this happens to be one of them. And this is a case that does not include USP standards. If there is any fault, it is FDA in this case.

But you are talking about a drug whose patent expired in 1966 and you are able to select this one case to add to a list that involves 15 or 16

drugs in the whole history of the business so far as anybody has been able to prove. On each occasion, we have had witnesses before the committee from the industry, we have asked for examples of cases where USP standards were met, but the drugs did not have therapeutic equivalency, and the industry has not produced them.

Now, they can produce all kinds of cases where there was bad quality control and the product on the market did not meet USP standards and therefore was not therapeutically equivalent. But it is a rare case so far as this committee can find out, where drugs meet USP standards, but are not equivalent. That is the crux of the whole matter.

As a matter of fact, I am sure you are aware that every formulary in America, both in public programs and private hospitals is based upon the assumption that if drugs meet USP standards, they are therapeutically equivalent. As I am sure you are aware from the testimony in the record, time after time when we asked doctors who practice in hospitals using a formulary, whether the generics included in the formulary produce results equivalent to the brand names, the answer was "Yes, they do."

So what you are arguing against here is the common practice in the whole of the medical profession in the finest of the hospitals in America where formularies are used on the assumption that if drugs meet USP standards, they are equivalent and experience has demonstrated that they are.

Yet the industry has come in today and said, "Well, we have a case here where the standards are met but the generic is not equivalent. There is a problem with this drug, in part because it just came off patent." Your company had the patent and the exclusive control over the production, marketing, and use of this drug for 17 years. When it came on the market, FDA established a standard which your tests prove to be inadequate. But then to proceed, as the industry does, to propagandize the idea that, on the basis of one example, you cannot trust legal standards, seems to me to be a very weak case, frankly. I have said this to every witness who has appeared.

Mr. CUTLER. Mr. Chairman, the next witness, Dr. Slesser, is prepared to testify on the frequency of the occasions in which drugs that contain the same active ingredients have been scientifically demonstrated not to be therapeutically equivalent, and the fact that USP itself specifically disclaims that meeting its standards results in therapeutic equivalency. They specifically deny that in the beginning of their own book.

Dr. Lueck is prepared to testify about chloramphenicol. If we could have Dr. Slesser then discuss with you the frequency with which these occurrences take place I think that might be more orderly.

Mr. GORDON. But, Mr. Cutler, although Dr. Lueck is discussing chloramphenicol, he is drawing broad conclusions, from this one case only.

One other thing, Dr. Lueck, is it not also correct that a patent on the process expired only in July of 1967, only a few months ago.

Dr. LUECK. I can't be sure of that, Mr. Gordon.

Mr. GORDON. Well, the Pink Sheet recently made a statement to the effect that many firms would be unable to manufacture Chloromycetin

because a very important process patent does not expire until July 1967. I was just wondering if you have any information on that.

Dr. LUECK. I do know this, that it was, in terms of patent rights, legally possible for other companies to market and distribute chloramphenicol in the United States from about October 4, 1966.

Mr. GORDON. But not if they needed the important process that you were using and had patented, and which expired, as I understand it, only a few months ago.

Dr. LUECK. I think that chloramphenicol could have been produced by a procedure, chemical synthesis that would produce a certifiable product as soon as the patent on chloramphenicol itself ran out in October 1966.

Senator NELSON. What was that?

Dr. LUECK. I think that other companies legally could produce chloramphenicol and distribute it in the United States as far as any patent rights were concerned——

Senator NELSON. So far as any what?

Dr. LUECK. Patent rights were concerned. They would, of course, have to have, to be legal, the approval of the Food and Drug Administration and the FDA would have to certify them batch by batch.

Senator NELSON. What did your Chloromycetin patent protect, then?

Dr. LUECK. It protected the product, the fundamental scientific discovery of chloramphenicol as a chemical entity and therapeutic agent.

Senator NELSON. But you are saying chloramphenicol could have been produced by anybody despite the patent?

Dr. LUECK. No; only after October 4, 1966, after the patent ran out, Mr. Chairman.

Senator NELSON. We will take this up when Dr. Slesser appears. I will just read one sentence on this question of USP standards and then submit it for the record in its entirety.

Dr. Miller, in a statement dated November 29, 1967, states:

> We are aware of six proven cases of clinical difficulties with drug products which did or could have met U.S.P. standards. * * * Of these proven cases, one involves a product believed to have been distributed only in Canada.

(The material referred to follows:)

STATEMENT BY DR. LLOYD C. MILLER, DIRECTOR OF REVISION, OF THE U.S. PHARMACOPEIA, NEW YORK CITY, NOVEMBER 29, 1967

The current U.S. Pharmacopeia lists about 900 drug substances or products prepared from them all for which suitable tests and standards are provided. The standards are sometimes questioned as being insufficient to insure that the products will give the full therapeutic effects expected of them.

We dealt with this topic with a statement made to your subcommittee on June 27, but perhaps too briefly out of a desire to save time. Some specific supplementary comments may therefore be in order at this time.

We are aware of six proven cases of clinical difficulties with drug products which did or could have met the U.S.P. standards. These are:

Item:	*Approximate date of discovery of problem*
Thyroid tablets	Prior to 1940
Bishydroxycoumarin tablets	1957
Spiromolactone tablets	1960
Aspirin coated tablets	1960
Prednisone tablets	1962
Diphenylhydantoin tablets	1967

Of these proven cases, one involves a product believed to have been distributed only in Canada—namely Bishydroxycoumarin by Charles Frosst and Company. Even counting this case in, however, the "deficiency ratio" is six in 900 or less than 0.7%.

It is U.S.P. policy to correct at once every form in inadequacy that is possible with the scientific information available. The U.S.P. Revision Committee is responsible for putting this policy into effect. The Committee consists of 60 members, each an expert in his own field. The members charged with the revision of standards are mostly chemists who are associated with pharmacy schools or pharmaceutical firms. At present, the number in each group is 17 and 12 respectively.

It should be stressed that regardless of the nature of his bread-winning job, each member serves as an individual, not as a representative of his school or firm. The members consult other experts widely. For example, as a matter of long-standing policy no F.D.A. staff members serve on the U.S.P. Committee. However, the closest sort of cooperation exists between the F.D.A. and the U.S.P., so the progress on drug standards is shared early and fully. In fact, Arthur F. Flemming, speaking as Secretary of the Department of Health, Education, and Welfare, observed in 1960, "I do not know of any organization that has a more interesting and significant relationship to the government of the United States than your organization."

The same relationship exists with scientists within the industry. Avenues of contact with industries are kept open in many directions. It is always possible that thoe who produced the drugs will discover better ways of testing them. Although the U.S.P. standards are generally regarded as being the highest in the world, they are also looked upon as subject to improvement as technical advances from it. A good example is that of the standards for thyriod tablets which, as indicated above, have been known to be deficient for years. These standards are about to be made as exacting as those for any other drugs through the application of findings made in the last few months and not yet published.

In summary, U.S.P. standards form the bedrock upon which the quality of American drugs rest. But like any foundation, the standards can be made broader and stronger as science progresses.

We trust that these comments will be helpful.

Senator NELSON. In any event, the insistence by USP and others is that there are rare cases where although these standards are met a drug may be produced that is not therapeutically equivalent. Everybody knows that you can coat a tablet so that it does not have any effect at all, even if you have the same active ingredients and the same excipients. But then it would not be within the USP standards. If USP set a standard that didn't guarantee absorption, they would correct it just as soon as the knowledge was available.

Dr. LUECK. Mr. Chairman, I respect the gentlemen you mentioned, Dr. Miller, Dr. Feldmann, Dr. Modell. But I believe there is quite an element of opinion in their statements. Now, I respect their opinion, but I think that to prove the opposite, the products must be tested side by side to prove the affirmative as well as prove the negative.

The fact is that there is an appreciable amount of information showing that products that meet certain chemical standards are not equivalent, and Dr. Slesser will cover that point; it is a long, laborious process to compare products.

For example, the study that we are engaged in presenting right now, Mr. Chairman, required something like 8,000 analytical tests just for this small study.

Senator NELSON. You say Dr. Slesser is going to address himself to this precise question?

Dr. LUECK. Yes, and provide additional information in that area.

Senator NELSON. I know he did from his prepared testimony, but

yours covers the same area. That is the reason I raised the question to you.

Dr. LUECK. Yes.

Senator NELSON. All right, go ahead.

Dr. LUECK. The results of the blood plasma level tests, both chemical and microbiological, are shown in charts 10 and 11.

May we have chart 10?

Mr. Chairman, this chart refers to plasma levels as determined by the colormetric clinical test for Chloromycetin, product A, product B, and product C. In a glance at the chart, it is readily discernible that differences between these plasma levels, resulting from the administration of the respective products, are quite different.

May we have chart 11, please?

Chart 11 depicts the blood levels as determined by the microbiological analytical technique and we see again that appreciable differences are noted between the products, and these results compare very favorably with the colormetric analytical results and corroborate the fact that the testing procedure is being followed accurately.

Now, the results of the urinary excretion rate tests are shown in chart 13.

May we have chart 13, please?

It again can be seen that there is a significant variation between the products. I would like to point out that the official package insert for all these products reads that 70 to 90 percent of the drug should be excreted in the urine over a 24-hour period. That 70 to 90 percent is depicted in the crosshatch area at the top of the figure. You can please note that Chloromycetin is the only product that reached those levels in this test.

Now, our clinical consultants believe that the difference shown in Studies I, II, and III would be very significant in the treatment of infectious diseases. The higher and earlier blood plasma levels produced by Chloromycetin capsules, Parke, Davis indicates that more rapid and thorough absorption of the dose occurred than with the competitive chloramphenicol capsules. Indeed, the blood plasma levels indicated for products A and B are low and product C is disturbingly low. Their clinical efficacy is open to question.

The total urinary excretion of chloramphenicol and its metabolites was shown by the studies to be substantially less for the competitive chloramphenicol capsule products than that demonstrated by Chloromycetin capsules, Parke, Davis. The Food and Drug Administration approved labeling for all the chloramphenicol capsule products indicates that the chloramphenicol dosage should be absorbed into the human body so that 70 to 90 percent of the drug is excreted by the kidneys within 24 hours. It is evident from the urinary excretion data in chart 13 that none of the other companies' chloramphenicol capsules reached the proper degree of excretion as prescribed in the package insert which accompanies the drug. They all are below the labeled limits of 70 to 90 percent.

It must be emphasized that when a physician prescribes an antibiotic to be administered orally, he must assume that the drug will be absorbed rapidly and thoroughly from the product into the blood stream. A product which does not meet the above criteria may impair the recovery of a patient.

In conclusion, it is evident that information obtained by laboratory and clinical studies is essential in determining the absorption, dosage range, duration of action, excretion rate, and so forth, of a drug. To put it another way, a manufacturer should not have the right to simply copy another company's package insert for a product which has been carefully studied in the clinic by the originator and then imply that the two drugs are therapeutically equivalent merely because his product meets the minimum U.S.P. and FDA laboratory test requirements.

We believe we have demonstrated that laboratory tests alone which indicate that certain drugs contain similar chemical ingredients provide no assurance that these drugs will behave in the same way in the human body. Thus, we have confirmed what experts have repeatedly said, that chemical similarity is not necessarily indicative of therapeutic equivalency.

Thank you, Mr. Chairman. That concludes my formal statement.

(The charts attached to Dr. Lueck's supplemental statement follow:)

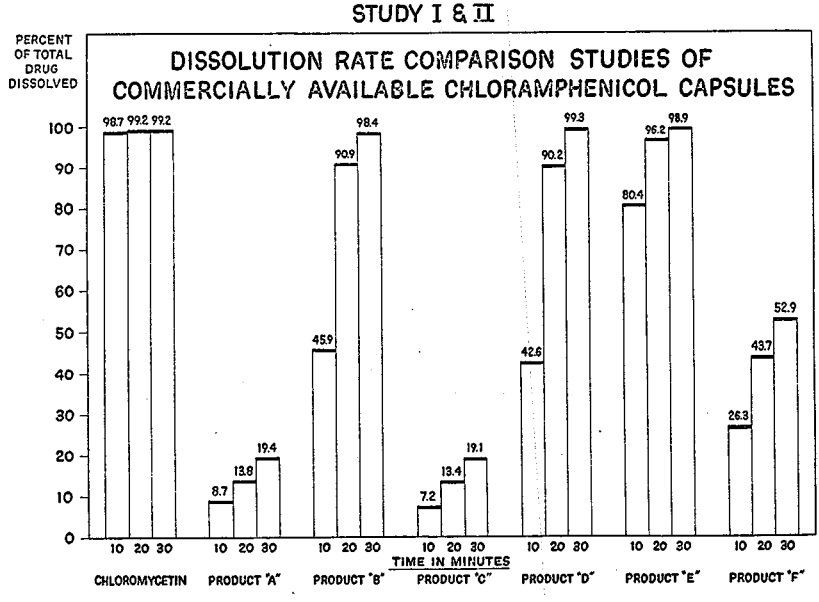


CHART 1

STUDY I

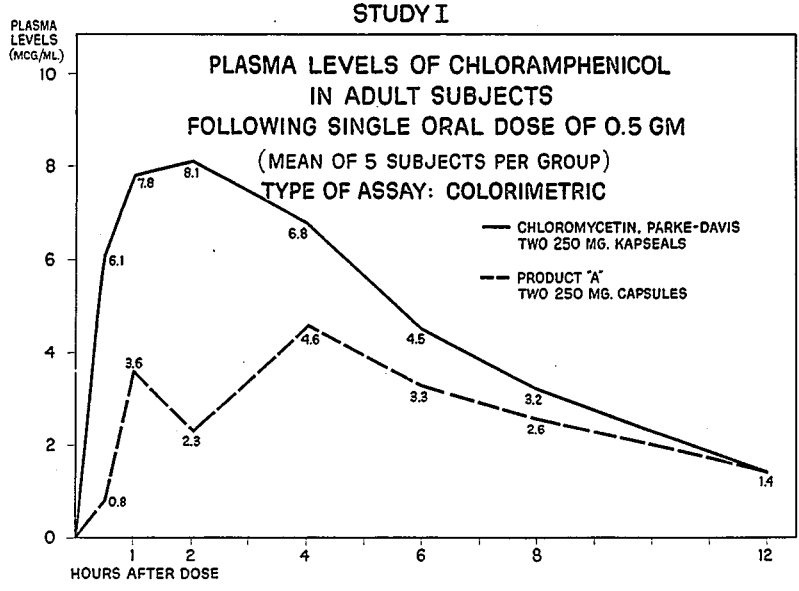
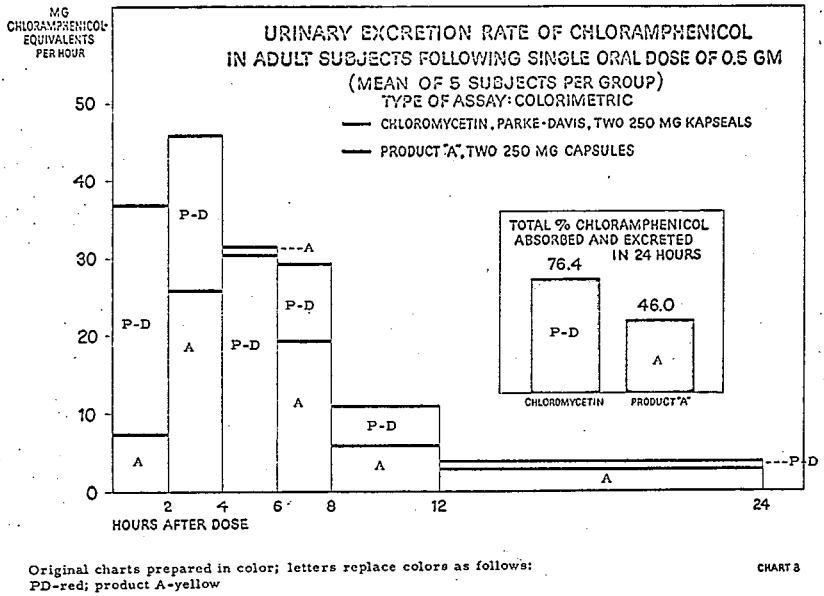


CHART 2

STUDY I



Original charts prepared in color; letters replace colors as follows: PD-red; product A-yellow

CHART 3

STUDY I

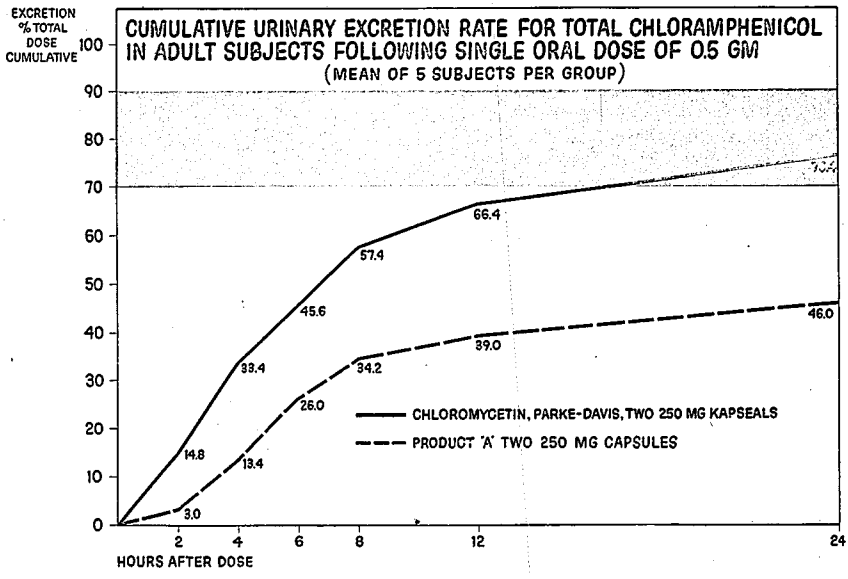


CHART 4

STUDY II

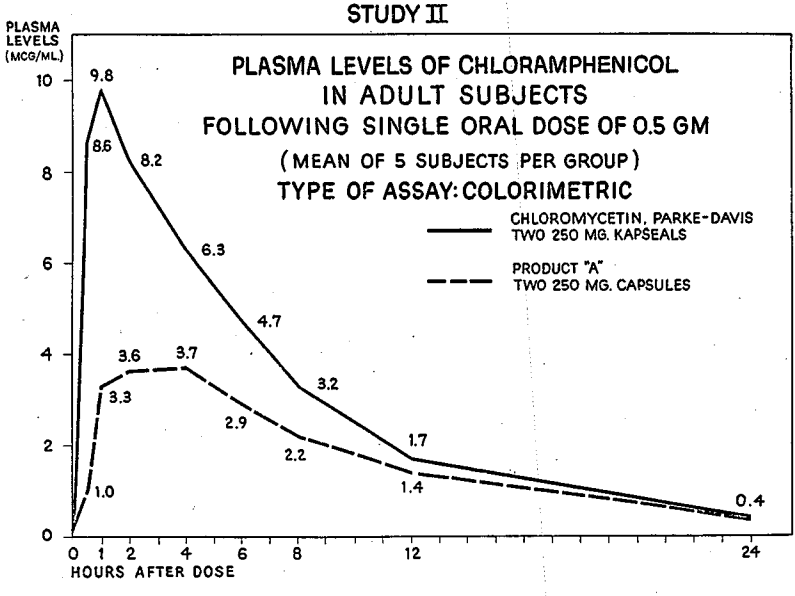


CHART 5

STUDY II

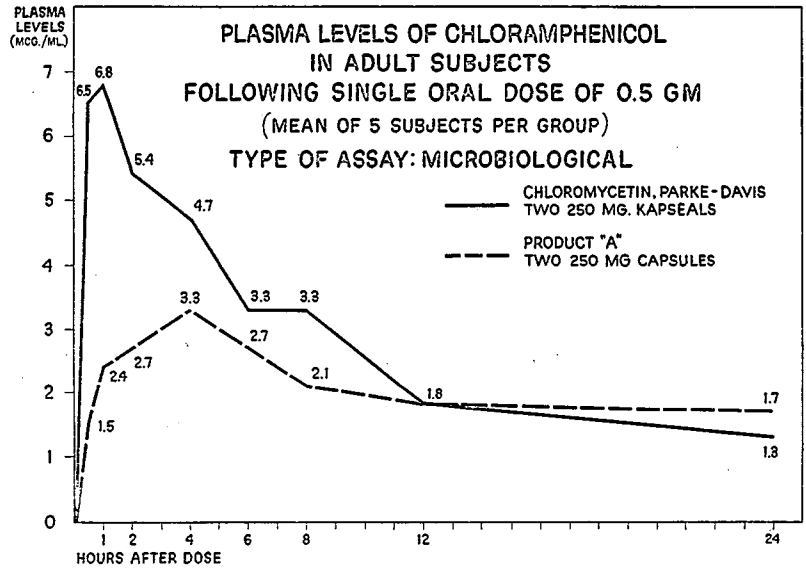
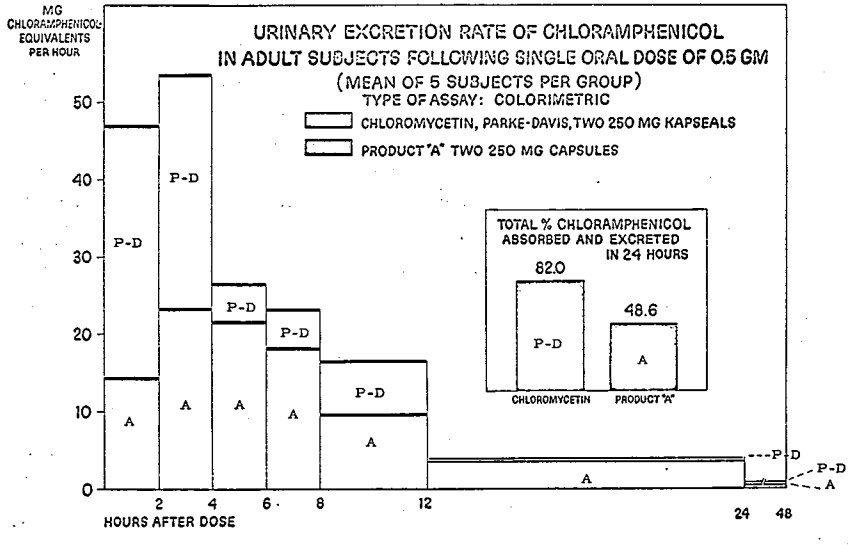


CHART 6

STUDY II



Original chart prepared in color; letters replace colors as follows: PD-red; product A-yellow.

CHART 7

STUDY II

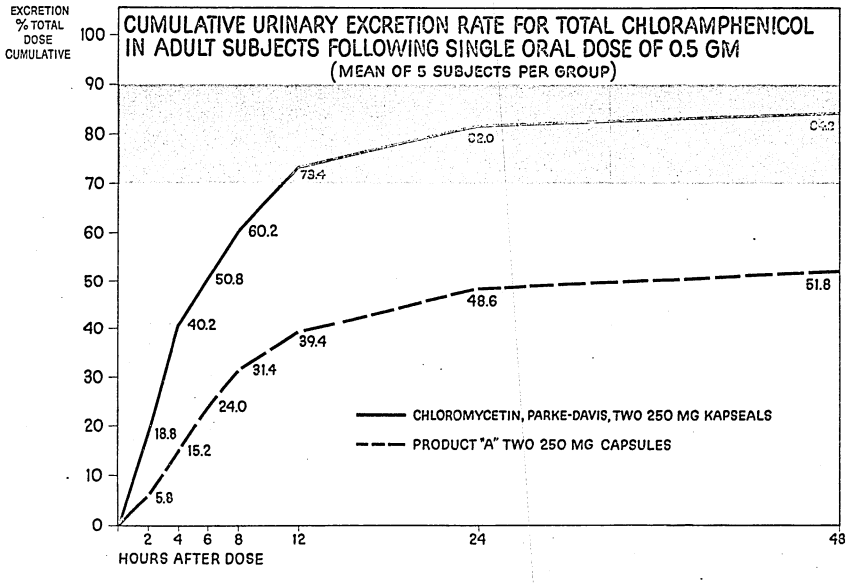


CHART 8

STUDY III

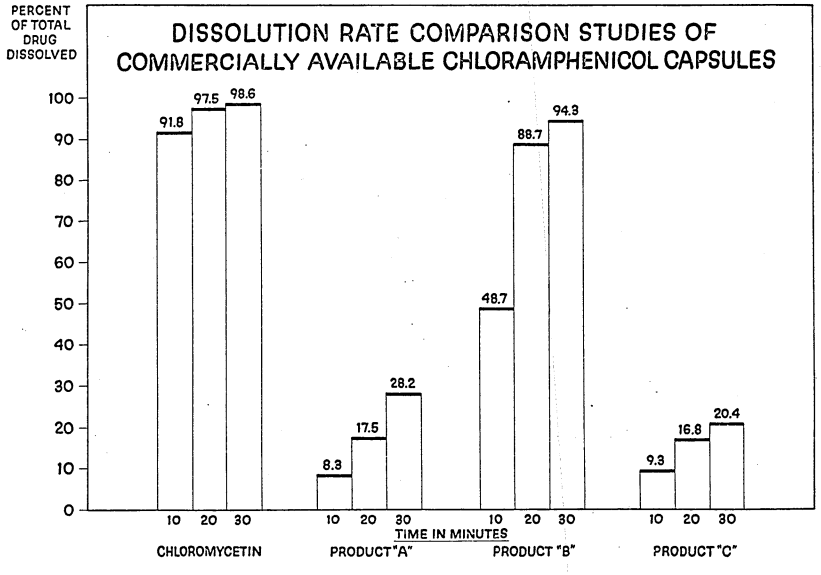


CHART 9

STUDY III

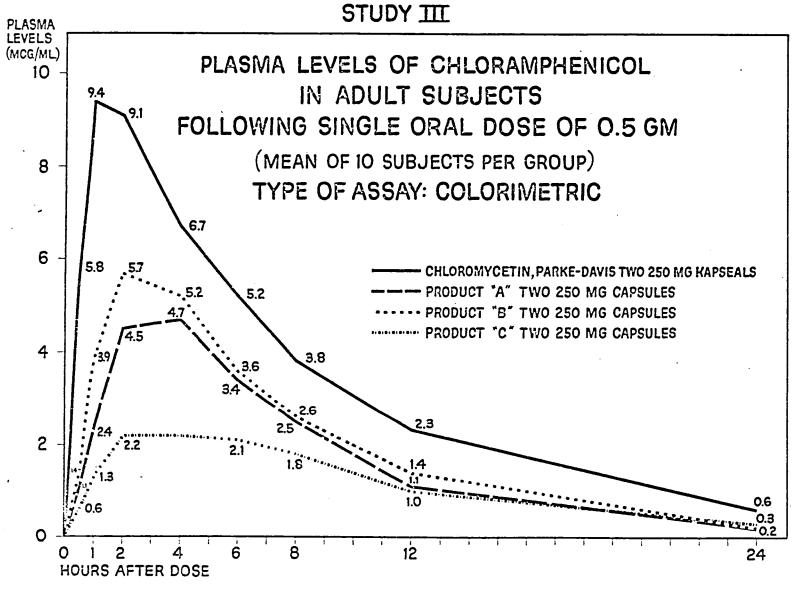


CHART 10

STUDY III

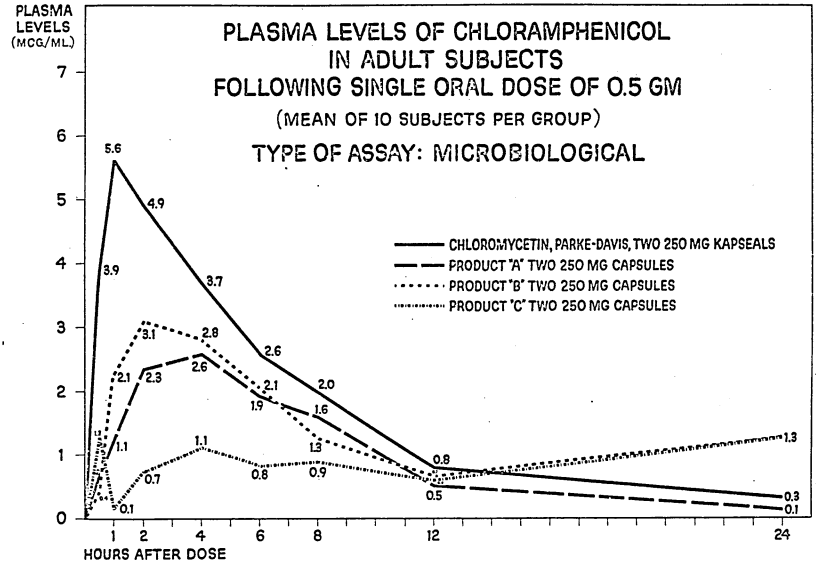
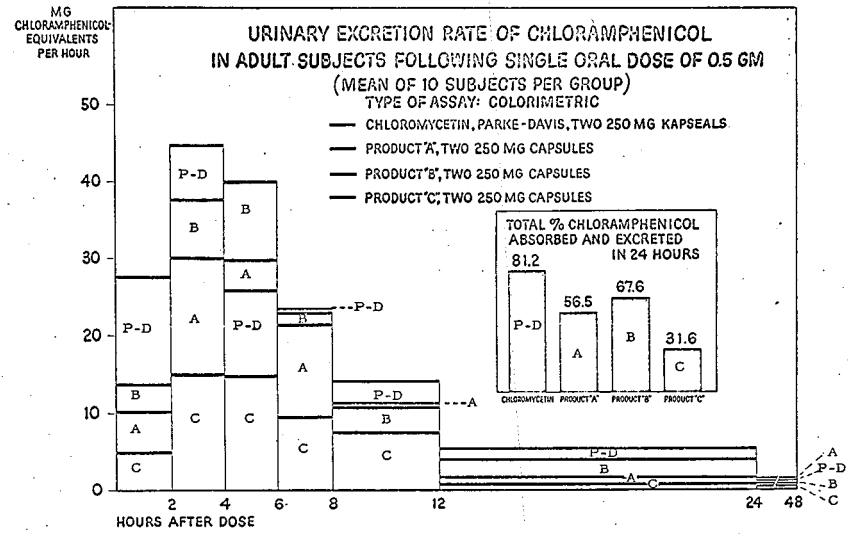


CHART 11

STUDY III



Original charts prepared in color; letters replace colors as follows: PD-red; product A-yellow; product B-blue; product C-green.

CHART 12

STUDY III

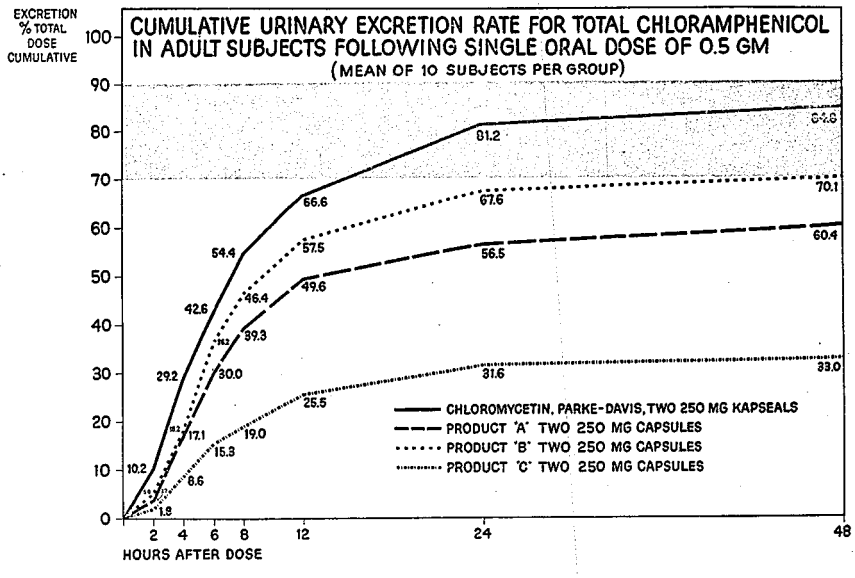


CHART 13

Senator NELSON. Let me comment on your last statement:

Thus we have confirmed what experts have repeatedly said, that chemical similarity is not necessarily indicative of therapeutic equivalency.

I have never heard of anybody saying that it is. The statement is really, I think, Doctor, quite meaningless. Nobody says that. That is not the argument. The argument is, as you said earlier, whether or not in almost all cases, with a rare exception, if USP standards are met, the drugs are therapeutically equivalent. That is what the issue is.

Now, Parke, Davis, which is the manufacturer of Chloromycetin, has had on the Committee on Revisions of the USP, Mr. F. O. Taylor, from 1950–1960——

Dr. LUECK. Yes, sir.

Senator NELSON. And Mr. Marina from 1960 to date, is that correct?

Dr. LUECK. Yes, sir.

Senator NELSON. Now, when the USP adopted FDA standards, did these representatives of Parke, Davis give them the benefit of their advice as to what standards had to be set in order to produce a therapeutically equivalent or effective drug?

Dr. LUECK. I would like to comment on two things, with your permission, Mr. Chairman.

I would like to state for the record that Parke, Davis & Co. feel that the USP and NF and the FDA antibiotic regulations are the strongest standards in the world.

Senator NELSON. Every witness from every company has agreed with that.

Dr. LUECK. I would like to go on to say that this is evidenced by the distinguished people who have spent their entire careers in Parke, Davis who have contributed to the USP and NF over the years and who will continue to do so.

I would like to point out, though, for the chairman, that Chloromycetin or chloramphenicol is an antibiotic, Mr. Chairman, and is therefore not covered in the standards in the U.S.P. It is covered in the antibiotic regulations. The antibiotic regulations cover chloramphenicol.

Senator NELSON. I understand. Correct me if I am wrong about this: Does not the USP adopt, then, the FDA standards?

Dr. LUECK. No; they generally——

Senator NELSON. Or do they just do nothing about it?

Dr. LUECK. No; they just list the monograph, and in a few moments, I will find it. They just list the monograph in the USP and mention that this is under the antibiotic regulations. So Chloromycetin or chloramphenicol is not controlled by the monograph in the USP. It is controlled standardwise by the antibiotic regulations.

I would read from, Mr. Chairman, if you please, from the rubric of the USP on chloramphenicol, page 114:

Chloramphenicol contains not less than 90 percent—

It gives the clinical formula:

It conforms to the regulations of the Federal Food and Drug Administration concerning antibiotic drugs. See Antibiotics, page 768.

So it refers entirely to the standards in the antibiotic regulations.

Senator NELSON. In this case, you had both a product patent and a process patent, is that correct?

Dr. LUECK. I am sorry, I cannot comment on the process patent with certainty at the moment.

Senator NELSON. I am reading from the Pink Sheet, April 25, 1966:

Parke, Davis Chairman Harry Loynd at April 19 stockholders meeting predicted another $70 million Chloromycetin year for 1966 despite the expiration in October of the product patent, the first basic one on the drug. Even after October, it will be illegal for anyone to manufacture Chloromycetin in the U.S. A key process patent doesn't expire until July, 1967.

Is that an accurate statement from the Pink Sheet?

Dr. LUECK. I would have to presume, Mr. Chairman, that it is an accurate statement.

Senator NELSON. So the record is clear, we have a case here which does not involve standards set by the U.S. Pharmacopeia at all.

Dr. LUECK. Yes, sir.

Senator NELSON. We have a case here in which the FDA set the standards under law.

Dr. LUECK. Yes, sir.

Senator NELSON. Do you know whether or not your experts from Parke, Davis were consulted by FDA as to what those standards ought to be?

Dr. LUECK. Yes, sir.

Senator NELSON. And they agreed with the standards that the FDA established?

Dr. LUECK. Well, the normal procedure, Mr. Chairman, was followed in the case of Chloromycetin, where the drug was discovered and researched and our information supplied to the Food and Drug Administration requesting permission to distribute the product for certain medicinal needs.

Senator NELSON. No; I mean when the patent ran out.

Dr. LUECK. Oh, no; when the patent ran out, there was no communication between Parke, Davis and the Food and Drug Administration on changing standards.

Senator NELSON. Did the FDA then just adopt the standards that had been agreed upon between the FDA and Parke, Davis up until the expiration of the patent?

Dr. LUECK. Yes; the same standards that applied before the patent ran out still applied after the patent ran out. They still prevail.

Senator NELSON. Were the experts in Parke, Davis aware that if only those standards were met, the drug manufactured by another firm would not be therapeutically effective?

Dr. LUECK. No, sir; we were not. We were only aware of the therapeutic equivalency of our own product.

Senator NELSON. Therapeutic effectiveness, you mean?

Dr. LUECK. That is right.

Senator NELSON. Because you did not have any equivalency test.

Dr. LUECK. I am sorry, I used the wrong word. Thank you for correcting me.

Senator NELSON. So even the best experts in Parke, Davis that had been manufacturing this drug on an exclusive basis for 17 years did

not know that the standards adopted by the FDA would not produce a therapeutically effective drug.

Dr. LUECK. We are not aware of any laboratory standards, Mr. Chairman, that will beyond any reasonable doubt, determine the therapeutic equivalency or therapeutic effectiveness of the drug. This is the point in question, that you cannot rely on laboratory standards to do this job for you.

Senator NELSON. But you did not know that the standards set would not do the job?

Dr. LUECK. No; by means of the standards set in the antibiotic regulations, plus the care and experience that Parke, Davis & Co. had with chloramphenicol and Chloromycetin, and based on our clinical experience, we maintained a product of excellent quality through the years. We had in the United States no means or no way of comparing Chloromycetin to another product.

Senator NELSON. I am still getting at the point that your experts did not know that the standards established were not sufficient to duplicate the same therapeutic effectiveness in chloramphenicol that Parke, Davis produced in theirs; is that correct?

Dr. LUECK. That is correct, and we do not know of any laboratory standards at this moment, Mr. Chairman, that would provide that information for Chloromycetin that was not proven in the clinic.

Senator NELSON. There is another rollcall on the Senate floor.

(Short recess.)

Senator NELSON. I apologize for the interruption.

As I understand your last statement, it was that, in your view, a company should not be permitted simply to copy the drug of another company and put it on the market without performing additional clinical tests.

Dr. LUECK. Mr. Chairman, I could probably clear up a few questions that you might have by just very briefly reviewing the information that Parke, Davis & Co. submitted to the Food and Drug Administration. I can do that very briefly and this may answer some fo your questions.

Senator NELSON. Very well.

Dr. LUECK. Back in 1947, 1948, and 1949, when Chloromycetin was first discovered and researched, of course, Parke, Davis & Co. submitted to the Food and Drug Administration clinical evidence of its safety and effectiveness. Tests were adopted at that time by the Food and Drug Administration to form the basis of a New Drug Application. The approval of the New Drug Application was on the basis of clinical effectiveness and adequate controls to maintain quality of the product in Parke, Davis' manufacturing facilities.

Now, to illustrate further, in 1964, Parke, Davis & Co. changed the synthetic process for manufacturing Chloromycetin and at that time, we were requested by the Food and Drug Administration to run animal tests, human tests, and chemical tests to verify the safety and efficacy of our product. We did all of these things at extreme lengths so that Chloromycetin has been of excellent quality at all times through the years. The controls established for Chloromycetin have been based on studies in human subjects, that the drug is effective.

Now, in 1966, when the introduction of competitive products to Chloromycetin was imminent, Parke, Davis & Co. suggested to the

Food and Drug Administration that before those products entered distribution in the United States, they, too, should be tested in the clinic, in human subjects.

So we did correspond with the Food and Drug Administration in 1966 relative to effectiveness of possible competitive products, but there were no changes made in the specification or the standards for the antibiotic at that time.

Senator NELSON. If a company licenses another company to produce its product, does the licensee have to do clinical testing before it can put the product on the market?

Dr. LUECK. Frequently, yes.

Senator NELSON. Do they always have to?

Dr. LUECK. It would depend upon the situation, what was licensed. If it were just the license of a procedure, a chemical synthesis, for example, Mr. Chairman, to be followed, it would be necessary, in our opinion, to do clinical testing to make certain that the proper controls were placed on that chemical procedure.

Now, if the company who owned the effective New Drug Application produced the product, it could be assumed that they would produce the same quality product. In other words, if you sold the bulk chemical to the next company, it could be assumed that clinical testing was not required. But if the chemical process was moved to another operation, conducted by other people, other technicians, then efficacy should be proven, in our opinion, in human subjects. This is what Parke, Davis did with Chloromycetin.

Senator NELSON. So that I understand you correctly, you are saying that if the bulk chemical itself were produced by the licensee holder of the New Drug Application, the firm who is granted the New Drug Application, and it licenses company A to produce the product and furnishes company A with the bulk product, this licensee may produce the tablet without conducting its own clinical testing?

Dr. LUECK. No; I think I misled you slightly. It would not be necessary, in my opinion, to check the quality measures of the synthetic process. But in my opinion, it would be necessary to check the efficacy of the product form produced by the licensee if there indeed was any difference.

Now, I would have to perhaps explain that a little further. The bulk chemical—suppose it was placed into a capsule with other diluent materials and so forth, it would be necessary, in my opinion, then, to perform sufficient clinical trials to prove that that product form, that capsule, was clinically effective.

Senator NELSON. The present law?

Dr. LUECK. It is up to the Food and Drug Administration, Mr. Chairman, to make that decision.

Senator NELSON. Is it ever the practice for the company that has been granted the New Drug Application to license other companies and furnish them with all the information they have concerning the method of production? Is that a common practice?

Dr. LUECK. It is my understanding that that has been done. I would like to remind the chairman that my concern in Parke, Davis & Co. does not include that area of our business and I am not the most familiar with it. But it is my understanding that arrangements like that have been made in the pharmaceutical industry.

Senator NELSON. Do you have somebody here who can address himself to that point?

Dr. LUECK. I think we have members of the panel who can.

Senator NELSON. Who here could answer my question?

Mr. CUTLER. Mr. Chairman, I do not think we have anyone here who can answer that question for a variety of companies, but we can certainly try to get you the answer.

Senator NELSON. Is there anybody here who can answer it for any company as to what the law requires, and as to whether it is a practice that is followed by the industry at all.

Mr. CUTLER. I think I can answer as to the law, Mr. Chairman. There is nothing in the Food and Drug law or the patent law that would prohibit one company from turning all of its manufacturing and know-how information over to another company. It would then be up to the Food and Drug Administration, under the law, assuming the product is a new drug, to determine what evidence would be required from the second company.

Senator NELSON. Is there any reason at all why, after a patent has been granted by the public to a company for 17 years, that at the conclusion of the 17 years, all the processes, methods, and benefits accumulated by that company from its experience and public protection for 17 years should not be turned over to the FDA and then made a matter of public information?

Mr. CUTLER. Well, I believe all of the company's processing information is turned over to the FDA to the extent the FDA requires it. And, of course, all of the information that the company was required to disclose in order to obtain the patent is published in the patent itself.

Dr. LUECK. I would like to comment if I may——

Senator NELSON. But all the processes, I understand, are not.

Mr. CUTLER. If it is a process patent—well, there is no proprietary know-how not subject to patent that is kept by companies, by individual companies, each for itself. But the information on which the patent was granted is, of course, published.

Senator NELSON. What I am getting at is that the testimony repeatedly heard from representatives of the industry is that even if you include the same active ingredients, maybe even if you include the same inert ingredients, even if you do all kinds of things the same way chemically, you may not get the same result.

Mr. CUTLER. Right.

Senator NELSON. What I am saying is, as a matter of public policy, we could pass legislation to require the publication of all relevant production information. The American people have said, in order to encourage discovery, research, they will protect the patentable item in this field for 17 years. I do not have any reason to quarrel with this policy. I think it has produced some good results.

Now, once the 17-year period has expired and the company is dealing with a product which directly affects the public health, should not all the information on how they produce the product be made available to any other company so that any firm, once the patent period is over, will be able to use the same processes and duplicate the drug if they wish?

Mr. CUTLER. You are raising, Mr. Chairman, a fundamental issue of patent law; that is whether the information disclosed and published in the patent is sufficient to confer the monopoly granted by the patent or whether the inventor should be compelled to disclose a lot of additional information in order to get his patent.

It is an awfully complicated question and the job of the Patent Office is to see that the information disclosed is sufficient so that the benefits of the discovery will become available to the public after the monopoly period has expired.

Senator NELSON. But the argument here is that a particular company in such a case does some things better than anybody else does them. All I am saying is that after 17 years of protection, why should not, for example, the FDA make public all the information on the production of that product, and say to a firm, "If you want to produce this drug, following exactly the procedures followed by X company that has had 17 years of experience, 17 years to make back its investment and make a profit, we will furnish you all the production information, and you can go out on the market without further clinical testing. If, however, you want to do some additional experimenting, maybe to refine the product, try to improve the product, then you have to do clinical testing because we do not know what the result may be." I am just asking, as a matter of policy, why should not that be the practice?

Mr. CUTLER. It seems to me it would be a much simpler policy to require the second company to do the clinical testing. The point we are trying to make here is that there are some 40 or 50 chloramphenicol products on the market——

Senator NELSON. What kind of products?

Mr. CUTLER. There are some 40 to 50 chloramphenicol products on the market today and judging by tests that Parke, Davis has conducted on three of those products in addition to its own clinical tests, the other products do not come up to the clinical effectiveness of the Parke, Davis product, Chloromycetin or, indeed, what is in their own labeling. It would be simple enough to require those companies to make the tests.

Senator NELSON. We know in this case, assuming your experiments are correct, that this is a case where the FDA standard is not adequate. I just repeat for the record that we have hundreds of cases of drugs on the market that meet the FDA or USP standards which are adequate to produce an effective drug. I am just saying why should not a company that has had the benefit of the protection of a patent for 17 years then make public all the information that would allow another company to exactly duplicate that drug.

Dr. LUECK. I would like to comment briefly in regard to Chloromycetin in answer to your question.

During the 17 years that Parke, Davis Co., was under the patent rights for Chloromycetin, some more than 14,000 references or articles appear in the scientific literature on Chloromycetin. The very tests that we used to gather the information presented here today have been published by Parke, Davis scientists a number of years ago for anyone to use. It is our firm belief that the literature contains such information and the total amount of information that Parke, Davis & Co. has,

except experience. We cannot give another company experience. And to gain experience, it is my firm belief that a fundamental thing that the company must do is clinically compare its product with the standard that is in existence. In this case, the standard was clearly Chloromycetin. They could either make the product better or at least, they have to make it at least as good.

Senator NELSON. Of course, you testified a while back that even though your own experts helped develop the standard that FDA adopted, they either did not know or did not disclose to the FDA a sufficient amount of information to make it possible to produce a drug that would be therapeutically effective.

Dr. LUECK. No, sir, Mr. Chairman; I wish to correct one point.

Parke, Davis & Co. made available to the Food and Drug Administration all the information that we have on Chloromycetin and chloramphenicol. We recommended that clinical testing of the competitive products should be carried out before those products were allowed to go into distribution.

Senator NELSON. I know you recommended that. But is it not true that if a company took all your best experience and produced this tablet, using the same ingredients you do and following your procedures exactly, the company could produce the exact same product.

Dr. LUECK. No, sir; apparently that is not the case with Chloromycetin, Mr. Chairman.

Senator NELSON. Has anybody exactly duplicated your tablet? You do not know what the problem is. It may be that the coating on that tablet does not dissolve rapidly enough. But, if the manufacturer had known your formula and followed it exactly, then he would be capable of producing anything your company can produce, given the information, would he not?

Dr. LUECK. I assume so if they do the proper testing. Yes; if they research the product——

Senator NELSON. No; if you furnish them all the information.

Dr. LUECK. If we furnish the information and produce the product, then I would stand behind that product as being similar. If they produce the product in a different procedure or different facility, even using the same procedure, then our products such as Chloromycetin, in our opinion, should be tested for clinical equivalence. As a matter of fact, we have to reject some of our own material that we manufacture, Mr. Chairman. We cannot manufacture this product perfectly each time ourselves.

Senator NELSON. That is correct. Neither would any other company.

Dr. LUECK. That is right.

Senator NELSON. But you are testifying that if the best experts you have in your company advised any other high quality, brand-name company as to exactly how you produced a drug, that the other firm could not duplicate your product? It that what you are saying?

Dr. LUECK. We have a prime example before us to answer that question, Mr. Chairman. In my opinion, when Parke, Davis changed the clinical process to produce Chloromycetin in 1964, we did exhaustive animal tests, we did exhaustive human tests in subjects with typhoid fever, comparing the old process with the new process. And we did not rely only on laboratory tests.

Mr. CUTLER. Senator, the point we are trying to make is that the second manufacturer may be able to do as well as the first, but that you cannot prove it is as good as the first without the chemical testing. And the fact is that these brands or products are on the market and that a generic prescription for chloramphenicol might have been filed with one of these other brands. That is the heart of the matter.

Senator NELSON. The heart of the matter is, as you know, that every formulary in America uses drugs which meet USP standards and then tests them out in the hospitals. They buy generic drugs and they buy brand names. They do not clinically test them before they use them and they have had good results with them.

Mr. CUTLER. They often change as a result of their own clinical experience.

Senator NELSON. Well, anybody might do that. You do it with your products or anybody else's product. That is not really the heart of the argument.

Dr. Harry Williams of Emory University, Atlanta, Ga., and Grady Hospital testified here that—

Prior to 1960, as I said, the hospital administration had watched its drug bill rise fairly steadily from $183,901 in 1935 to $470,000 in 1959. This rise could not be accounted for by an increase in prescriptions or patient care. The surveying drug purchase policies and prescribing habits at the hospital, the new formunary committee found that, except for a very few old drugs such as aspirin, drugs were being ordered by trade names rather than generic names; there were confusing duplications of drugs that had the same therapeutic action and that the pharmacy was in chaos attempting to keep multiple trade-name equivalents of the same drug in stock. In addition, the hospital was spending as much as $50,000 yearly for drugs which had no proved useful therapeutic action.

A few examples, many could be cited. The hospital was paying $167 per thousand—these were wholesale costs—for a trade-name cortisone-type drug when a comparable generic product could be bought for $6 per thousand.

I think this is prednisone, but I am not sure.

Anyway, $167 per thousand versus $6 per thousand.

Senator NELSON. Then you did change in your formulary to the comparable $6 per 1,000 generic drug; is that correct?

Dr. WILLIAMS. Yes, we did.

Senator NELSON. And have the physicians in the hospital observed any difference in the therapeutic effect of the $6 per 1,000 versus $167 per 1,000 drug?

Dr. WILLIAMS. None whatsoever.

Mr. CUTLER. Well, Mr. Chairman, even——

Senator NELSON. Let me finish:

Those of us who had veen vaguely aware that trade named items were more expensive than non-trade-named items were nonetheless appalled when trade named items were found, as shown by the examples above, to be in many cases 20 to 30 times as expensive as their generic equivalents. Not 2, 5, or 10 percent more as might be expected in other areas of commerce, but 2,000 to 3,000 percent more.

Now, the whole record is loaded with testimony from distinguished doctors who have worked in hospitals which use a formulary. Grady Hospital did not do clinical tests on this $6 a thousand drug versus the $167 product. They tested it chemically, if anything, to see if it met USP standards, they used it, and it worked. We have heard the same story from other witnesses as well. You would have to eliminate a part of every formulary in America if you were to follow your theory.

Mr. CUTLER. No, Mr. Chairman. In every one of those formularies from the Department of Defense on down, the hospital or procuring agent does not just say, "Give me prednisone, any old prednisone."

Senator NELSON. Nobody ever says, "Give me any old prednisone," certainly.

Mr. CUTLER. But in this committee, you are advocating that a doctor say on his prescription any old prednisone.

Senator NELSON. When did this committee say that?

Mr. CUTLER. Has not the thrust of this committee been that there should be generic prescribing?

Senator NELSON. I think you ought to read the testimony.

Mr. CUTLER. I have, sir.

Senator NELSON. Then you have not read it carefully. I have never said at any time, nor has anybody on this committee recommended, that a doctor prescribe any old prednisone. That is nonsense and you know it. We suggest that physicians ought to prescribe drugs of high quality. We suggest a doctor ought to prescribe by generic name and, if they want a brand name, that they should name the brand in addition.

The doctors who testified here have said one of the problems involved here is the confusion caused by prescribing by trade name and not putting the generic name on the label. We had testimony by a very distinguished doctor here on thalidomide who said that deformed children were born because of this poor method of prescribing. You know this is true.

Nobody suggests prescribing any prednisone. But I would suggest to you that the Medical Letter tested 22 prednisones. One of them is Schering's at $17.90. One of them is Merck's at $2.20. One of them sells at 59 cents. Another at 75 cents. The Medical Letter said they are all equivalent.

Mr. CUTLER. They said there was no proof that they are not equivalent.

Senator NELSON. That is correct.

Mr. CUTLER. Which is a double negative.

Senator NELSON. Do you have any proof they are not equivalent?

Mr. CUTLER. I do not; but you cannot prove a positive by a double negative.

Senator NELSON. If you were a doctor in a hospital, looking at the medical aspects of prescribing, looking at the cost of running a hospital, on what method would you make the decision that you would use a drug that costs $17.90 versus Merck's $2.20 tablet?

Mr. CUTLER. If I were satisfied there were two products that were therapeuticaly substantially equivalent, I would prescribe the cheaper one.

Senator NELSON. How would you satisfy yourself on that?

Mr. CUTLER. I am a lawyer, but doctors, I understand, do it on the basis of their experience. When there are hospital formularies or

Department of Defense formularies, they supplement that by the laboratory clinical tests of the entire medical organization.

Senator NELSON. In order to make the selection in the first place, unless they have some clinical evidence to go on, and in many instances they do not, they go on the assumption that if it meets USP standards it is therapeutically equivalent. That is the testimony before this committee.

Mr. CUTLER. The USP says right in its own introduction that meeting USP standards does not assure pharmacological availability, which, as I understand it, is therapeutic equivalence.

Senator NELSON. Dr. Miller of the USP on page 508 of the hearing record, part 2 says:

The important point, however, is that not more than a dozen drugs have presented problems with respect to physiological availability.

Exactly your words.

Thus, to damn the entire Pharmacopeia of some 2,000 drugs for the failure of a mere handful is unscientific in the extreme.

This is Dr. Miller's direct, flat refutation of what you have just said.

Mr. CUTLER. Here is page XVII of the preface of USP:

The term "physiological availability" connotes attribute of the dosage form of a drug that constitutes a measure of the extent to which the active ingredient is taken up by the body in a useful form. From a practical standpoint, the attribute is of useful significance only in respect to the dosage forms intended for oral administration. Progress has been slow in developing methods to measure physiological availability that would be suitable for USP use. Consequently, however desirable it is to give assurances of complete 'availability' to every patient requiring a USP article, the problem of providing objective standards and methods remains in the exploratory stage at this time.

Senator NELSON. Nobody argues with that.

Let me quote to you from Dr. Goddard's testimony.

The problem remains. There is no perfect chemical test to guarantee physiological availability. The perfect test is in a human being. But listen to Dr. Goddard:

I do not think anyone can provide absolute assurance that they are putting equivalent combinations for every drug in the marketplace. But by the same token, I have not seen any good evidence from any firm, large or small, that their drugs are superior to anybody else's. I hear the statement made time and time again. I have challenged firms who have made this statement, show me evidence that their drugs are superior.

The assumption when you design a formulary, according to the testimony before the committee, is that if drugs meet USP standards they are equivalent. There are a handful of cases where evidence to the contrary has been shown. You have one of the handful before us, chloramphenicol, and we are going to get at the question of how careful your testing was on that drug and the deaths that have been caused by your product.

Now, Doctor, I understand that your product, Chloromycetin, has been responsible for deaths resulting from bone marrow disorders, is that correct?

Dr. LUECK. I do not know in what frame of reference you are phrasing the question. If you mean Chloromycetin and all chloramphenicol products have official labeling approved by the Food and Drug Administration, required statements on the labeling, that include indications for use, how to use the product, with warnings, actions, and side effects, that information is explicitly——

Senator NELSON. Maybe you did not understand the question. I said I understand that your product, Chloromycetin, has been responsible for deaths from bone marrow disorders. Is that correct or incorrect?

Dr. LUECK. I do not know in what reference you are phrasing that question. I know that Chloromycetin, the Parke, Davis brand of chloramphenicol——

Senator NELSON. Has never resulted in any deaths?

Dr. LUECK. No, I did not say that.

Senator NELSON. Maybe I did not put the question correctly.

Some people have died from the administration of Chloromycetin, I understand. Will you tell me what you know about that?

Dr. LUECK. I understand that Chloromycetin has been alleged to be related to or associated with some serious side effects, some serious reactions. Those things are related and detailed in considerable length in the package information, in the labeling, Mr. Chairman.

Senator NELSON. You say you understand. You really are not sure that any deaths have resulted from this drug?

Dr. LUECK. I think that there have been instances where some reactions can be related to the use of Chloromycetin.

Senator NELSON. Have you ever read the warning that your company now belatedly puts in its advertising for this drug? Here is an ad from the Journal of the American Medical Association, February 20, 1967:

Warning: Serious and even fatal blood dyscrasias aplastic anemia, hypoplastic anemia—

And so forth—

are known to occur after the administration of chloramphenicol.

Were you aware of that?

Dr. LUECK. Yes, sir.

Senator NELSON. That was my question, Doctor: Do you know of any cases of fatal side effects occurring after the administration of Chloromycetin?

Dr. LUECK. I was attemping to respond to your question by referring to this warning statement in the labeling, which is precisely identical to that in the advertising. I am sorry if I misled you.

Senator NELSON. You did not mislead me. You are aware, then, that deaths have occurred in this case?

Dr. LUECK. Absolutely.

Senator NELSON. What has Parke, Davis done about quality control to overcome that problem?

Dr. LUECK. I would like to state, Mr. Chairman, that Chloromycetin, like many other drugs, is a very potent drug. As the packaging infor-

mation, the labeling information, indicates, it is to be used in serious infections. In that regard, it is no different from many other drugs, and in many instances, safer than other drugs. The physician, every time he prescribes, must balance the risk of the bad against the risk of the good.

Senator NELSON. You are saying that nothing done about quality control can affect the inherent danger of this drug, is that what you are saying?

Dr. LUECK. So far as I know, that statement is correct.

But in the case of the example we have before the committee today, Mr. Chairman, another point that can come into play is that a subpotent therapeutic product can endanger the life of the patient by not treating the disease properly for which the drug is being administered.

Senator NELSON. I do not think there is any question about that. Are there any cases you know about of deaths resulting from the drug not being physiologically available?

Dr. LUECK. Not that I know of.

Senator NELSON. But we do have cases of deaths occurring where it was physiologically available?

Dr. LUECK. Yes; it is true of penicillin, true of streptomycin, true of a number of our famous drugs.

I would like to review very briefly for the chairman the fact that Chloromycetin, at the request of the Food and Drug Administration, was reviewed in 1952 by the National Research Council and reviewed again in 1960 by that same body in terms of its safety and effectiveness.

Senator NELSON. By what council?

Dr. LUECK. The National Research Council.

Senator NELSON. What is the membership of the council, do you know?

Dr. LUECK. Just a moment, please.

Senator NELSON. You can furnish it for the record.

Dr. LUECK. The consultants used in preparing the opinion of the National Research Council were, in our opinion, among the great of our time in medicine. They include Dr. Cluff——

Senator NELSON. How many, Doctor? What organizations are represented is what I was getting at?

Is that a long list?

Dr. LUECK. Not too long. Drs. Connelly, Damashek, Dowling, Elbert, Finch, Finland, Keefer, Moore, Smadel, Spink, Wintrobe, and the Chairman, Dr. Cannan.

Senator NELSON. Are they representative of various organizations, or just simply——

Mr. CUTLER. Mr. Chairman, this is a branch of the National Academy of Sciences.

Senator NELSON. Would you submit for the record their identification? Otherwise, one reading the record would not know who these physicians are.

Mr. CUTLER. These are the leading medical authorities of the country in the National Academy of Sciences.

Senator NELSON. Go ahead.

Dr. LUECK. The National Academy of Sciences is recognized as the highest ranking scientific body in the United States.

It might be of interest, Mr. Chairman, to note that it operates under Government funds.

Now, the National Research Council has responded, as I said, on two occasions to inquiries from the Food and Drug Administration as to the place of Chloromycetin in the therapeutic armementarium of physicians.

I might quote, on January 11, 1961, the Chairman of the Division of Medical Sciences of the National Research Council replied by letter and among other things, he commented as follows:

> Chloramphenicol is considered to be a valuable drug that should remain on the market. In fact in certain infections, it is a drug of choice. The newer antibiotics that have appeared on the market since chloramphenicol was last evaluated by the National Academy of Science's National Research Council in 1952 can't replace satisfactorily in all cases.

Point 2, and I quote further:

> A restriction of the usage of chloramphenicol to hospitalized patients is not deemed to be indicated. * * *
>
> 3. A knowledge of the untoward side effects that may occur with this drug should be adequately known to all prescribers. The information should be disseminated as a warning on the drug label and elaborated in an enclosure in the drug package. Beyond this, there is need for the continuing education of the physician through the media of medical meetings and the medical literature. This, of course, is a responsibility of the leaders of medicine and not of the FDA.
>
> Point 6. Almost, if not all, potent therapeutic agents cause some undesirable side effects. Therefore, it should be pointed out that chloramphenicol is not the only antibiotic that may cause unfavorable reactions of a serious and sometimes fatal nature.

In addition to the National Research Council review, the Food and Drug Administration in 1957 published comparative data of side effects comparing various antibiotics.

Now, Mr. Chairman, let us look at this article in this publication, and let us look at the potential dangers of chloramphenicol in true perspective; in other words, comparing it to other anti-infective agents or other antibiotics. Let us take a look at disabling and death-dealing reactions that may occur with the other antibiotics. The last significant and overall review of severe reactions to antibiotics was communicated to the medical literature by personnel of the FDA in 1957. Now, it consisted of a nationwide study, including more than 800 hospitals and interviews with 1,600 physicians, and uncovered 1,070 severe antibiotic reactions that were life-threatening.

Senator NELSON. Any deaths in that list?

Dr. LUECK. Yes. In a paper published in Antibiotic Medicine and Clinical Therapeutics, 1957, these authors brought out the fact that

penicillin was found to produce the greatest number and the most severe reactions of all antibiotics presently available.

Mr. GORDON. This was when?

Dr. LUECK. 1957.

Mr. GORDON. And when did Chloromycetin appear on the market?

Dr. LUECK. 1949.

Further, in order of their frequency, the life-threatening reactions to antibiotics are anaphylactoid shock, super-infections, severe skin reactions, blood dyscrasias and anguineurotic edema, with respiratory-tract involvement. Please note, Mr. Chairman, that blood dyscrasias—which can be related to chloramphenicol therapy are—next to the last on the list of life-threatening reactions.

These authors further noted that the tetracyclines account for most of the cases of super-infections.

Mr. GORDON. Excuse me, sir. What was the date of that particular report?

Dr. LUECK. The specific date I don't know. It was 1957.

Mr. GORDON. Are you aware of the fact, however, that the risk at that time was considered to be considerably less than it is today? For example, I think the risk at that time was considered to be one in 800,000. A recent report to the California State Assembly and Senate by the California Medical Association and the State Department of Public Health, has revealed that the risk, on the basis of an average dose of 7.5 grams, is 1 in 24,000.

Dr. LUECK. Mr. Gordon, with your permission, I would like to comment on the California report and I will finish my brief review of the 1957 FDA publication in just a moment. Then I would go on to the California report.

Mr. GORDON. But isn't it correct that considerably more is known today about the effects of chloramphenicol than was known, say, 12 or 13 years ago? Is that not correct?

Dr. LUECK. I do not know that we have a higher incidence of side effects now than we had in 1957. I will treat that subject in a moment, Mr. Gordon.

But at any rate, the 1957——

Mr. GORDON. Could you answer my question, Doctor?

Dr. LUECK. I am sorry.

Mr. GORDON. I asked the question: Is it not correct that we know considerably more today about the side effects and dangers of chloramphenicol than we did say 12 or 13 years ago when that particular report was written?

Dr. LUECK. No, sir; I do not believe we do.

Mr. GORDON. You do not believe we know any more today than we did at that time?

Dr. LUECK. I do not believe we know any more. The California report is largely the same as the National Research Council report. The recommendations are largely the same.

Mr. GORDON. When was the National Research Council report written?

Dr. LUECK. 1961.

Mr. GORDON. That was how many years ago?

Dr. LUECK. The California report suggests that the occurrence of I think aplastic anemia may be one in 24,000 to one in 40,000, and we are not going to argue with that figure.

Mr. GORDON. They also give the figure: one in 24,200.

Dr. LUECK. That is what I thought I was trying to quote. I am trying to quote from memory now, Mr. Gordon. I thought they quoted one to 24,000 or 40,000.

Mr. GORDON. Now, I want to get your answer absolutely clear in my mind. You say that we do not know any more today about the side effects and risks involved in the use of chloramphenicol than we did 12 or 13 years ago?

Dr. LUECK. Mr. Gordon, in my opinion, we do not.

Mr. GORDON. Thank you, very much.

Dr. LUECK. But I am not a medical person and I am not qualified in all of these areas, obviously. I am qualified, however, to read a report which is published on the drug, so that is what I am doing.

Senator NELSON. So the record might be clear on that point, is there anyone here who is qualified to answer that question, one of the doctors? Do we know any more today about the side effects than we did 10 years ago?

Dr. SCHEELE. I am president of Warner-Lambert Research Institute. We know more in the sense that there has been a longer experience. However, no new side effects have developed in the course of time. We know no more about this phenomenon which is in the patient who reacts to this particular drug, or even the sensitivity phenomenon that occurs in people who become sensitive to penicillin and have severe reactions and of even deaths. In a sense, we do not know any more. There has been a lot of experience. I do not think there has been any medical data that has turned up that suggests that the population at large has within it more susceptibility of having this idiosyncracy which leads them under treatment by this drug to develop aplastic anemia.

Mr. GORDON. You knew that 8 or 10 years ago?

Dr. SCHEELE. Yes. It was not known in the beginning. It was learned after the product was marketed. It continues. But I doubt that the incidence is higher now in the population—that is, the potential of this is any higher now than it was then.

Mr. GORDON. You mean the incidence per 1,000 treated?

Dr. SCHEELE. That is right, but I mean the idiosyncrasy within the patients themselves to have this happen if he is given the drug.

Mr. GORDON. So that the record may be clear, then, you have accumulated additional information; but do I understand you to say that you do not have any more information about side effects now than you had 10 or 12 years ago?

Dr. SCHEELE. That is correct, and the physician who uses it does it on the basis that the disease he is treating, the risk—that is, the need for the drug is greater than the hazard as far as he is concerned in prescribing the drug.

Mr. CUTLER. Mr. Chairman, you might want to have the record show that Dr. Scheele is the former Surgeon General in the United States and not without experience in this.

Dr. SCHEELE. I helped gather some of the data for the FDA some years ago.

Senator NELSON. The record will show that because I saw the reporter writing it down.

I would like to ask you a question about something that puzzles me.

You were aware of the occurrence of serious blood dyscrasias, even fatal blood dyscrasias 5 or 10 years ago.

Your ad in 1960, an ad in the Antibiotics and Chemotherapy magazine, was a one page ad that we will submit for the record which says: "True broad-spectrum coverage, proved clinical efficacy, Chloromycetin, outstandingly effective against a wide range of pathogens," and so forth. It compares various other antibiotics A, B, C, versus Chloromycetin.

Then the written legend is: "Chloromycetin is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy."

There is nothing here that would scare anybody. Your claim was for a potent therapeutic agent and because certain blood dyscrasias had been associated with its administration, you simply said that the drug should not be used indiscriminately.

(The advertisement follows:)

[From Antibiotics and Chemotherapy magazine, April 1960]

Senator NELSON. Now, on February 20, 1967 the Journal of the American Medical Association ran an ad which we will print in the record. I shall not read all of the fine print. It reads:

Because of its wide antibacterial spectrum and its ability to diffuse into infective foci, Chloromycetin may be of value in the treatment of selected severe respiratory tract infections due to susceptible microorganisms.

And so on. Then it gets down to the boxed-in section here. I will read part of the warning:

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects.

(The advertisement follows:)

[From Journal of the American Medical Association, Feb. 20, 1967]

may be indicated in certain severe respiratory infections

Because of its wide antibacterial spectrum and its ability to diffuse into infective foci, CHLOROMYCETIN may be of value in the treatment of selected severe respiratory tract infections due to susceptible microorganisms. However, as with any antibacterial agent, the administration of CHLOROMYCETIN must be adjunctive to the overall therapeutic approach to this family of diseases. Appropriately treated, good results can be expected in bacterial pneumonia and empyema; in bacterial complications of bronchiectasis and bronchitis; all of which are severe disorders often chronic and difficult to eradicate.

The decision to choose CHLOROMYCETIN from among a group of antibiotics suggested by *in vitro* studies to be potentially effective against a specific respiratory tract pathogen(s) should be guided by severity of infection, relative susceptibility of the pathogen(s) to the various antibacterial drugs, relative efficacy of the various drugs in this family of infections, and the important additional concepts contained in the "warning box."

Patients with respiratory tract infections usually become afebrile in 18 to 72 hours on recommended doses; roentgenographic clearing may be slower.

Neoplastic, fungal, and mycobacterial disease as a cause of persisting respiratory disease should be ruled out by appropriate means.

Chloromycetin

Detailed information, including indications and dosage, appears in the package inserts of CHLOROMYCETIN products for systemic use. Consult the appropriate package insert.

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective. It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia.

CHLOROMYCETIN, an antibiotic having therapeutic activity against a wide variety of organisms, must, in accordance with the concepts in the "warning box" above, be used only in certain severe infections.

Contraindications: Chloramphenicol is contraindicated in individuals with a history of previous sensitivity reaction to it.

It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections.

Precautions and Side Effects: Untoward reactions in man are infrequent; however, they have been reported with both short-term and prolonged administration of the drug. Among the reactions reported are blood dyscrasias as mentioned in the warning. When, during the course of therapy, blood counts show unusual deviations which may be attributable to the drug such as reticulocytopenia, leukopenia, or thrombocytopenia, therapy with chloramphenicol should be discontinued. Also reported are certain gastrointestinal reactions resulting in glossitis and stomatitis, which are indications to stop the drug. On rare occasions, superimposed infection by *Candida albicans* may produce widespread oral lesions of the thrush type. Diarrhea and irritation of perianal tissues have been reported. Pseudomembranous enterocolitis has been reported in a few patients. Hypersensitivity reactions manifested by angioneurotic edema and vesicular and maculopapular types of dermatitis have been reported in chloramphenicol-sensitive patients. Urticaria and vesicular lesions have been observed. They are usually mild in character and ordinarily subside promptly upon cessation of treatment.

Febrile reactions have been reported.

A reaction of the Jarisch-Herxheimer type has been reported following therapy in syphilis, brucellosis, and typhoid fever. Typhoid fever patients have exhibited a "shock-type reaction" characterized by circulatory collapse attributed to sudden release of endotoxin. Neurotoxic reactions, including optic and peripheral neuritides, headache, mild depression, "dazed feelings," internal ophthalmoplegia, mental confusion, and delirium have been reported. Symptoms of peripheral neuritis or decreased visual acuity call for prompt withdrawal of the antibiotic and the possible use of large doses of oral or parenteral vitamin B complex. When prolonged high dosage is necessary, toxic side effects may occur which call for dosage reduction or discontinuance of chloramphenicol therapy. Adults and children with impaired liver or kidney function, or both, may retain excessive amounts of the drug. In such instances, dosages should be adjusted accordingly.

Toxic reactions, the signs and symptoms of which have been referred to as the "gray syndrome," with some fatalities, have resulted from high concentrations of the drug in the premature and newborn age groups. One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. The following summarizes the clinical and laboratory studies that have been made on these patients: (1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life. (2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol. (3) The symptoms appeared in the following order: (a) abdominal distention with or without emesis; (b) progressive pallid cyanosis; (c) vasomotor collapse, frequently accompanied by irregular respiration; and (d) death within a few hours of onset of these symptoms. (4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules. (5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol after repeated doses. (6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

Precautions: See "warning box" for precautions.

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. Constant observation of the patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, the drug should be discontinued and appropriate measures should be taken.

Monitoring of liver and kidney function should be accomplished during therapy in patients with existing liver or kidney disease.

Supplied: CHLOROMYCETIN is available in a variety of forms including Kapseals® of 250 mg.

PARKE-DAVIS

Senator NELSON. How do you explain that you knew how serious these effects could be 10 years ago and yet in 1960, you were running an ad that did not call this sharply to the attention of the doctor, but then suddenly, 7 years later, you are running this ad?

Dr. LUECK. Mr. Chairman, I would like to comment on the fact that since 1952, every ad, every advertisement that has appeared on Chloromycetin, has first been reviewed with the Food and Drug Administration before that ad was ever submitted for publication in any journal.

Senator NELSON. I am prepared to indict the FDA along with your company for that.

Dr. LUECK. This was the opinion, the combined opinion, apparently, of the experts in Parke, Davis, the experts in the Food and Drug Administration, that adequate warning was included in those ads and in the labeling at any given time. We have diligently worked with the Food and Drug Administration and disseminated the information to the best of our ability on any changes or improvements in that labeling through the years. And to carry the message to the physician, Mr. Chairman, each and every time.

Senator NELSON. Do you really mean to tell me, Doctor, that you think this first ad says the same thing as the second ad? Do you really mean to say that?

Dr. LUECK. I am not saying that they say the same thing.

Senator NELSON. Do they give the same warning?

Dr. LUECK. Yes; I think they give the essential warning.

Senator NELSON. Let's read it again. I think that this is preposterous.

Mr. CUTLER. Mr. Chairman, I hope I will not sound impertinent, but may I ask what this has to do with the evidence Dr. Lueck has submitted with regard to the evidences of differences of therapeutic brands?

Senator NELSON. I can give you several answers, but I will give you one that ought to satisfy you. If quality control is important, and I think it is as important as you say it is in the production of drugs for the marketplace, quality control of advertising is just as important.

It does not do any good to have good quality control so the drug will do exactly what you expect it to do and then be outright dishonest about what it will do. I think quality control in advertising is as important as quality control in the production of a drug. That is exactly what I am getting at.

Now, I will read the two ads again. I will let the public judge this one. You tell me if they both tell the doctor the same thing, and I am going to ask the doctors who testify what their opinion is. We will put into this record the opinion of distinguished doctors on this question. And, if you want me to, you can select a number of doctors to appear on this question.

The testimony has been that you knew as much about the dangers of this drug 10 years ago as you know now, and your ad stated in April 1960:

> Chloromycetin is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made if the patient requires prolonged or intermittent therapy.

If the doctor reads that, is there anything in there to alert him that there have been deaths indirectly attributed to this drug?

If you knew 10 years ago what you know today, why, in 1967, do you have a severe warning boxed in heavy print:

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia—

And so forth—

are known to occur after the administration of chloramphenicol. Blood dyscrasias have occured after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects.

Do you consider these to be equivalent warnings?

Dr. LUECK. The second warning is an exact duplicate of the package insert and, in my opinion, would be considered a stronger warning, Mr. Chairman.

Senator NELSON. I bless you for that.

Dr. LUECK. I would like to repeat that all of the ads on Chloromycetin were reviewed by Parke, Davis & Co. with the Food and Drug Administration since 1952 before they were published or submitted to a journal or any advertising media.

Also, I would like to——

Senator NELSON. Let me say at this point, if I may, that I do not have any higher opinion of the FDA's judgment in permitting this kind of advertising then than I do of the company's running this ad. I do not think it protects you any to come up and say the FDA approved of a lousy ad. Most of the industry is attacking the FDA most of the time, anyway.

Dr. LUECK. Well, I think if Parke, Davis & Co. had improper ads, we would have been cited by the Food and Drug Administration, as some people have, and we have not. So our advertising of all our products——

Senator NELSON. I am sorry, I have another vote. It is 12:45. Why not take 45 minutes for a long lunch?

(Whereupon, at 1:45 p.m., the hearing was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

Senator NELSON. Doctor, would you resume?

STATEMENT OF DR. LESLIE M. LUECK ET AL.—Resumed

Dr. LUECK. So, Mr. Chairman, I think our advertising of all our products has been much in order with the keeping of the day and regulatory requirements appropriate to advertising the product and to inform the advertising.

Senator NELSON. Well, my questions have been directed at the proposition that the evidence was available several years ago that there were some major serious side effects, and that the ads did not indicate it. For example, there had already been known deaths—I think that is indisputable—by 1954.

The National Research Council in 1952 made statements which were brought to the attention of the industry and Parke, Davis, in particular. You read some of the conclusions of the Council, one of which

was that certain cases of serious blood dyscrasias had been associated with chloramphenicol—that was 1952—and still an ad in the General Practitioner, in March 1954, did not mention this fact.

Do you have a copy of that? This ad only said in 1954 that:

> Since its introduction over four years ago, Chloromycetin has been used by physicians in practically every country of the world. More than eleven million patients have been treated with this important antibiotic, truly one of the world's outstanding therapeutic agents.

That is all that is there.

How do you explain that at that stage, even 2 years after the National Research Council's statement about side effects that there is no warning at all in the ad?

Dr. LUECK. Mr. Chairman, I would like to point out that the warnings and so forth on Chloromycetin were introduced into the official labeling and were delivered to practicing physicians by Parke, Davis and Co., following the first report from the National Research Council.

Senator NELSON. I did not follow that. What about the physicians?

Dr. LUECK. That the physicians, a major attempt was made to inform the physicians of the information then included in a warning statement on Chloromycetin and it is our firm belief——

Senator NELSON. In what way were the physicians informed?

Dr. LUECK. Both by letters to the physicians——

Senator NELSON. Every physician in the United States received a letter?

Dr. LUECK. Yes.

Senator NELSON. That was at the direction of the FDA?

Dr. LUECK. With the cooperation of the FDA.

Senator NELSON. Well, was it at their direction? Did they order it?

Dr. LUECK. I do not know whether they ordered it or not. It would not have made any difference to Parke, Davis whether they had ordered it or not. It is a means of communicating this information.

Senator NELSON. Do you have a copy of the information you sent?

Dr. LUECK. Just a moment, please.

I have a copy of the letters that were sent to physicians in the country. I would be happy to submit it to the chairman for the record if he pleases.

Senator NELSON. Do you have the date of the letter?

Dr. LUECK. It will be all on the letter.

Senator NELSON. You do not know the date?

Dr. LUECK. Just a moment. I think I can remember some of the letter.

Mr. Chairman, there are three letters and the different letters are required for this purpose: One went to the medical profession, one went to the osteopathic profession, and the third to the pharmaceutical profession. The letters are dated February 15, 1961. They include a letter with the current package insert.

Senator NELSON. A letter and what?

Dr. LUECK. And the package insert, the official labeling.

Senator NELSON. That was in 1961?

Dr. LUECK. That is February 15, 1961.

Senator NELSON. Those letters will be printed in the record.

(The material referred to follows:)

Parke, Davis & Company

RESEARCH LABORATORIES
2800 PLYMOUTH ROAD
ANN ARBOR, MICHIGAN
NORMANDY 3-7585

OFFICE OF DIRECTOR
DEPARTMENT OF CLINICAL INVESTIGATION

February 15, 1961

To the Medical Profession:

The enclosed copies of recently revised package inserts required by new regulations of the Food and Drug Administration will accompany all oral and parenteral Chloromycetin products. This is our means of promptly placing this information into your hands. These inserts provide the latest essential information regarding warnings, precautions, indications and dosage for the proper use of this antibiotic.

Sincerely yours,

J. K. Weston, M. D.

Director,
Department of Clinical
Investigation

Enclosures

CHLOROMYCETIN® SUCCINATE AND CHLOROMYCETIN FOR PARENTERAL ADMINISTRATION

(Chloramphenicol Succinate, Parke, Davis & Company)
(Chloramphenicol, Parke, Davis & Company)

WARNING

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

Chloramphenicol is a broad-spectrum antibiotic which clinical experience has shown to have specific therapeutic activity against a wide variety of organisms. Its activity was demonstrated initially in culture filtrates from a species of soil organism collected in Venezuela, later designated as *Streptomyces venezuelae*. The antibiotic was subsequently isolated from culture filtrates, identified chemically, and later synthesized.

Experimental development of bacterial resistance to chloramphenicol by staphylococci *in vitro* occurs comparatively slowly and only to a moderate degree. Strains of decreased susceptibility to chloramphenicol are relatively short-lived both *in vitro* and in man. In a survey of experimental and clinical experiences on susceptibility of staphylococci to chloramphenicol, it was found that the incidence of chloramphenicol-resistant staphylococci appears unrelated to frequency or to intensity of use of this antibiotic. Development of resistance to chloramphenicol can be regarded as minimal for staphylococci and many other species of bacteria.

ANTIMICROBIAL AND PHARMACOLOGICAL PROPERTIES OF CHLORAMPHENICOL

Chloramphenicol injected intravenously is readily distributed throughout the circulating blood. Peak blood concentrations will be dependent upon the rapidity of injection. After conditions of equilibrium with body fluids and tissues obtain, approximately 50 per cent reduction in blood concentrations will occur in the ensuing 3 to 4 hour period.

Chloromycetin Intramuscular (Steri-Vial 65) injected intramuscularly behaves as a repository material. Peak blood levels will occur much later, will not be as high, and persist for a longer period than those seen after intravenous injection or oral administration. Older children and adults, i.e. those patients who have mature enzyme systems, conjugate and eliminate chloramphenicol rapidly and attain lower peak blood levels than with other forms of administration. Premature and newborn infants show reduced ability to conjugate and eliminate chloramphenicol and in general will achieve blood levels much higher and of considerably longer duration than will older children or adults.

Chloromycetin Succinate (the sodium salt of the succinic acid ester of chloramphenicol) requires conversion to free chloramphenicol before exhibiting marked antimicrobial activity. When given intravenously its distribution is approximately the same as that of intravenous chloramphenicol (Ampoule 258); however, it requires some time before conversion to the effective free form. Intramuscular injection is followed by rapid conversion, and peak blood levels occur approximately 2 hours following injection.

Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half that found in the blood. This antibiotic has also been reported to occur in pleural and in ascitic fluids, saliva, and in milk, and it diffuses readily into all parts of the eye. Transport across the placental barrier occurs, with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

Seventy to ninety per cent of a single oral dose of 50 mg. of chloramphenicol is excreted in 24 hours in the urine of human subjects, with 5 to 10 per cent as free chloramphenicol and the remainder as microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most nitro compounds in the blood are in the form of free chloramphenicol. Despite the small proportion of unchanged drug excreted in the urine, concentrations therein are relatively high, amounting to several hundred mcg./ml./24 hours in patients receiving 50 mg./kg./day. Small amounts of active drug are also found in bile and in feces. The disposition of the drug given by parenteral routes is similar.

PRODUCTS FOR PARENTERAL USE AND DOSAGE RECOMMENDATIONS

CHLOROMYCETIN SUCCINATE (Steri-Vial No. 57)

This is the preferred and the only suitable parenteral product form for intramuscular, intravenous, and subcutaneous use.

The powder in the Steri-Vial is prepared for injection by the addition of an aqueous diluent such as Water for Injection or 5% Dextrose Injection. Although Chloromycetin Succinate is highly soluble, the rate of solution is somewhat slower in the more highly concentrated solutions. Gentle shaking of the vial hastens solution. The following dilution table may be used as a guide for preparing solutions for injection.

DILUTION TABLE

Strength of Solution		Volume of Diluent Required
%	mg. per cc.	
40	400	2 cc.
25	250	3.8 cc.
10	100	11 cc.

Adults—dose recommendations: For most infections due to susceptible organisms, adults should receive 50 mg./kg./day. Patients with infections due to less susceptible organisms often require 100 mg./kg./day. Severe infections may require even higher doses. In either case, this should be divided into 4 doses at 6-hour intervals. Note carefully the dosage table below.

DOSAGE TABLE

Dose	Volume to be Injected		
	40% Solution	25% Solution	10% Solution
1 Gram	2.5 cc.	4 cc.	10 cc.
500 mg.	1.25 cc.	2 cc.	5 cc.
100 mg.	0.25 cc.	0.4 cc.	1 cc.

The following methods of administration are recommended on the basis of tolerance, ease of handling and safety:

1. *Intramuscularly*, as a 25 to 40 per cent solution injected deep into the muscle at one of the common sites of intramuscular injection.
2. *Intravenously*, as a 10 per cent solution to be injected over a one-minute interval. If desired, the solution can be added to a larger volume of parenteral fluid for intravenous infusion.
3. *Subcutaneously*, as a 10 per cent solution injected through a short, small gauge needle. As with the intravenous route, the concentrated solution can be added to fluids for subcutaneous clysis.

Children—dose recommendations: Chloromycetin Succinate is the preferred parenteral dosage form for pediatric use. Dosage of 50 mg./kg./day is adequate for infections caused by most susceptible organisms. Severe infections, e. g. septicemia or meningitis, especially when adequate cerebrospinal fluid concentrations are desired may require dosage up to 100 mg./kg./day. However, dosage should be reduced to 50 mg./kg./day as soon as clinical response occurs. When prolonged high dosage is necessary, possible toxic side effects may occur. In this event dosage should be immediately reduced or discontinued. Chloromycetin Succinate may be administered intramuscularly, intravenously, or subcutaneously, as above and should be divided into doses at 6-hour intervals.

Premature and Newborn Infants—dose recommendations: Chloromycetin Succinate may be used in an initial dose of 25 mg./kg. followed by 25 mg./kg./day in 3 equal doses at 8-hour intervals which produces and maintains concentrations in blood and tissues adequate to control most infections. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range, as best determined by available microtechniques. Full term newborn infants ordinarily may receive from 25 to 50 mg./kg./day equally divided into 3 doses at 8-hour intervals. The same routes of administration as noted above may be employed; generally intramuscular administration is preferred.

These dosage recommendations are extremely important because blood concentration of chloramphenicol in the premature and newborn infant differs from that of an infant over one month of age. This difference is due to variations in the metabolic disposition of this and other drugs in this age group which depends upon the maturity of the metabolic function and status of the liver and the kidneys. When these systems are immature (or seriously impaired in adults) high concentrations of the drug are found which tend to increase with succeeding doses. Toxic reactions and some fatalities have occurred in the premature and newborn age group, these being associated with higher than recommended dosages. The following summarizes the clinical and laboratory studies that have been made:

1. In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.

2. Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol (100 mg./kg./day or more).

3. The symptoms appeared in the following order: (a) abdominal distention with or without emesis; (b) progressive pallid cyanosis; (c) vasomotor collapse, frequently accompanied by irregular respiration; and (d) death within a few hours of onset of these symptoms. This has been referred to in some institutions as the "gray syndrome".

4. The progression of symptoms from onset to exitus was accelerated with higher dose schedules.

5. Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol after repeated doses.

6. No characteristic pathological changes attributable to the use of chloramphenicol were found in any of the organ systems, including the hematopoietic system.

7. Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

Infants and Children with Immature Metabolic Processes—dose recommendations: In young infants (those between one month and one year of age) and others in whom immature metabolic

processes are suspected, a dose of no more than 50 mg./kg./day but not less than 25 mg./kg./day of the succinate will produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by available microtechniques. Again, the routes of administration noted above apply.

CHLOROMYCETIN INTRAMUSCULAR (Steri-Vial No. 65)

For use only by intramuscular injection. Not recommended for pediatric use. Supplied in Steri-Vials. Suspension for use is prepared by injecting 2.5 cc. water for injection (not containing benzyl alcohol) into the Steri-Vial and suspending the contents by agitation.

2.5 cc. of suspension prepared with water will contain 1 Gm. chloramphenicol and 10 mg. sodium carboxymethylcellulose in 0.9 per cent sodium chloride solution containing 1:10,000 Phemerol Chloride (benzethonium chloride, Parke, Davis and Company) as a preservative.

Adults—dose recommendations: May be given in divided doses at 8- or 12-hour intervals. Blood levels achieved with 50 mg./kg./day with this preparation will be adequate for infections due to very susceptible organisms. Normal adults require 150 mg./kg./day the first day to achieve peak blood levels comparable to those achieved with the lower dosage of other parenteral dosage forms. This should be followed by 50 mg./kg./day thereafter. Since blood concentrations of the drug rise slowly, this product is unwieldy for treating infections caused by less susceptible organisms.

CHLOROMYCETIN SOLUTION AMPOULES (Ampoule No. 258)

For use only by intravenous infuston as a temporary substitute for other more preferable preparations. Not recommended for pediatric use. 2 cc. ampoules containing 0.5 gram chloramphenicol dissolved in 50 per cent aqueous solution of N,N-dimethylacetamide, with tartaric acid and sodium tartrate equivalent to 5 mg. tartaric acid per cc. Occasionally crystals or a second liquid layer may form at low temperatures. These will redissolve when the ampoules are warmed to body temperature and shaken. Withdraw contents of ampoule into sterile dry syringe and needle and add rapidly under surface of diluent (physiological sodium chloride solution or 5 per cent dextrose solution). Each ampoule should be diluted to at least 100 cc. but not more than 250 cc.

Adults—dose recommendations: 50 mg./kg./day divided into 4 doses at 6-hour intervals by intravenous infusion is effective in most infections due to susceptible organisms.

SIDE EFFECTS OF CHLORAMPHENICOL THERAPY

Untoward reactions in man are infrequent with chloramphenicol. Reactions attributed to chloramphenicol may be considered under the following headings:

Blood Dyscrasias

Aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia have been associated with the administration of chloramphenicol.

The following statement is quoted from NEW AND NONOFFICIAL DRUGS 1960, evaluated by the A. M. A. Council on Drugs, page 82:

"Although serious and even fatal blood dyscrasias are known to occur after the administration of chloramphenicol, current data seem to indicate that these reactions are rare. Blood dyscrasias have occurred with both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, the physician may use chloramphenicol in the treatment of serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used in treating colds, influenza, viral infections of the throat, or as a prophylactic agent to prevent bacterial respiratory disease."

When blood counts show unusual deviations such as leukopenia or thrombocytopenia, chloramphenicol should be discontinued.

Gastrointestinal Reactions

Gastrointestinal reactions which have been reported with oral administration of chloramphenicol have not been a problem with parenteral administration.

Hypersensitivity Reactions

Angioneurotic edema and vesicular and maculopapular types of dermatitis have been reported in patients sensitive to chloramphenicol. Urticaria and vesicular lesions also have been observed. Dermal lesions, usually mild, ordinarily subside promptly when the drug is stopped.

The Jarisch-Herxheimer reaction has been reported after chloramphenicol therapy in patients with syphilis, brucellosis, and typhoid fever. In patients with typhoid fever treated with chloramphenicol, several investigators have recorded a "shock-type reaction" characterized by circulatory collapse, attributed to sudden release of typhoidal endotoxin in an already weakened patient. Unlike the Herxheimer reaction, temperature is usually depressed, but exacerbation of fever has been reported. Recrudescense usually appears within 24 hours of the start of chloramphenicol therapy and persists from 24 to 48 hours.

Neurotoxic Reactions

Headache, mild depression, "dazed feelings", internal ophthalmoplegia, mental confusion, and delirium have been described in patients receiving chloramphenicol for a variety of infectious diseases. Optic and peripheral neuritides as probable effects of prolonged chloramphenicol therapy have been reported. Analysis of these cases suggests that these neurotoxic reactions were related both to large total doses of chloramphenicol and long periods of administration. The range of total dosages of chloramphenicol was from 190 to 1600 Gm. Toxic symptoms appeared between 42 days and 22 months after the start of therapy. Five patients had blurred vision as the most prominent symptom and in a sixth, the initial complaint was blindness. This latter was the only one with permanent impairment of vision. Peripheral neuritis resolved in all patients except one, who still had minor residual symptoms 13 months after onset. If symptoms of decreased visual acuity or peripheral neuritis occur during therapy, prompt withdrawal of the drug is indicated and large doses of oral or parenteral vitamin B complex should be considered.

Other Reactions

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, particularly monilia. Constant observation of the

patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

CLINICAL USE OF CHLORAMPHENICOL

Rickettsial Diseases

The response of patients with rickettsial infections, including epidemic and murine typhus fevers, Brill's disease, scrub typhus fever, Rocky Mountain spotted fever, and rickettsial pox, has been dramatic with virtual elimination of mortality and marked shortening of the course of illness. Average length of the febrile period after administration of chloramphenicol is 2 days in patients with epidemic typhus fever and 3 days in those with other typhus fevers. Treatment should be given for a minimum of 6 days or 4 days after temperature returns to normal.

Relapse may occur when treatment is given only for 48 hours early in the disease. This can be prevented by giving additional doses on the fifth and sixth days after the initial course. Also, patients in relapse respond as readily to treatment as do those with primary infection.

In patients with Rocky Mountain spotted fever, defervescence occurs about the fourth day after therapy is started. Treatment should be continued for 24 hours after normal temperature is attained.

Typhoid Fever

Chloramphenicol has been established as the drug of choice for this disease. After therapy is started, fever subsides in 3 or 4 days regardless of age, severity of illness, or stage of disease. To lessen possibility of relapse, it is important that therapy be continued for from 8 to 10 days after reaching the afebrile period. Close observation of the patient for complications of the disease, and for the aforementioned side effects of the drug, is essential. Results of chloramphenicol treatment for the carrier state are equivocal.

Other Salmonelloses

While chloramphenicol has proved to be a useful therapeutic agent in ameliorating and shortening the clinical course of salmonella infections other than typhoid, results are not as uniform. Recommended duration of treatment is the same as for typhoid fever.

Urinary Tract Infections

Treatment for infections of the urinary tract should be based upon sensitivity of bacteria and on anatomic factors contributing to the infection. The more common organisms encountered in the urinary tract infections are *Escherichia coli, Aerobacter aerogenes, Pseudomonas aeruginosa, Proteus sp., Staphylococcus aureus* and *Streptococcus fecalis.*

Chloramphenicol has been found effective in treatment for about 70 per cent of urologic infections, particularly those caused by *Escherichia coli, Streptococcus fecalis,* and *Proteus sp.* Relief of symptoms and repeated bacteriological studies should be depended upon to indicate duration of treatment.

Surgical Infections

Surgical infections such as post-operative wound infections, cellulitis, infected sinus tract, and peritonitis or intra-abdominal abscess from ruptured intestine, diverticulae, or appendix, usually are due to microorganisms sensitive to chloramphenicol. The antibiotic is given, adjunctively to surgical intervention, in the recommended dosage for an average of from 10 to 16 days.

Respiratory Tract Infections

Chloramphenicol may be employed for severe infections of the respiratory tract due to susceptible microorganisms and in the presence of contraindications or lack of response to other agents. Patients on recommended doses become afebrile in from 18 to 72 hours; roentgenographic clearing will be slower.

Meningeal Infections

Many microorganisms causing meningitis are susceptible to chloramphenicol. The drug's high diffusibility results in effective concentrations in the cerebrospinal fluid. Institution of therapy cannot be delayed until results of laboratory tests are known. Many clinicians consider chloramphenicol the drug of choice for meningitis caused by *H. influenzae* as almost all strains are sensitive to this antibiotic. Parenteral dosage is recommended until the patient is afebrile, after which oral medication may be used. Medication should be continued for a minimum of 7 days to avoid relapse.

Miscellaneous Infections

Chloramphenicol has proved to be useful and frequently effective in treatment for many diverse infections, including brucellosis, bartonellosis, relapsing fever, granuloma inguinale, plague, and ornithosis. Other effective therapeutic agents should receive consideration as the treatment of choice. Whenever definite contraindications are known, such as hypersensitivity to these agents, or clinical response is poor, the judicious use of chloramphenicol is warranted, keeping in mind aforementioned warnings, precautions, and side effects, particularly in patients requiring prolonged or intermittent treatment.

PACKAGE INFORMATION

Steri-Vial No. 57, Chloromycetin Succinate provides the equivalent of 1 Gram chloramphenicol in a rubber-diaphragm-capped vial. Available individually and in packer units of 10.

Steri-Vial No. 65, Chloromycetin Intramuscular provides 1 Gram chloramphenicol in a rubber-diaphragm-capped vial. Available individually and in packer units of 10.

Ampoule No. 258, Chloromycetin Solution provides 0.5 Gram chloramphenicol in 2 cc. of solution, sealed in a glass ampoule. Available in packages of 10.

CHLOROMYCETIN® FOR ORAL ADMINISTRATION

(CHLORAMPHENICOL, PARKE, DAVIS & COMPANY)

WARNING

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

Chloramphenicol is a broad-spectrum antibiotic which clinical experience has shown to have specific therapeutic activity against a wide variety of organisms. Its activity was demonstrated initially in culture filtrates from a species of soil organism collected in Venezuela, later designated as *Streptomyces venezuelae*. The antibiotic was subsequently isolated from culture filtrates, identified chemically and later synthesized.

Experimental development of bacterial resistance to chloramphenicol by staphylococci *in vitro* occurs comparatively slowly and only to a moderate degree. Strains of decreased susceptibility to chloramphenicol are relatively short-lived both *in vitro* and in man. In a survey of experimental and clinical experiences on susceptibility of staphylococci to chloramphenicol, it was found that the incidence of chloramphenicol-resistant staphylococci appears unrelated to frequency or to intensity of use of this antibiotic. Development of resistance to chloramphenicol can be regarded as minimal for staphylococci and many other species of bacteria.

ANTIMICROBIAL AND PHARMACOLOGICAL PROPERTIES OF CHLORAMPHENICOL

Chloramphenicol is absorbed rapidly from the intestinal tract, producing detectable concentrations in blood within one-half hour after administration and peak concentration in from 1 to 3 hours. Peak blood concentration is roughly proportional to the dose. Following absorption of the drug and attainment of equilibrium conditions with body fluids and tissues, concentration in blood falls approximately 50 per cent in succeeding 3- to 4-hour periods. **Chloromycetin Palmitate** requires enzymatic hydrolysis to chloramphenicol before absorption. Resulting blood concentration is similar to that produced by the oral administration of chloramphenicol.

Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood. This antibiotic has also been reported to occur in pleural and in ascitic fluids, saliva, and in milk, and it diffuses readily into all parts of the eye. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

Seventy to ninety per cent of a single oral dose of 50 mg. of chloramphenicol is excreted in 24 hours in the urine of human subjects, with 5 to 10 per cent as free chloramphenicol and the remainder as microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most nitro compounds in the blood are in the form of free chloramphenicol. Despite the small proportion of unchanged drug excreted in the urine, concentrations therein are relatively high, amounting to several hundred mcg./ml., in patients receiving divided doses of 50 mg./kg./day. Small amounts of the drug are also found in bile and in feces.

DOSAGE RECOMMENDATIONS FOR ORAL CHLOROMYCETIN PRODUCTS

The majority of microorganisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood should fall within this range over a major portion of the treatment period. Dosage of 50 mg./kg./day divided into 4 doses at intervals of 6 hours will achieve levels of this magnitude. Except in certain circumstances (e.g., premature and newborn infants) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, *must* be prescribed at recommended doses known to have therapeutic activity. The following recommendations apply to all oral preparations:

Adults

Adults should receive 50 mg./kg./day in divided doses at 6-hour intervals. Patients with infections due to moderately susceptible organisms or with severe infections often require doses up to 100 mg./kg./day.

Children

Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., septicemia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg./kg./day; however, dosage should be reduced to 50 mg./kg./day as soon as clinical response occurs. When prolonged high dosage is necessary, possible toxic side effects may occur. In this event the dosage should be immediately reduced or discontinued.

Premature and Newborn Infants

An initial dose of 25 mg./kg. may be given to rapidly achieve effective concentrations in blood serum. This should be followed by administration of 25 mg./kg./day in 4 equal doses at 6-hour intervals, which produces and maintains concentrations in blood and tissues adequate to control most infections. Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. Full term newborn infants ordinarily may receive from 25 to 50 mg./kg./day equally divided into 4 doses at 6-hour intervals.

For comatose or gravely ill patients, chloramphenicol is available in several forms for parenteral administration.

These dosage recommendations are extremely important because blood concentration of chloramphenicol in the premature and newborn infant differs from that of an infant over one month of age. This difference is due to variations in the metabolic disposition of this and other drugs in this age group which in turn depends on the maturity of the metabolic function and status of the liver and the kidneys. When these systems are immature (or seriously impaired in adults) high concentrations of the drug are found which tend to increase with succeeding doses. Toxic reactions and some fatalities have occurred in the premature and newborn age group, these being associated with higher than recommended dosages. The following summarizes the clinical and laboratory studies that have been made:

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.

(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol (100 mg./kg. daily or more).

(3) The symptoms appeared in the following order: (a) abdominal distension with or without emesis; (b) progressive pallid cyanosis; (c) vasomotor collapse, frequently accompanied by irregular respiration; and (d) death within a few hours of onset of these symptoms. This has been referred to in some institutions as the "gray syndrome."

(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.

(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol after repeated doses.

(6) No characteristic pathological changes attributable to the use of chloramphenicol were found in any of the organ systems, including the hemopoietic system.

(7) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

Infants and Children with Immature Metabolic Processes

In young infants (those between one month and one year of age) and others in whom immature metabolic processes are suspected, a dose of no more than 50 mg./kg. but not less than 25 mg./kg./day, will produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by available microtechniques.

SIDE EFFECTS OF CHLORAMPHENICOL THERAPY

Untoward reactions in man are infrequent with chloramphenicol. Reactions attributed to chloramphenicol may be considered under the following headings:

Blood Dyscrasias

Aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia have been associated with the administration of chloramphenicol.

The following statement is quoted from NEW AND NONOFFICIAL DRUGS 1960, evaluated by A.M.A. Council on Drugs, page 82:

"Although serious and even fatal blood dyscrasias are known to occur after the administration of chloramphenicol, current data seem to indicate that these reactions are rare. Blood dyscrasias have occurred with both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, the physician may use chloramphenicol in the treatment of serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used in treating colds, influenza, viral infections of the throat, or as a prophylactic agent to prevent bacterial respiratory disease."

When blood counts show unusual deviations such as leukopenia or thrombocytopenia, chloramphenicol should be discontinued.

Gastro-Intestinal Reactions

After several days of therapy, glossitis may occur. Stomatitis, when it occurs is generally mild and usually consists of congestion and tenderness of the buccal mucosa. This is an indication to stop the drug. On rare occasions, superimposed infection by *Candida albicans* may produce

widespread oral lesions of the thrush type. Diarrhea and irritation of perianal tissues have been reported after prolonged administration of chloramphenicol and in patients previously treated with the antibiotic. These conditions are usually mild and disappear when chloramphenicol therapy is stopped, although occasionally they are protracted.

The pathogenesis of pseudomembranous enterocolitis of the intestines is not clear, but commonly staphylococci have been implicated. This severe reaction occurs in patients already ill with pneumonia or peritonitis, or it may follow surgical operation. Pseudomembranous enterocolitis has been reported in a few patients receiving chloramphenicol.

Hypersensitivity Reactions

Angioneurotic edema and vesicular and maculopapular types of dermatitis have been reported in patients sensitive to chloramphenicol. Urticaria and vesicular lesions also have been observed. Dermal lesions, usually mild, ordinarily subside promptly when the drug is stopped.

The Jarisch-Herxheimer reaction has been reported after chloramphenicol therapy in patients with syphilis, brucellosis, and typhoid fever. In patients with typhoid fever treated with chloramphenicol, several investigators have recorded a "shock-type reaction" characterized by circulatory collapse, attributed to sudden release of typhoidal endotoxin in an already weakened patient. Unlike the Herxheimer reaction, temperature is usually depressed, but exacerbation of fever has been reported. Recrudescense usually appears within 24 hours of the start of chloramphenicol therapy and persists from 24 to 48 hours.

Neurotoxic Reactions

Headache, mild depression, "dazed feelings," internal ophthalmoplegia, mental confusion, and delirium have been described in patients receiving chloramphenicol for a variety of infectious diseases. Optic and peripheral neuritides as probable effects of prolonged chloramphenicol therapy have been reported. Analysis of these cases suggests that these neurotoxic reactions were related both to large total doses of chloramphenicol and long periods of administration. The range of total dosages of chloramphenicol was from 190 to 1600 Gm. Toxic symptoms appeared between 42 days and 22 months after the start of therapy. Five patients had blurred vision as the most prominent symptom and in a sixth the initial complaint was blindness. This latter was the only one with permanent impairment of vision. Peripheral neuritis resolved in all patients except one, who still had minor residual symptoms thirteen months after onset. If symptoms of decreased visual acuity or peripheral neuritis occur during therapy, prompt withdrawal of the drug is indicated and large doses of oral or parenteral vitamin B complex should be considered.

Other Reactions

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, particularly monilia. Constant observation of the patient is essential. If new infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

CLINICAL USE OF CHLORAMPHENICOL

Rickettsial Diseases

The response of patients with rickettsial infections, including epidemic and murine typhus fevers, Brill's disease, scrub typhus fever, Rocky Mountain spotted fever, and rickettsial pox, has been dramatic with virtual elimination of mortality and marked shortening of the course of illness. Average length of the febrile period after administration of chloramphenicol is 2 days in patients with epidemic typhus fever and 3 days in those with other typhus fevers. Treatment should be given for a minimum of 6 days or 4 days after temperature returns to normal.

Relapse may occur when treatment is given only for 48 hours early in the disease. This can be prevented by giving additional doses on the fifth and sixth days after the initial course. Also, patients in relapse respond as readily to treatment as do those with primary infection.

In patients with Rocky Mountain spotted fever, defervescence occurs about the fourth day after therapy is started. Treatment should be continued for 24 hours after normal temperature is attained.

Typhoid Fever

Chloramphenicol has been established as the drug of choice for this disease. After therapy is started, fever subsides in 3 or 4 days regardless of age, severity of illness, or stage of disease. To lessen possibility of relapse, it is important that therapy be continued for from 8 to 10 days after reaching the afebrile period. Close observation of the patient for complications of the disease, and for aforementioned side effects of the drug, is essential. Results of chloramphenicol treatment for the carrier state are equivocal.

Other Salmonelloses

While chloramphenicol has proved to be a useful therapeutic agent in ameliorating and shortening the clinical course of salmonella infections other than typhoid, results are not as uniform. Recommended duration of treatment is the same as for typhoid fever.

Urinary Tract Infections

Treatment for infections of the urinary tract should be based upon sensitivity of bacteria and on anatomic factors contributing to the infection. The more common organisms encountered in the urinary tract infections are *Esch. coli, A. aerogenes, Ps. aeruginosa, Proteus sp., Staph. aureus* and *Strep. fecalis*.

Chloramphenicol has been found effective in treatment for about 70 per cent of urologic infections, particularly those caused by *Esch. coli, Strep. fecalis*, and *Proteus sp.* Relief of symptoms and repeated bacteriological studies should be depended upon to indicate duration of treatment.

Surgical Infections

Surgical infections such as post-operative wound infections, cellulitis, infected sinus tract, and peritonitis or intra-abdominal abscess from ruptured intestine, diverticulae, or appendix, usually are due to microorganisms sensitive to chloramphenicol. The antibiotic is given, adjunctively to surgical intervention, in the recommended dosage for an average of from 10 to 16 days.

Respiratory Tract Infections

Chloramphenicol may be employed for severe infections of the respiratory tract due to susceptible microorganisms and in the presence of contraindications to other agents. Patients on recommended doses become afebrile in from 18 to 72 hours; roentgenographic clearing will be slower.

Meningeal Infections

Many microorganisms causing meningitis are susceptible to chloramphenicol. The drug's high diffusibility results in effective concentrations in the cerebrospinal fluid. Institution of therapy cannot be delayed until results of laboratory tests are known. Many clinicians consider chloramphenicol alone (or in combination with other effective agents) the drug of choice for meningitis caused by *H. influenzae* as almost all strains are sensitive to this antibiotic. Parenteral dosage is recommended until the patient is afebrile, after which oral medication may be used. Medication should be continued for a minimum of seven days to avoid relapse.

Miscellaneous Infections

Chloramphenicol has proved to be useful and frequently effective in treatment for many diverse infections, including brucellosis, bartonellosis, relapsing fever, granuloma inguinale, plague, and ornithosis. Other effective therapeutic agents should receive consideration as the treatment of choice. Whenever definite contraindications to these are known, such as hypersensitivity, or clinical response is poor, the judicious use of chloramphenicol is warranted, keeping in mind aforementioned warnings, precautions, and side effects, particularly in patients requiring prolonged or intermittent treatment.

PACKAGE INFORMATION

Kapseals No. 379, Chloromycetin, each contain 250 mg. chloramphenicol, supplied in packages of 16 and 100.

Capsules No. 477, Chloromycetin, each contain 50 mg. chloramphenicol, supplied in packages of 25 and 100.

Capsules No. 480, Chloromycetin, each contain 100 mg. chloramphenicol, supplied in packages of 25 and 100.

Suspension Chloromycetin Palmitate, each 4 cc. represents 125 mg. chloramphenicol. (each cc. contains chloramphenicol palmitate equivalent to 31.25 mg. chloramphenicol with 0.5% sodium benzoate as preservative), in bottles of 60 cc.

PARKE, DAVIS & COMPANY

DETROIT, MICHIGAN, U.S.A.

Feb. 1961 AB

Parke, Davis & Company

RESEARCH LABORATORIES
2800 PLYMOUTH ROAD
ANN ARBOR, MICHIGAN
NORMANDY 3-7585

OFFICE OF DIRECTOR
DEPARTMENT OF CLINICAL INVESTIGATION

February 15, 1961

To the Osteopathic Profession:

The enclosed copies of recently revised package inserts required by new regulations of the Food and Drug Administration will accompany all oral and parenteral Chloromycetin products. This is our means of promptly placing this information into your hands. These inserts provide the latest essential information regarding warnings, precautions, indications and dosage for the proper use of this antibiotic.[1]

Sincerely yours,

J. K. Weston, M.D.

Director,
Department of Clinical
Investigation

1 See package insert following letter to Medical Profession.

Parke, Davis & Company

RESEARCH LABORATORIES
2800 PLYMOUTH ROAD
ANN ARBOR, MICHIGAN
NORMANDY 3-7585

OFFICE OF DIRECTOR
DEPARTMENT OF CLINICAL INVESTIGATION

February 15, 1961

To the Pharmaceutical Profession:

The enclosed copies of recently revised package inserts required by new regulations of the Food and Drug Administration will accompany all oral and parenteral Chloromycetin products. This is our means of promptly placing this information into your hands. These inserts provide the latest essential information regarding warnings, precautions, indications and dosage for the proper use of this antibiotic.[1]

Sincerely yours,

J. K. Weston, M. D.

Director,
Department of Clinical
Investigation

1 See package insert following letter to Medical Profession.

Senator NELSON. Is that the first letter of warning that was sent to the physicians?

Dr. LUECK. Mr. Chairman, I am informed that in 1952, the report from the National Research Council and the conclusions drawn from this report by the Food and Drug Administration were disseminated to the physicians in the United States, in 1952.

Senator NELSON. What information was disseminated at that time, sir?

Dr. LUECK. The National Research Council report of 1952, plus the conclusions that the Food and Drug Administration arrived at as a result of that report.

Senator NELSON. I will go back to that in a moment. But now that you mention the report, are you aware of what notice Parke, Davis sent to its detail men at that time?

Dr. LUECK. Am I aware of what, Mr. Chairman?

Senator NELSON. What information on that point was sent to the detail men from Parke, Davis at that time?

Dr. LUECK. No; I would not be specifically advised on that.

Senator NELSON. From the 1961 report of June 27—the hearing of the Committee on the Judiciary of the U.S. Senate, Subcommittee on Antitrust and Monopoly, on page 196, it says:

> The third item contains the following passage which the detail man was instructed to memorize and repeat verbatim to the physicians:
> "Intensive investigation by the Food and Drug Administration carried on with the assistance of the Special Committee on imminent specialists, appointed by the National Research Council, resulted in unqualified sanctions of continued use of Chloromycetin for all conditions for which it had been previously used."

Do you see any warning there to the detail men to notify the physician that there were serious blood dyscrasia problems associated with the drug?

Dr. LUECK. Mr. Chairman, I would like to state a detail man would have these official labels with him and leave them when he talked to the physician.

Mr. GORDON. Dr. Lueck, I just tried to read it. You need a magnifying glass to read it. I could not read it.

Senator NELSON. The real point is at that time, even though the detail man may have had the insert—whether or not he gives it to the doctor, I do not know—but the instruction was to say that this study by the specialists of the National Research Council "resulted in unqualified sanction of continued use of Chloromycetin for all conditions for which it has been previously used."

Dr. LUECK. Which is in the labeling for the uses, Mr. Chairman, that are listed and described in the labeling.

Senator NELSON. I hope I am not misinterpreting this Kefauver report, but the National Research Council said in item 1 that certain cases of serious blood dyscrasia had been associated with chloramphenicol. The only point I am making is that in the instructions to the detail man, Parke, Davis did not say anything about that. They said the report resulted in an unqualified sanction of use of the drug.

It does not seem to me that that National Research Council statement is an unqualified sanction. Do you now think that would mislead a detail man?

Dr. LUECK. I think what is unqualified in my opinion, Mr. Chairman, is that the labeling qualifies the product and its users and what the detail man was saying is that those uses still remain, and they have.

Senator NELSON. Do you really think that, when the detail man receives this kind of instruction about Chloromycetin, he is going to qualify this instruction from his own company. As the report says, the detail man was instructed to memorize and repeat the instructions verbatim to the physicians.

Do you think the detail man is then going to say to the doctor, "There are really qualifications. If you will read the report of the National Research Council, you will see that there are serious blood dyscrasia associated with chloramphenicol."

Do you think it is natural for the detail man to start emphasizing that when the company has told him something else?

Dr. LUECK. I do not think that the company told him something else. Along with that was this labeling that the doctor should read, which carried the warnings and which carried the uses and the recommended dosage, Mr. Chairman. This is official labeling. We do not want our detail men to paraphrase this. This is physician language and he must make the decision; the physician.

Senator NELSON. Why does not the instruction to the detail man specifically say, not that there is unqualified sanction, but that there are serious blood dyscrasia and this ought to be called to the attention of the physician?

Why should not the company have said that to the detail man? They did not.

Dr. LUECK. We have said that many times to physicians in our correspondence with them and the fact that millions of these package inserts or official pieces of labeling have been printed and disseminated with every product of Chloromycetin in the history of that drug——

Senator NELSON. Well, I am well aware of that. But the companies have testified repeatedly here that one of the responsibilities of the detail man is to be well informed and inform the doctor about what the drug is, how it is to be used, and all benefits and risks involved in the use of the drug so the doctor will be well informed. Yet what was set out to the detail man in this case did not say that at all.

Farther up on the page, on page 196, same reference, it reads, "An attachment to planned presentation 10," which under the heading "Suggested Details" suggests the exact language to be used by the detail man in presenting his argument. The covering letter stated:

So physicians are of the opinion that Chloromycetin has been taken off the market or it is just restricted. So physicians have formed the impression that this antibiotic has been associated with the development of blood dyscrasias in large numbers of patients and will be amazed when you point out the facts.

Now, is this not all calculated to instruct the detail men to play down the fact that there are blood dyscrasia at all and the fact that the National Research Council suggested some qualification—that is, caution about how it is administered because of the blood dyscrasia? Is that not your interpretation of that instruction?

Dr. LUECK. Our detail men, I will repeat again, Mr. Chairman, have instructions to leave with the physicians the official package insert that is current at that time. That is the document on which the physician must make his judgment as far as Parke, Davis & Co. is concerned. He can render judgment on his own experience or other experiences gained from the literature or his own personal experience. But our detail men leave the package insert with the physician. It is the most effective and thorough way we know of, of informing the physician, which is one of the things that Council recommended that we do.

Senator NELSON. I might say that, even with my brandnew glasses, I have to concentrate very hard to read the warning on the insert.

Dr. LUECK. I would like to comment on that. I personally have changed that. That was the package insert that was current in 1961. This is the one that is current today.

Senator NELSON. Can you read that more easily?

Mr. CUTLER. Yes.

Senator NELSON. All right; to go back to reading from that report again.

Dr. LUECK. Mr. Chairman, if I may, I would like to read to you or suggest that we did precisely in 1952, in the way of following up on the 1952 National Research Council report, that Parke, Davis & Co. followed out the instruction of the Food and Drug Administration specifically and I have a document here that is an FDA press release of August 14, 1952, that we did intend following their instructions to the letter.

Senator NELSON. Well, I have no evidence that you did not follow any instructions. I think it is a rather sad commentary that the FDA at that period in history did not have any greater concern for the public interest than they demonstrated by what they did in this and other cases. It does not persuade me that there is not something the company ought to do itself regardless of the FDA. I have been familiar in my long period in politics that regulatory agencies are often controlled by the people they are supposed to regulate. I think if you will look at the history of this one, the FDA did not protect the public at all. It is a shocking case. The FDA's actions should not be the defense on which the company stands. The pharmaceutical industry has been a great American industry which has made a great contribution to the health and welfare of the people of this country and I trust will continue to do so. But if they continue with this kind of shoddy practice, I might say to you quite frankly, the industry is going to run into some tough regulations. It does not mean it is a bad

industry. It just means that the industry is doing things that are not in the public interest.

I do not think anybody can read what the Kefauver report says about the instructions to the detail men without thinking that the company was doing its best to avoid giving the doctor the information that blood dyscrasias could occur as a consequence of the use of this drug and that it should be used only in very serious cases. We have a document here which we will get to later which tells that Chloromycetin was administered to people who had sore gums, and a lady died from it; to a 5-year-old with a little acne and a sore finger and somebody else with a sore throat, and they both died. They should never have had the drug. It does not make any sense at all. It ought to be the moral responsibility of the industry, the companies who know about this, to protect the public interest. But look at the instructions here, this same letter that I was referring to, and I quote from the Kefauver hearings—these are not my words. This is a report made back in 1961:

> Parke, Davis perverted the permission for continued use under these restrictions into a blanket "clearance of the drug." The same letter contains a highly misleading assertion: "Thus, Chloromycetin has successfully passed three intensive investigations originally by Parke, Davis Company, next by officers of the Food and Drug Administration, then by a special committee of authorities in the field of hematology and chemotherapy and the research by the National Council."

I think all of these instructions to the detail man were meant to convince him to peddle the story that there are really not any serious side effects here that the doctor ought to be worried about.

I have to answer another vote.

(Short recess.)

Senator NELSON. I am sorry about the continual interruptions. I did not plan them. I realize that they are unfair to the witness, because it seems that every time I make a statement and ask a question, I leave. It is unintentional.

Go ahead. I have finished what I had to say about that.

Did you want to respond?

Dr. LUECK. Mr. Chairman, I did not remember quite where we were or if I had to respond.

(Whereupon, the reporter read the record.)

Dr. LUECK. I think I have responded to that question a number of times for the record, Mr. Chairman. I think we could proceed.

Senator NELSON. All right.

Just a couple more points on these ads before I conclude.

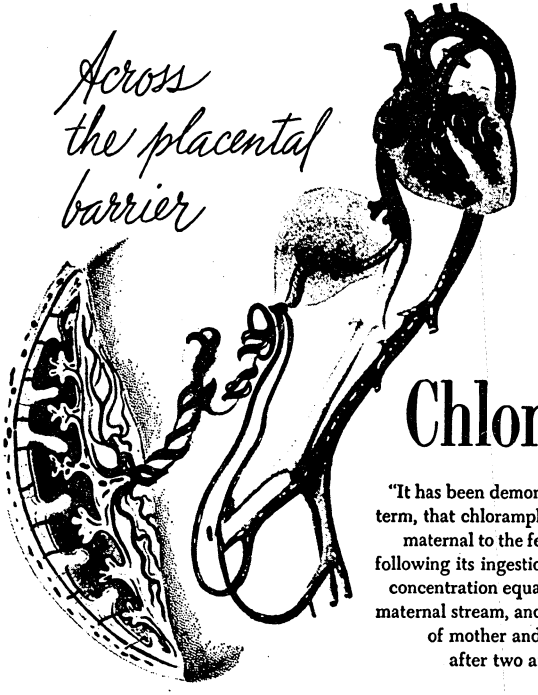
There are, and I would ask that they be put in the record, a series of ads from 1951 through 1967. Give the witnesses copies of these so they know what I am referring to.

I ask that they be put in the record.

(The advertisements referred to follow:)

[From Antibiotics and Chemotherapy magazine, Sept. 1951]

[From Antibiotics and Chemotherapy magazine, Mar. 1952]



Chloromycetin®

"It has been demonstrated, in pregnant women at term, that chloramphenicol passes from the maternal to the fetal blood stream in one hour following its ingestion, that it there attains a concentration equal to three-fourths of that in the maternal stream, and that the blood concentrations of mother and fetus are relatively the same after two and one-half hours."[1]

Therapeutic concentrations of well tolerated CHLOROMYCETIN (chloramphenicol, Parke-Davis) in the fetal blood stream are easily obtainable "by the simple oral administration of the drug to the mother."[2] Investigators have suggested, therefore, the empiric use of CHLOROMYCETIN in such virus infections as atypical pneumonia, in an attempt to avoid fetal damage.[3] Results with CHLOROMYCETIN in two patients with typhoid fever during pregnancy were reported recently as "quite satisfactory."[1]

Bibliography: (1) Stevenson, C. S.; Glazko, A. J.; Gillespie, E. C., and Maunder, J. B.: J.A.M.A. *146*:1190 (July 28) 1951. (2) Scott, W. C., and Warner, R. F.: J.A.M.A. *142*:1331 (April 29) 1950. (3) Ross, S., and others: J.A.M.A. *142*:1361 (April 29) 1950.

CHLOROMYCETIN is supplied in the following forms:
CHLOROMYCETIN Kapseals.® 250 mg., bottles of 16 and 100.
CHLOROMYCETIN Capsules, 100 mg., bottles of 25 and 100.
CHLOROMYCETIN Capsules, 50 mg., bottles of 25 and 100.
CHLOROMYCETIN Ophthalmic Ointment, 1%, ⅛-ounce collapsible tubes.
CHLOROMYCETIN Ophthalmic, 25 mg. dry powder for solution, individual vials with droppers.

MEDICAMENTA VERA · PD & CO.

Parke, Davis + Company
DETROIT, MICHIGAN

[From Postgraduate Medical magazine, July 1952]

in pelvic inflammatory disease.....

rapid response *with* **Chloromycetin®**

CHLOROMYCETIN produces prompt clinical response in the mixed infections commonly found in pelvic inflammatory disease. "In mixed infection [pelvic cellulitis and abscess] CHLOROMYCETIN appears to be superior to penicillin, streptomycin or sulfadiazine."[1]

"The clinical response to chloramphenicol consisted of marked symptomatic improvement, usually within 48 hours....

"Women who had large pelvic abscesses were treated so effectively with chloramphenicol that posterior colpotomy, with drainage of the abscess, was not necessary in effecting a rapid cure in any of our patients who were treated with this antibiotic from the start."[2]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is supplied in the following forms:

CHLOROMYCETIN Kapseals®, 250 mg., bottles of 16 and 100.

CHLOROMYCETIN Capsules, 100 mg., bottles of 25 and 100.

CHLOROMYCETIN Capsules, 50 mg., bottles of 25 and 100.

CHLOROMYCETIN Ophthalmic Ointment, 1%, ⅛-ounce collapsible tubes.

CHLOROMYCETIN Ophthalmic, 25 mg. dry powder for solution, individual vials with droppers.

1. Greene, C. C.: Kentucky M. J. *50*:8, 1952.
2. Stevenson, C. S., et al.: Am. J. Obst. & Gynec. *61*:498, 1951.

MEDICAMENTA VERA · PD & CO.

Parke, Davis + Company

[From General Practitioner magazine, Jan. 1953]

in the hands of the physician

Often the critical evaluation of the drug to be administered is as important to the patient's recovery as is the diagnosis of his condition. In each case correct procedures can be determined only by the physician.

CHLOROMYCETIN is eminent among drugs at the disposal of the medical profession. Clinical findings attest that, in the hands of the physician, this widely used, broad spectrum antibiotic has proved invaluable against a great variety of infectious disorders.

Chloromycetin®

notably effective
well tolerated
broad spectrum antibiotic

The many hundreds of clinical reports on CHLOROMYCETIN emphasize repeatedly its exceptional tolerance as demonstrated by the infrequent occurrence of even mild signs and symptoms of gastrointestinal distress and other side effects in patients receiving the drug.

Similarly, the broad clinical effectiveness of CHLOROMYCETIN has been established, and serious blood disorders following its use are rare. However, it is a potent therapeutic agent, and should not be used indiscriminately or for minor infections—and, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including:
CHLOROMYCETIN Kapseals,® 250 mg., bottles of 16 and 100.
CHLOROMYCETIN Capsules, 100 mg., bottles of 25 and 100.
CHLOROMYCETIN Capsules, 50 mg., bottles of 25 and 100.
CHLOROMYCETIN Ophthalmic Ointment, 1%, ¼-ounce collapsible tubes.
CHLOROMYCETIN Ophthalmic, 25 mg. dry powder for solution, individual vials with droppers.

MEDICAMENTA VERA

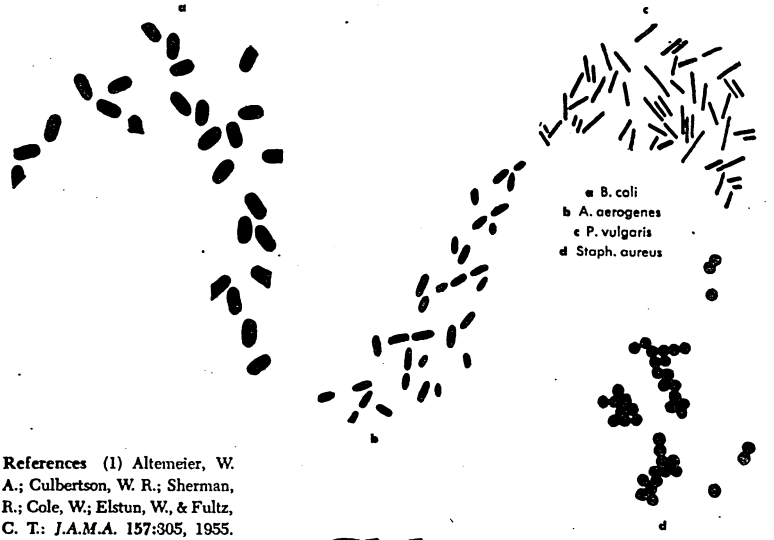
Parke, Davis & Company

[From General Practitioner magazine, Mar. 1953]

[From Antibiotics and Chemotherapy magazine, Nov. 1954]

[From Antibiotics and Chemotherapy magazine, Oct. 1955]

less resistance encountered...



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Chloromycetin®

for today's problem pathogens

Recent in vitro tests and clinical studies again demonstrate the unsurpassed efficacy of CHLOROMYCETIN (chloramphenicol, Parke-Davis) against a wide variety of pathogens. For example, against urinary infections, now characterized by increased incidence of resistant gram-positive and gram-negative strains, CHLOROMYCETIN continues to provide outstanding antibacterial action.[1-11]

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

[From General Practitioner magazine, Jan. 1956]

[From General Practitioner magazine, Sept. 1956]

they never make faces at...

Suspension Chloromycetin®

Palmitate pleasant-tasting broad spectrum antibiotic preparation for pediatric use

When you prescribe SUSPENSION CHLOROMYCETIN PALMITATE for your young patients, therapeutic response is rarely marred by missed doses or spilled doses. Children really like the taste of this custard-flavored preparation. And it slips soothingly down the sorest throat.

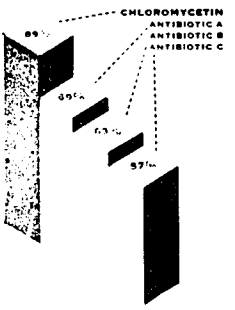
SUSPENSION CHLOROMYCETIN PALMITATE keeps without refrigeration, a convenience appreciated by mothers. Its liquid form permits easy adjustment of dosage according to your directions.

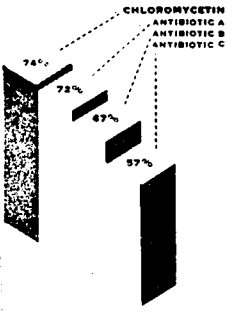
CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

supplied: SUSPENSION CHLOROMYCETIN PALMITATE, containing the equivalent of 125 mg. of CHLOROMYCETIN (chloramphenicol, Parke-Davis) per 4 cc., is available in 60-cc. vials.

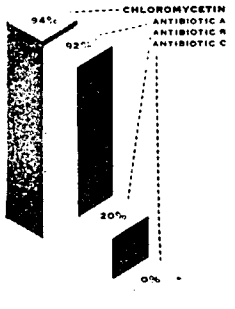
Parke, Davis & Company DETROIT, MICHIGAN

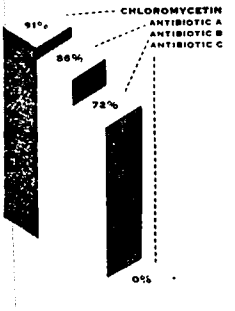
[From Antibiotics and Chemotherapy magazine, Feb. 1957]





SENSITIVITY OF COMMON PATHOGENS TO CHOROMYCETIN AND THREE OTHER MAJOR ANTIBIOTICS*





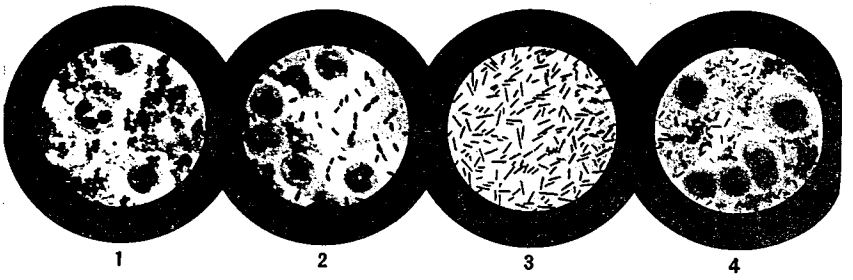
[From General Practitioner magazine, June 1958]

THIS 5-YEAR STUDY SHOWS... CONTINUED EFFICACY

CHLOROMYCETIN®

COMBATS MOST CLINICALLY IMPORTANT PATHOGENS

Recent reports comparing the effectiveness of various antibiotics against commonly encountered pathogens indicate that CHLOROMYCETIN (chloramphenicol, Parke-Davis) has maintained its high degree of effectiveness.[1-5] It is still highly active against many strains of staphylococci,[1-8] streptococci,[2,7] pneumococci,[2] and gram-negative[1,2,7,9,10] organisms.

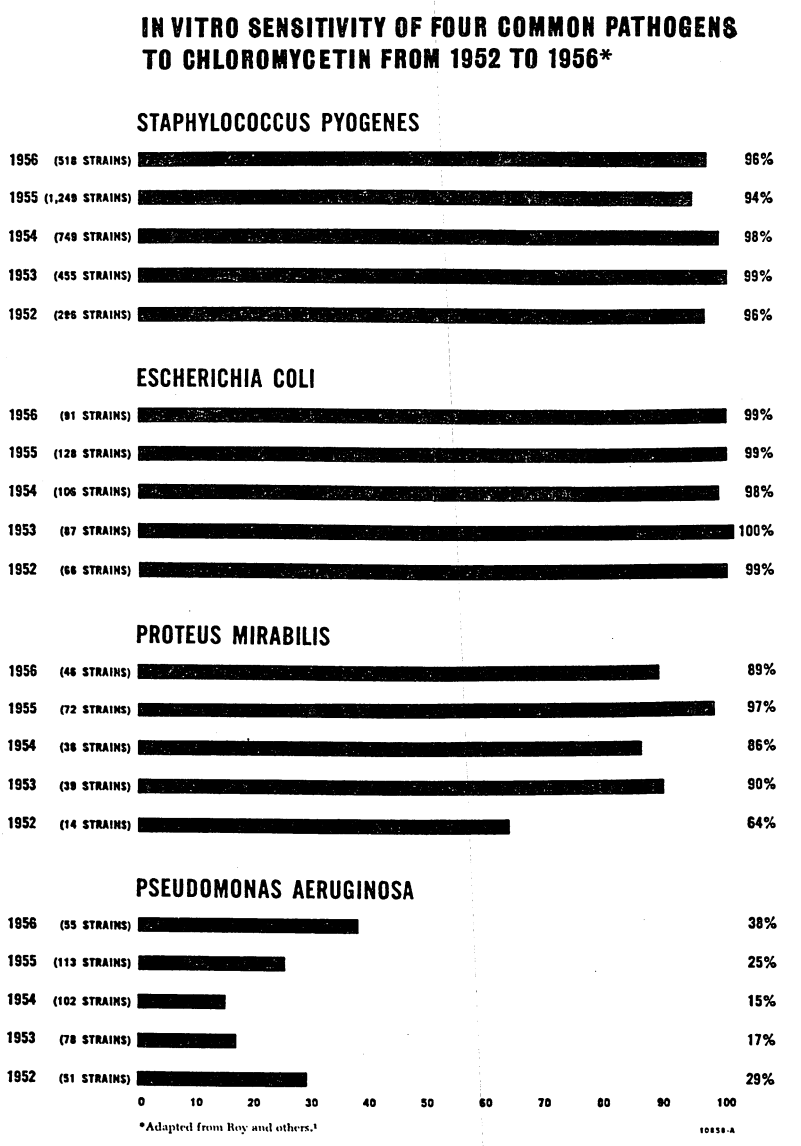


CHLOROMYCETIN is a potent therapeutic agent, and because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

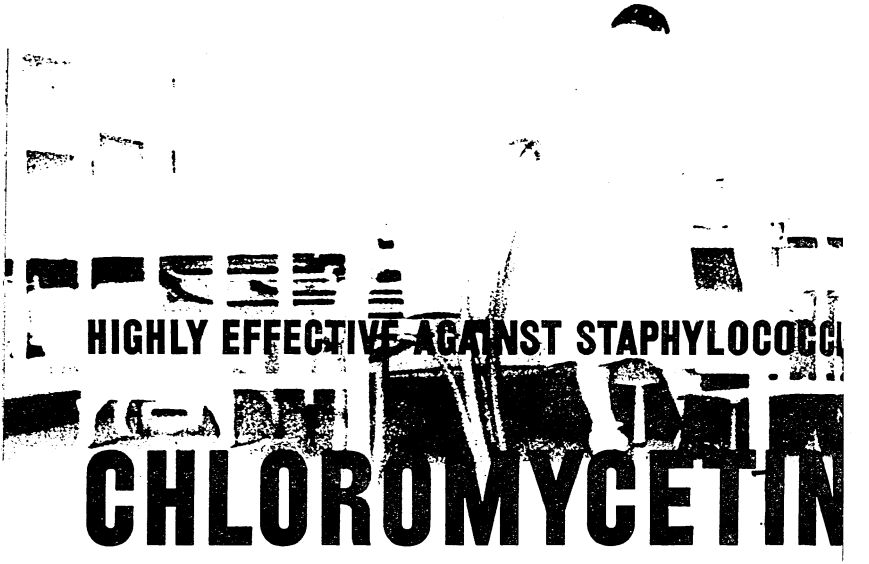
REFERENCES: (1) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M.A.J.* 77:844 (Nov. 1) 1957. (2) Schneierson, S. S. *J. Mount Sinai Hosp.* 25:52 (Jan.-Feb.) 1958. (3) Koch, R., & Donnell, G.: *California Med.* 87:313, 1957. (4) Waisbren, B. A., & Strelitzer, C. L.: A Five-Year Study of the Antibiotic Sensitivities and Cross Resistances of Staphylococci in a General Hospital, paper presented at Fifth Ann. Symp. on Antibiotics, Washington, D. C., Oct. 2-4, 1957. (5) Doniger, D. E., & Parenteau, Sr. C. M.: *J. Maine M. A.* 48:120, 1957. (6) Boyer, A.: Changes in Resistance to Various Antibiotics of Staphylococci and Other Microbes, paper presented at Fifth Ann. Symp. on Antibiotics, Washington, D. C., Oct. 2-4, 1957. (7) Hasenclever, H. F.: *J. Iowa M. Soc.* 47:136, 1957. (8) Josephson, J. E., & Butler, R. W.: *Canad. M.A.J.* 77:567 (Sept. 15) 1957. (9) Rhoads, P. S.: *Postgrad. Med.* 21:563, 1957. (10) Holloway, W. J., & Scott, E. G.: *Delaware M. J.* 29:159, 1957.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

[From General Practitioner magazine, June 1958]



[From General Practitioner magazine, Dec. 1958]



Reports on studies of *in vitro* activity of CHLOROMYCETIN over the past few years indicate that this antibiotic has maintained its effectiveness against most strains of staphylococci.[1-4] "...Staphylococci do not acquire resistance to chloramphenicol [CHLOROMYCETIN] as they do to other antibiotics, in spite of heavy use of chloramphenicol [CHLOROMYCETIN]."[1]

These *in vitro* studies are borne out by excellent clinical results with CHLOROMYCETIN in treatment of patients for severe staphylococcal infections, including staphylococcal pneumonia,[5] postoperative wound infections,[6] postoperative parotitis,[7] and puerperal breast abscesses.[8]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals* of 250 mg. in bottles of 16 and 100.

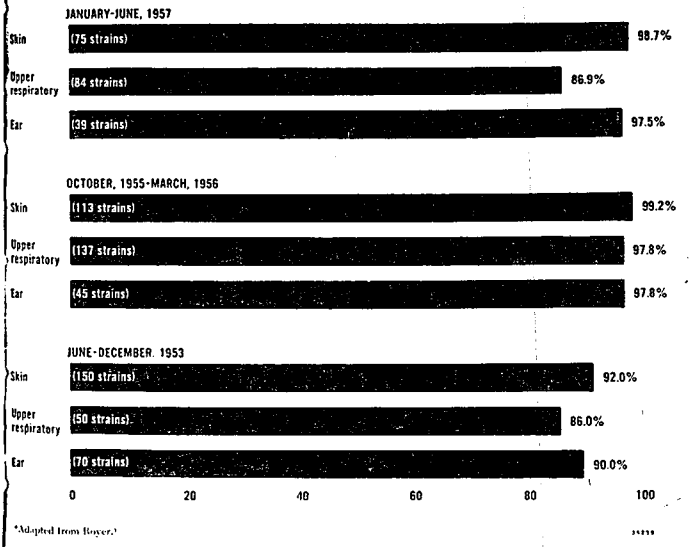
CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES: (1) Royer, A., in Welch, H., & Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc. 1958, p. 783. (2) Waisbren, B. A., & Strelitzer, C. L.: *Arch. Int. Med.* 101:397, 1958. (3) Koch, R., & Donnell, G.: *California Med.* 87:31 1957. (4) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M. A. J.* 77:844, 1957. (5) Cooper, M. L., & Keller, H. M *J. Dis. Child.* 95:245, 1958. (6) Caswell, H. T., *et al.*: *Surg., Gynec. & Obst.* 106:1, 1958. (7) Brown, J. V.; Sedwitz, J. L., & Hanner, J. M *U. S. Armed Forces M. J.*: 9:161, 1958. (8) Sarason, E. L., & Bauman, S.: *Surg., Gynec. & Obst.* 105:224, 1957.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

[From General Practitioner magazine, Dec. 1958]

IN VITRO SENSITIVITY OF STAPHYLOCOCCI FROM THREE FOCI OF INFECTION TO CHLOROMYCETIN FROM 1953 TO 1957*



*Adapted from Boyer.[1]

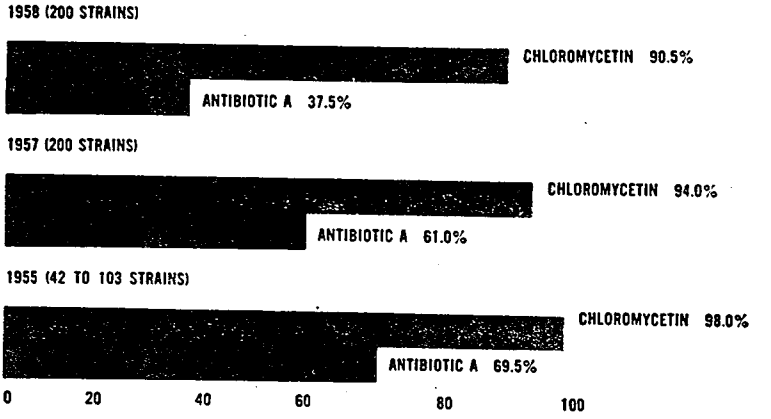
[From Antibiotics and Chemotherapy magazine, Jan. 1959]

EFFECTIVE AGAINST MOST STRAINS OF STAPHYLOCOCCI

CHLOROMYCETIN

COMBATS MOST CLINICALLY IMPORTANT PATHOGENS

IN VITRO SENSITIVITY OF PATHOGENIC STAPHYLOCOCCI TO CHLOROMYCETIN AND TO ANOTHER WIDELY USED BROAD-SPECTRUM ANTIBIOTIC FOR 1958, 1957, and 1955*



*Adapted from Holloway, W. J., & Scott, E. G.: *Delaware M. J.* 30:175, 1958. In this study CHLOROMYCETIN and Antibiotic A were used in identical strengths of 5 mcg.

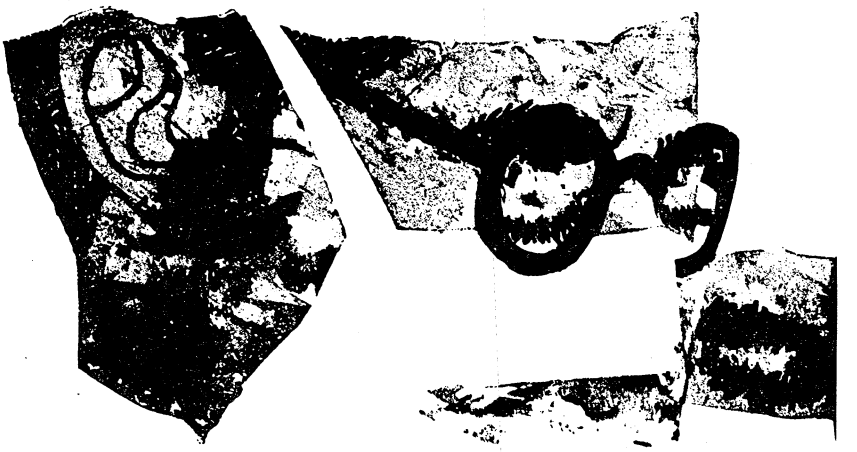
CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

71453

[From General Practitioner magazine, May 1961]



inside as well as outside the hospital...
staphylococci usually remain sensitive to

CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

That the sensitivity patterns of "street" staphylococci differ widely from those of "hospital" staphylococci is a well-established clinical fact.[1-5] Although strains of staphylococci encountered in general practice have remained relatively sensitive to a number of antibiotics,[6] the problem of antibiotic-resistant staphylococci appears to be a threat to all patients in hospitals today. It is encouraging to note, however, "...that a relatively small percentage of strains develop resistance to chloramphenicol, despite the consumption of large amounts of this antibiotic."[7]

In one hospital, for example, CHLOROMYCETIN "...was the only widely used antibiotic to which few of the strains were resistant."[8] In another hospital, despite steadily increasing use of CHLOROMYCETIN since 1956, "...the percentage of chloramphenicol-resistant strains has actually been lower in subsequent years."[1] Elsewhere, insofar as hospital staphylococci are concerned, it appears that "...the problem of antibiotic resistance can be regarded as minimal for chloramphenicol."[2]

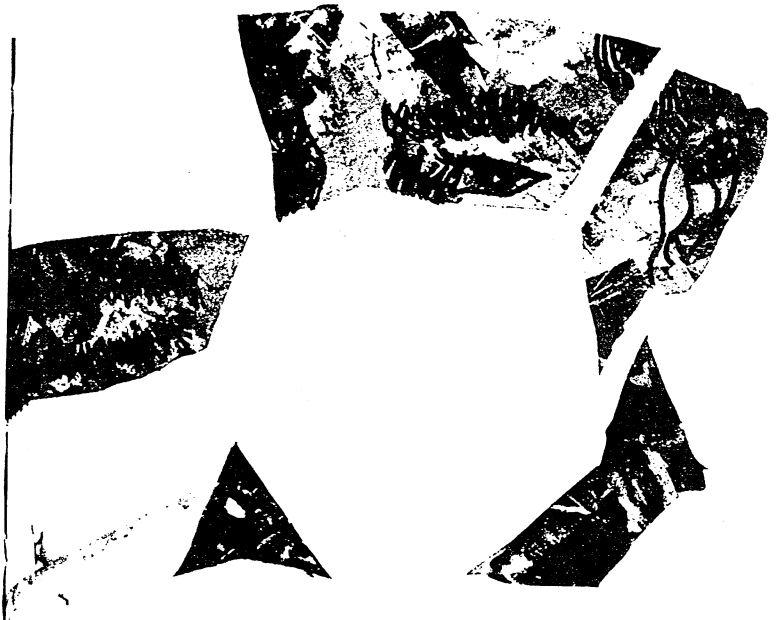
CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

See package insert for details of administration and dosage.

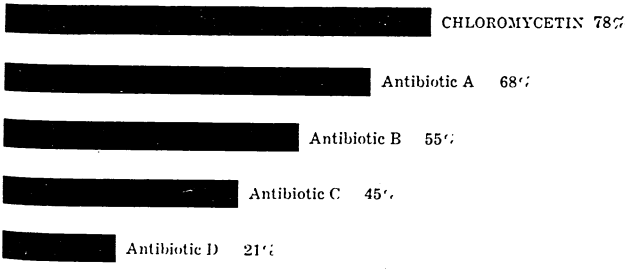
Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short-term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

[From General Practitioner magazine, May 1961]



IN VITRO SENSITIVITY OF 250 STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN AND TO FOUR OTHER ANTIBIOTICS*



These strains of coagulase-positive staphylococci were isolated from hospitalized patients at a large county hospital during the year 1959. Sensitivity tests were done by the disc method.

*Adapted from Bauer, Perry, & Kirby†

References: (1) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960. (2) Fisher, M. W.: *Arch. Int. Med.* 105:413, 1960. (3) Cohen, S.: *Circulation* 20:96, 1959. (4) Edwards, T. S.: *Am. J. Ophth.* 48, Part II:19, 1959. (5) Smith, I. M.: Staphylococcal Infections, Chicago, The Year Book Publishers, Inc., 1958, p. 148. (6) Petersdorf, R. G.; Rose, M. C.; Minchew, H. B.; Keene, W. R., & Bennett, I. L., Jr.: *Arch. Int. Med.* 105:398, 1960. (7) Editorial: *J.A.M.A.* 173:544, 1960. (8) Finland, M.; Jones, W. F., Jr., & Bennett, I. L., Jr.: *Arch. Int. Med.* 104:365, 1959.

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

[From Medical World News, Feb. 2, 1962]

[From Medical World News, Feb. 2, 1962]

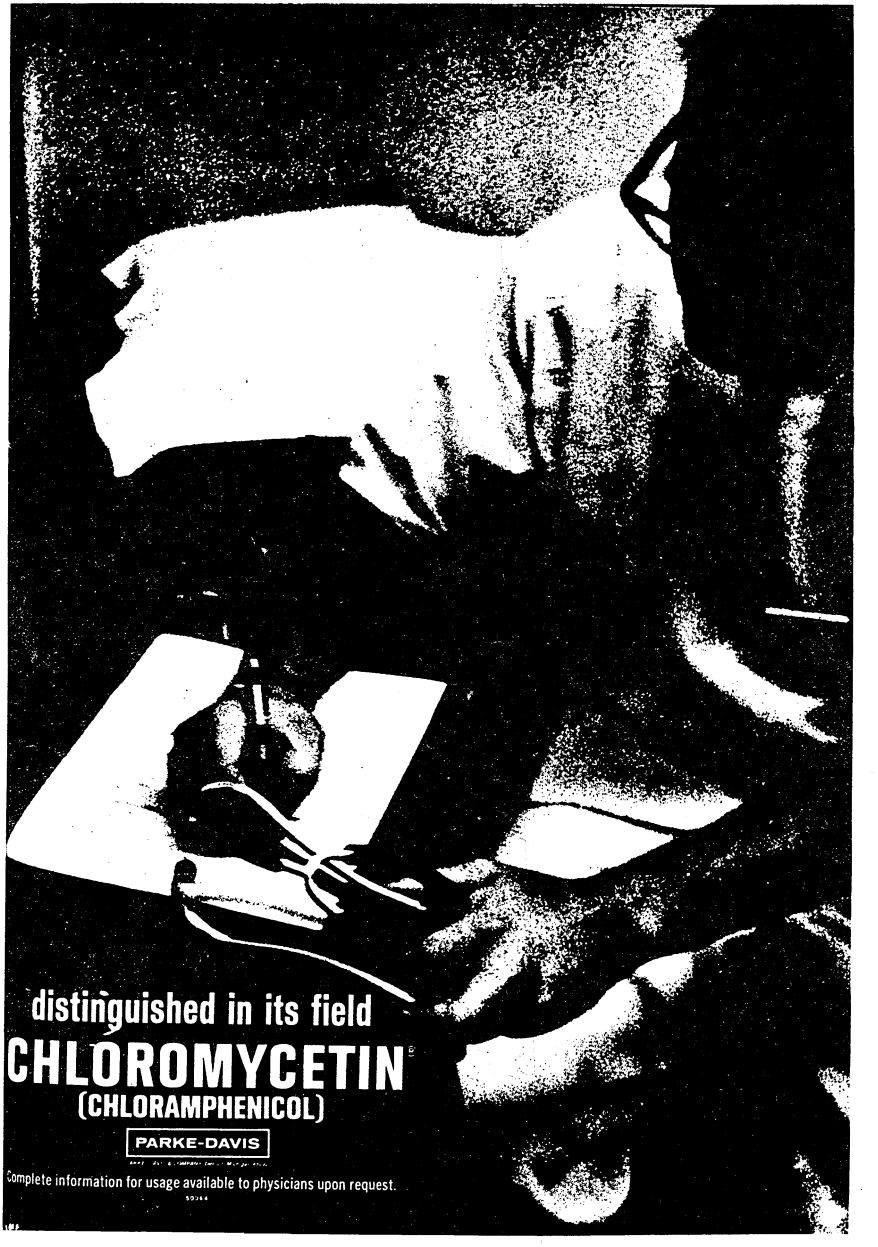
[From General Practitioner magazine, June 1962]

[From General Practitioner magazine, Sept. 1962]

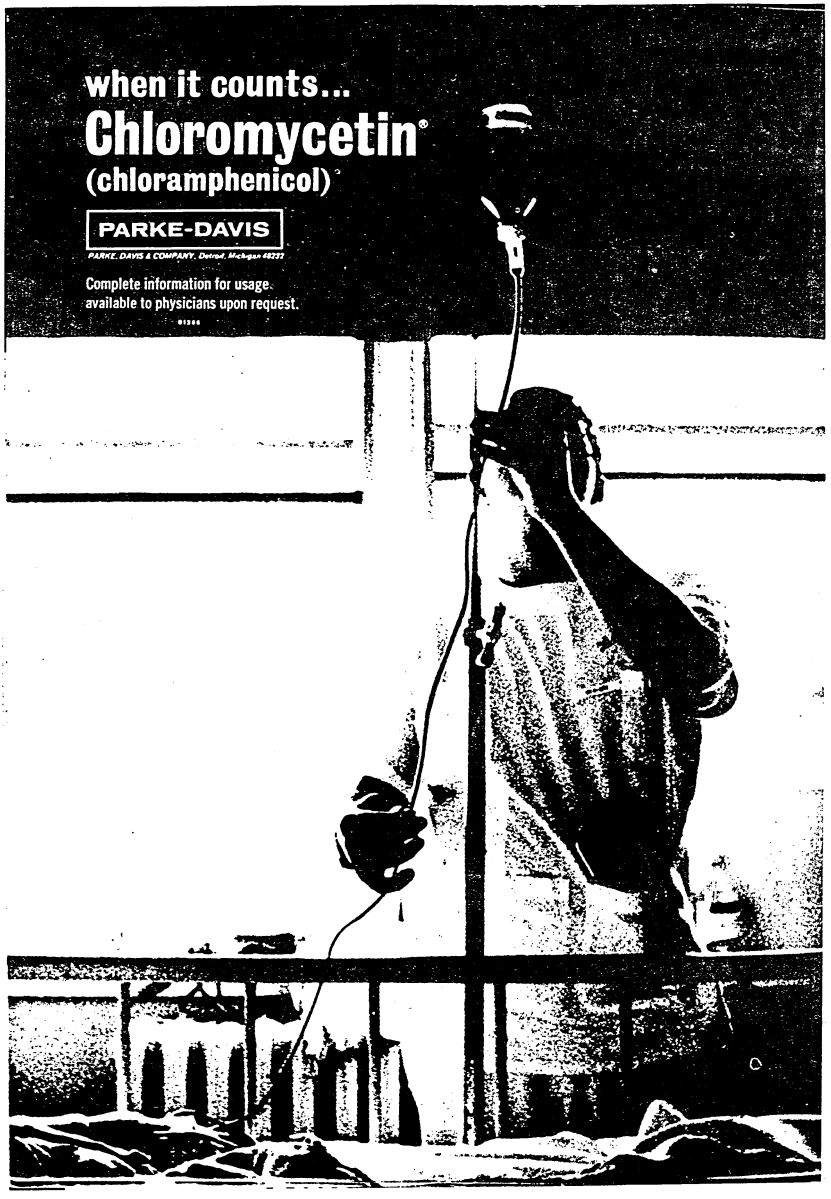
[From Modern Medicine, Sept. 17, 1962]

[From Southern Medical Journal, Jan. 1963]

[From the New England Journal of Medicine, Feb. 25, 1965]



[From Southern Medical Journal, Apr. 1967]



Senator NELSON. None of the ads that you have referred to have very strong warnings in them.

Mr. CUTLER. The only ads we have are the ones that are 15 and 16 years old.

Senator NELSON. I was just about to refer to the ad of February 20, 1967, the ad that I spoke of before. Does the witness have a copy of that?

Dr. LUECK. I believe so.

Senator NELSON. It says, "When it counts, Chloromycetin"—on the front.

Dr. LUECK. Yes, sir.

Senator NELSON. Is it the intent of the company henceforth to publish this kind of a warning in all of its ads?

Dr. LUECK. Yes, sir. When the ad includes indications for usage, Mr. Chairman, and dosage schedules, we will include the full warning statements, all the side effects, and so forth.

Senator NELSON. You mean that you would still run an ad like the one you ran in the General Practitioner or some of these other ads, where there is no warning at all?

Let me take one we talked about before, the January 1961.

It says, "Resistant staphylococci among outpatients emerge less frequently, disappear more readily," and then the warning that is there simply says:

Chloromycetin (chloramphenicol, Parke, Davis) is available in various forms, including Kapseals of 250 mg., in bottles of 16 and 100.

Chloromycetin is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

You mean the company will run ads henceforth with that little warning in them?

Dr. LUECK. Mr. Chairman, I do not have the ad you have in your hand, apparently, and before I respond to that question, I want to make certain what I am addressing myself to.

Senator NELSON. This is the ad I read to you earlier, to contrast that with the much stronger warning in the February 20, 1967 ad. Is that warning in the 1961 ad adequate in view of what we now know about this drug from what you said in your February 20, 1967 ad?

Dr. LUECK. Mr. Chairman, when Parke, Davis & Co. either cites an indication in the ad, an indication for use that physicians might elect to prescribe Chloromycetin for that drug entity and/or if we include any dosage recommendations in any ad, the entire warning statement as depicted in this ad, the ad of February 20, 1967, published in the Journal of the American Medical Society, will be followed.

Senator NELSON. Do you mean to say that you will run ads to physicians urging their use of this drug, and omit the warning that says "serious and even fatal blood dyscrasias may occur"?

Dr. LUECK. No, sir; we are being misunderstood. I am merely saying that we will print what is in the package insert nearly verbatim, as we have in the February 20, 1967 ad.

Senator NELSON. Then take the ad I just gave you. You would not run that 1961 ad again, then?

Dr. LUECK. No, sir; we would not run that 1961 ad.

Senator NELSON. You do not think that it is adequate?

Dr. LUECK. No, sir; it does not meet the present requirements.

Senator NELSON. Do you think these present requirements, in view of the history of this product, are justifiable?

Dr. LUECK. Yes; I think they are. I think they are very adequate.

Senator NELSON. Now, let me ask you another question: This ad was published February 20, 1967?

Dr. LUECK. Yes, sir.

Senator NELSON. I have here an ad from the British Medical Journal of February 11, 1967, just 9 days away from this very detailed ad. That British ad does not have any warning in it at all. It says:

Clincally Unexcelled.

Clinical use throughout the world has established Chloromycetin (chloramphenicol B. P. Parke, Davis) as an antibiotic of outstanding efficacy in a wide variety of bacterial, viral and rickettsial infections. Chloromycetin possesses extremely high anti-microbial activity, crosses tissue barriers readily, diffuses widely and rapidly through nearly all body tissues and fluids, and is well tolerated. It is rapidly absorbed and bacterial resistance is minimal. And because of these notable properties, therapy with Chloromycetin generally results in prompt response and rapid recovery.

No warning at all in that ad. How do you explain that?

Dr. LUECK. Mr. Chairman, is that the complete ad?

Senator NELSON. Yes; do you not have a copy of it?

Dr. LUECK. I only have one page. I did not know if that was the complete ad or not.

Senator NELSON. Yes; I will show you the journal.

Dr. LUECK. I would like to comment that the medical feeling and impressions on the warning requirements on Chloromycetin are different in practically every country of the world. Parke, Davis & Co., has always met all the requirements, the legal requirements of whatever country we distributed our products in and we have met the necessity of the medical profession in that country. These ads, so far as I know, met all of those requirements.

Senator NELSON. Well, the effect of the drug is the same on people in other countries as it is here; is it not?

Dr. LUECK. Largely.

Senator NELSON. Do you know of some differentiation?

Dr. LUECK. Yes; there are some minor differentiations, but for the sake of this discussion, let us say they are the same.

Mr. CUTLER. Mr. Chairman, I think you will find that the point you are developing is true of every single ad in this magazine, which is a distinguished magazine of the British Medical Society and I assume it meets all of what they consider to be appropriate requirements.

Senator NELSON. I have not questioned whether or not it met their requirements. I have assumed that. There is a very serious moral question involved that ought to be brought up. It sure shocks me. What the witness says is we will meet the standards of the country where the drug is sold. That means, of course, there is not a single underdeveloped country in the world that has any defense against the exploitation of their people for profit by an American corporation who does not warn them of the serious, mighty serious, possibly fatal consequences here. So you mean to testify that your company will stand

on the proposition that we will send drugs to Tanganyika, we will send to Latin American countries, we will send drugs to all the underdeveloped countries in the world and since they do not have any standards, we will fool them all we can and make a great big profit and never tell the doctors that there is a risk of serious blood dyscrasias. Is that what you are telling the committee?

Mr. CUTLER. No, sir. I think you know that, sir. This is a British Medical Society. The British doctors are sophisticated doctors, just as sophisticated as the doctors in this country. This meets all their requirements. This is, of course, only a small part of the information that goes to a British doctor.

Senator NELSON. That is not the testimony.

Mr. CUTLER. You are indicting every drug company in Great Britain and the United States.

Senator NELSON. Any company, drug company or any other kind of company, that would do that, I would be pleased to indict on moral grounds. I think they ought to be indicted on moral grounds. Your testimony is that you will meet the standards of the country in which you are advertising, not the standards of safety which the witness has testified is a proper standard, the proper ad which gives this warning that is put in ads in this country. But in countries where the people do not know any better, where the country is not protected by laws, you will tell us that you have no compunction about running an ad that will fool a doctor, as you did in California in 1961.

I will read this to you. I would think you would not sleep at night, frankly, you or any drug company that would do that.

On page 11 of "By Prescription Only," by Morton Mintz, it says that Dr. L. A. M. Watkins, La Canada, Calif., physician, prescribed Chloromycetin to his own son. In 1952, the boy died. In November 1961, the physician went before a California Senate committee and testified: "I do not know of one single victim who would not be alive today had he only been permitted to get well by himself; by nature without the use of antibiotics." Here is an American doctor. I do not know what he read about chloramphenicol. But if he read these ads without any warning, he might very well prescribe it and lose his own son. I do not understand what standard of ethics would govern a great industry of this country that would find it satisfactory to finally, under compulsion in this country, warn the public and warn the doctors about serious blood dyscrasias and then cavalierly advertise in another country without telling those people about the risks. I should think you people would not be able to sleep.

Mr. CUTLER. Mr. Chairman, I think you are reaching awfully far to criticize a witness and a company that brought you some evidence that you have been asking for, for months, about therapeutic equivalency of various drugs. It so happens that the pharmaceutical industry, as you know, has believed that advertisements of drugs are not the primary source of information on which the doctor relies. In 1962, this issue was fought out in this Congress and it was decided by the Congress that all advertisements should contain brief summaries, warnings, of complications and side effects, and the FDA was given power to regulate in that area. These companies have done their very best to live up to that law, the need for which they did not agree

with at the time. They have observed that law, and you are digging back to 1952, some 15 years ago, to whip this company which brought you some evidence.

I must object to that, Mr. Chairman, most respectfully.

This witness did not come to testify about advertising. Neither you nor Mr. Gordon said anything to him in advance to indicate you intended to question him about advertising. If you want to query Parke, Davis about its advertising, give them notice and they will produce a witness to reply to you.

Senator NELSON. I am perfectly happy to have any statement you want to make in the record. I did not tell you what witnesses to bring. You are familiar with the questions that have been raised.

Mr. CUTLER. You knew what they were going to cover. This witness testified until 11 o'clock this morning on an issue you have been inviting the entire industry to bring in some evidence about; namely, therapeutic equivalency. He brought it in. You asked him perhaps half an hour of questions on that subject and ever since, you have been off on advertising as a way to harm this company.

Senator NELSON. I have not been discussing advertising as a way to harm this company. And, I do not blame this witness. He does not run the advertising.

But now that you mention it, you select the date, you bring in your advertising people, and we will stick to this one issue of advertising and we will take 1 day or 2 days or whatever amount of time you need to explain this kind of advertising and what you do in this country versus what you do in underdeveloped countries or in England or elsewhere.

Do you want to give me a date? I will cancel everything I have.

Mr. CUTLER. I cannot act for the company, sir, but if you wish to have a Parke, Davis witness, they will be happy to supply one.

Senator NELSON. We will be glad to have Parke, Davis come in at any time. We will set a date and we will go through all this advertising with them.

I have not been beating the company over the head unfairly. I think if you raised this issue on moral and ethical grounds before any objective citizen in America, he is going to say it is shocking.

Mr. CUTLER. Mr. Chairman, it is an issue that was fought and resolved in 1962. Everything you have said here has been put into the record of the Congress before 1962. The law was passed, the companies are doing their level best to comply with it. Parke, Davis, as this witness said, has never since been accused by FDA of issuing any improper ad, as I understand it. We are on a different issue now: namely, the issue of generic equivalency. That is what you invited people to come and testify about. That is what Dr. Lueck testified about and you do not have any questions to ask him about that.

Senator NELSON. The issue was not resolved in 1962. The issue I am talking about right now is February 20, 1967, and February 11, 1967. I am talking about two ads run by the same company. I am talking about the witness' testimony as a professional person that he thinks that this warning should be in the ad.

Mr. CUTLER. Speaking of warnings, Mr. Chairman, would it not have been appropriate for this committee to say to some representa-

tive of Parke, Davis or to us that you intended to ask some question today about those ads and you would like have a witness qualified on that subject?

Senator NELSON. We intend to ask questions about the whole spectrum of issues related to the drug industry as we have of every other witness who has come here. You are the first one to complain and you have not yet been a witness. I can't predict every question we will think of as various issues arise. But if you think this is unfair, as I say, you can notify my office as to when Parke, Davis wants to go through these ads with us and we will pick out a time very soon for Parke, Davis to bring their advertising people. Let them talk about the morality of this ad.

But it shocks me that you do not even blush when you defend a company advertising drugs in another country without the warning required here when the reason it is required in this country is because the ad without the warning does mislead doctors, it does cause people to prescribe a dangerous drug for illnesses that are not serious. That is why the ad is run with the warning. And you know it and everybody else knew it, too.

I would like an answer to that. If this is the standard of ethics by which the industry operates, I tell you, you fellows are in for some sad trouble. I do not think this country will stand for it.

I do not have any more questions of this witness.

Thank you, Dr. Lueck.

(The complete prepared statement and attachments submitted by Dr. Lueck for presentation on November 16, 1967, follows:)

STATEMENT OF LESLIE M. LUECK, PH. D., DIRECTER OF QUALITY CONTROL, PARKE, DAVIS & CO.

TOTAL QUALITY CONTROL OF MEDICINAL PRODUCTS

Mr. Chairman and Members of the Committee: My name is Leslie M. Lueck. I am director of Quality Control for Parke, Davis & Company. I am representing the Pharmaceutical Manufacturers Association today to provide you and members of the Subcommittee with an insight into the quality control operations of reputable drug firms.

I am a native of Wisconsin and a graduate of the University of Wisconsin having received a Ph.D in pharmacy from that school in 1954. After receiving my doctorate, I joined the Research staff of Parke, Davis & Company and spent the first seven years of my professional career in Product Development. Since 1961, I have devoted my efforts to Quality Control, becoming Director of Quality Control in April 1963.

My interest in the quality of medicinal products was, of course, first generated as a stuednt of the pharmaceutical sciences. However, it was enhanced to a great degree after joining Parke, Davis & Company for it was there, in Product Development, that I experienced *firsthand* the true meaning of quality in a medicinal product.

The philosophy of quality control of pharmaceutical products has changed a great deal since its inception in the late nineteenth century.

There is often a tendency to associate the quality control of drugs with enactment of the first Food and Drug laws in 1906. This, however, is not the case. Quality control was practiced by certain pharmacutical manufacturers before this law came into being and long before the term "quality control" was used to express the idea.

For example, prior to about 1880, there were no standard tests applied to a medicinal product. Compendia were primarily concerned with methods of preparation; recipe books, rather than books of standards.

The first standardized pharmaceutical product was controlled by a determination of the total amount of alkaloids present in various preparations. Subsequent

lots of the finished product were adjusted according to this specification; a crude method, indeed, in the light of present-day procedures. In the field of control of the quality of medicinal products, it can be likened to the first Wright brothers' flight as compared to present-day aviation.

Shortly thereafter, manufacturers of lesser quality products were forced, through the exercise of freedom of choice available to the prescribing physician to market standardized preparations. This, then, was the beginning of quality control.

Quality control is not a term that is exclusive to the pharmaceutical industry. Most major industries maintain extensive quality control departments. Their philosophy of quality control, however, is often based on one-hundred percent inspection of the finished product.

Inspection of every finished pharmaceutical product is not only impractical, but does not guarantee quality. Analysis is helpful, but cannot be done on *all* units of the product because it is destructive in nature and, of course, a one-hundred percent analysis would leave no product to administer to the patient.

Therefore, since inspection and analysis cannot alone assure quality in a product, a new approach to checking quality was born, the concept of control rather than analysis.

Control of the quality of a medicinal product is based on preventive measures. That is, the establishment of control procedures, methods, and systems involving all the components, the methods of manufacture, and the package and labeling of a product. These measures reduce or prevent errors or defects from entering into product, and thereby assures its quality.

Because of the advent of more and more complex pharmaceutical products with their diversified physiological actions, there has arisen a new concept in the realm of quality control—the theory and practice of "total quality control" as stated in the Principles of Total Quality Control recently adopted by the Pharmaceutical Manufacturers Association. A copy of this statement is attached as Exhibit A for inclusion in the record.

Guided by these principles, the function of the quality control division of a pharmaceutical company is to *coordinate, integrate, and provide an atmosphere within the company* for total quality control.

The term "quality" in a medicinal product can be defined as the assurance of safety, efficacy, and acceptability for the intended function of the product.

The product must be safe when used according to directions for the indications recommended. In other words, when the product is administered according to the directions on the labeling, using the recommended dosage, observing the cautions cited, and monitored by medical experts when needed, the product is considered to be safe within the framework of medical judgment.

The product must also be effective. It must do the job according to the claims which are made for it.

The efficacy of a product must be determined prior to the time of submission of a new drug application. The monitoring process, however, does not stop there. One aspect of total quality control requires that the effectiveness of a marketed product be under continuous surveillance. This is especially true in the area of individual patient responses, variations and tolerances, drug interaction, and long-term product stability.

The product must of course be acceptable. This refers, among other things, to the selection of the product form, such as a tablet, capsule or ampoule, etc. Packaging is also important. The package must preserve and protect, the product, be clearly and accurately labeled, and be convenient to the physician and patient.

Mr. Chairman, now that we have briefly defined safety, efficacy, and acceptability, I would like to consider how these goals may be achieved in each product, batch after batch. We feel the first step of building quality into a product begins in the research or design phase.

Design Phase (Please refer to Addendum I)

It is in research that quality is designed into the product.

As indicated by my associates, a new drug substance is first studied exxtensively in animals to establish toxicity, safety, and pharmacological activity.

Chemists, bacteriologists, biologists, and pharmacists then design various dosage forms for the product. They establish standards of purity, methods of preparation, formulas, analytical specifications and collect stability data. In general, they find out all they can about the product prior to initiating clinical investigation studies concerning safety and efficacy in human subjects.

Finally, thousands of individual clinical tests are performed. Patient records obtained from these tests are painstakingly kept and analyzed and a summary of the studies is written. These investigations form the basis for a new drug application.

The final labeling of the product is, of course, based on the results of the clinical trials.

After establishing the safety and efficacy of the product, the design phase of building quality into the product is complete.

Conformance Phase (Please refer to Addendum II)

Now that a product exists, it must be manufactured in a way that duplicates the *design* phase of total quality control. This is called the *conformance* phase.

This is the area in which the production, purchasing and quality control divisions of a pharmaceutical firm are most vitally involved.

There are many systems by which pharmaceutical manufacturers can control their product during the conformance phase.

I would like now to illustrate one of them.

It starts by preparing an elaborate set of specifications for all the components that make up a product.

These specifications include methods for determining the identity, purity, strength, physical characteristics, uniformity, quality, and many other parameters, depending upon the requirements expected of the raw material.

Package specifications and control procedures are also provided for such items as glass containers, bottle closurers, cap liners, filters, and even the glue used for labels.

If the material is to be purchased, the purchasing agent is provided with a set of these specifications.

Suppliers are selected on their ability to produce and deliver quality material.

Quality control personnel often visit the suppliers, firsthand, to verify whether or not confidence can be placed in them.

When the material from the supplier arrives in the plant, it receives an identifiying number. This number is never duplicated.

The incoming raw material is then quarantined until it is sampled, inspected, tested, and approved according to the established specifications.

Labeling the material also undergoes rigid inspection techniques. (Please see Addendum III) Samples of the labeling to be ordered are proofread by at least two qualified people before they are sent for printing.

All labeling material received is 100% inspected for proper identity, lot number, and all regulatory requirements. The labeling material is counted and inspected by both quality control personnel and the label storekeeper. The labeling material is then stored in a secure manner to prevent any label mixups.

All raw material must be approved by the quality control division before it is allowed to enter a product.

The next step is control of the manufacturing process. (Please refer to Addenda IV and V)

Some of these points have already been covered by Mr. Blazey in his submission for the record.

The manufacturing process is very carefully detailed on manfacturing process cards. These cards are precisely controlled by a manufacturing identity number which is assigned to each batch production record.

The entire history of a product, per batch, can be traced through a numbering system.

The particular lot or batch number of every component and manufacturing aid involved in the production of a product must be traceable from the lot number on the final package.

The quality control approved raw materials, clearly labeled, are then accurately weighed and checked for identity and accuracy of measurement by at least two qualified individuals at each dispensing step. The identification numbers of the materials dispensed are recorded on the batch production card.

All materials forwarded to a production department are very carefully labeled and quarantined by a system of control records.

Upon arrival in the manufacturing department, the materials are checked for identity by at least two qualified persons.

All material is then checked again for identity and quantity and verified by a qualified production control checker before it is allowed to be added to the product.

The materials are then combined in the processing operation according to the specific instructions on the batch production card.

During the manufacturing operation, each individual manufacturing process step is checked and endorsed by at least two individuals and their signatures entered on the batch production record.

In-process product and equipment checks and verifications are made and recorded during the processing operation, and production and control procedures are rigidly followed.

Intermediate granulations or mixtures are often tested for homogeneity.

The finished granulation or mixture is sampled, tested, analyzed, inspected, and the yield variation limits determined by the quality control division.

Approval by quality control is given only when all the predetermined specifications and standards are met, and the records are complete.

The approved blended powder mixture is now ready for further processing, such as into a tablet or capsule.

The mixture is now carefully filled into its dosage form. The product is inspected and tested to confirm the uniformity of composition of the active ingredients.

After processing into a final dosage form, chemical analysis and identity tests are performed by the quality control divisions to reaffirm the quantity, quality, and uniformity of the product.

Many firms identify their products by the use of an identity code written or stamped on each tablet or capsule. This aids the physician in identifying the medication being taken by their patients. It is also an aid in identifying the product as it proceeds through the manufacturing process.

The quality control division will approve the *bulk* product (capsules, tablets, etc.) for further processing if the results of the testing, the final yield verification, the documentation, and the control procedures have all been properly carried out according to the established product specifications and standards.

When an approved bulk medicinal product exists, the proper container, the correct labeling, and the packaging materials are joined together to produce a *finished* product. Each of these items, along with their identifying numbers, are recorded on the finishing record. (Please refer to Addendum VII).

Many checks, reconciliations, and identifications are made to control the finishing operations. Included are the following:

(1) A thorough cleaning and checking of the packaging line before the start of the operation.

(2) A check of the identity, quantity and quality of the packaging material and labels.

(3) In-process testing and control procedures on the product.

(4) Complete label reconciliation and a physical evaluation of the final product.

Finally, after all balances and reconciliations are made, product yield variations determined, and all required government approvals are obtained, the product is given final approval by the quality control division.

A reserve sample is removed and stored within the quality control division for reference. All the control documents pertaining to the batch are then filed in the quality control division.

Now the product is ready for distribution. (Please refer to Addendum VII).

Total quality control of a product does not stop here. A system of controlling the storage of the product in the warehouse, and also periodic inspections of the product of the pharmacy shelf, further assure its quality when it is dispensed to the patient.

It is important to remember that the purpose of the conformance phase of total quality control is to duplicate exactly the product produced during the design phase. This does not *just mean* that each batch or lot of product should have the same *physical* and *chemical* characteristics as another batch or lot. It is far more important that each tablet, capsule or pill must perform both *physiologically* and *pharmacologically* in exactly the same manner.

It is inconceivable to assume that merely analyzing a product for potency and purity *will assure* its *quality.*

At this time, I would like to differentiate between the terms "analysis" and "control".

Analysis is predicated on meeting minimum requirements after a product is manufactured. No degree of testing or analysis can change the quality aspects of the product after it is manufactured.

For example, in the case of a capsule filled with defects, it is obvious we cannot eliminate these defects by analyzing the final product.

A surprisingly large number of individuals still regard analysis as the only basis for establishing and maintaining quality. Testing by official methods *after* the product is produced and *after* most products are in commercial distribution offers inadequate assurance of quality.

Total quality control on the other hand uses analysis or testing only as a check to make sure that the manufacturing processes have been properly controlled.

Testing merely indicates, in part, that minimum legal or other requirements have been satisfied.

Testing does not show maximum levels of quality.

What are these minimum requirements. They are the tests and requirements as set forth in the USP, NF, and FDA antibiotic certification regulations.

It is important to note that industry considers the USP, NF, and FDA antibiotic regulations as essential and the tests and standards contained in them to be the strongest in the world. However, we must realize that these standards are not all-inclusive, and by no means should they be the sole basis for judging whether a product is suitable for use by a patient.

Analysis of a product and adherence to the standards established by the official compendia does *not* mean that two products containing the same active ingredient will necessarily perform the same way in the body.

Unfortunately, technology has not yet provided adequate laboratory tests to assure the pyhsiological equivalence of drug products. Therefore, the gap must be filled with a complete program of strict adherence to the total quality control concept.

As we started earlier, quality must be built into a product during its developmental stage. This must be followed by strict adherence to a system which assures that the quality which is built into a product will remain when it reaches the consumer. This is the ultimate goal of total quality control.

An understanding of this inadequacy of official tests and standards to control a product completely can be best demonstrated by specific examples.

One of the basic problems involved in relying strictly on chemical tests to ascertain the therapeutic equivalency of a drug is the nonspecificity of some of the tests. Many of the official monographs for the final dosage form of a drug utilize tests which detect a group or chemical class of drugs rather than a particular molecular arrangement of the drug.

The logical question evoked from this discussion is—why not develop new and more specific tests? Well, this is being done.

The ethical pharmaceutical industry in conjunction with the official compendia and academic research laboratories is constantly looking for newer and better chemical and biological tests. However, this is a slow and tedious job, requiring years, or even decades of work.

Another example of the limitations of official standards can be seen in the latest revision of the United States Pharmacopeia. A statement in the general notices section reads as follows: "Variations in composition are undesirable and substantial differences in the content of active ingredients between individual capsules, tablets, and other dosage units are to be avoided."

Yet, until just recently, most of the official monographs in the United States Pharmacopeia and National Formulary did not require tests to assure the uniformity of composition of each dosage form.

What does this mean? It means that some unit of a product could have 150 percent of label claim, others 50 percent of label claim, while still others may have no active ingredients present at all. The reason for this was that the assay required only that the *average* of a number of units fall within a range, for example, of 90 to 110 percent of label claim. Consequently, the product, though defective, would pass the official requirement.

Another example is illustrated by the lack of standards established for the particle size of a drug substance.

One of the big fallacies of the theory of "drug product equivalency" can be illustrated by the following example. Let me start by saying that the result of an assay of a product does not necessarily mean that the determined amount of active ingredients will be available to the patient upon ingestion. Thus, potency and purity of a product are not the only important characteristics of the quality

of a drug. There are many other important factors involved, such as the method of granulation or mixing the drug, the choice of inert ingredients used in combination with the active ingredient, and the product design which prevents impurities and defects from entering into the final product. All the above factors may influence the final availability of the active ingredients to the patient.

Physiological availability is, therefore, on essential quality characteristic that is not spelled out in any existing book of standards.

Specific examples can be pointed out which substantiate the contention that adherence to official standards does not guarantee clinical efficacy.

In testimony delivered earlier before this Committee by Congressman Durward Hall, reference was made to a Department of Defense experience with a drug of "supposed generic equivalency".

The drug mentioned was diphenylhydantoin which is used in the treatment of epilepsy. The Government had purchased at least three lots from three different producers other than Parke, Davis & Company. Documented complaints ensued from various military hospitals concerning the serious side effects elicited by patients taking the drug. Congressman Hall quoted a letter from the Chief Neurologist of one of the hospitals who recommended that:

"It has been my experience that patient response is significantly more erratic with diphenylhydantoin supplied by other than Park-Davis. Therefore, all further procurements of this drug should be made from Park-Davis."

Our product is now being procured by the Defense Supply Agency.

This difference in therapeutic effect between supposedly equivalent products is one of the reasons which led the military medical procurement agency of the Defense Department to require clinical testing data on the physiologic and pharmacologic efficacy of products offered for contract.

I believe that this testimony corroborates the stand we have taken. The firm I work for, Parke, Davis & Company, developed diphenylhydantoin, and through its many years of experience has been able to control the variables that are inherent in the production of this complex and useful medicine.

The FDA in the "1966 Drug Potency Study" announced in a published list that Parke-Davis' Thyroid Tablets were assayed and did not fall within the United State Pharmacopeia standard range.

The company was deeply concerned, and since FDA did not at first disclose the particular lot number of thyroid sample tested, it was of even greater concern. However, through inquiries, the company was finally able to ascertain the lot number of the thyroid tablets that were tested by the Food and Drug Administration. As it turned out, the lot of thyroid tablets tested by the Food and Drug Administration was not the company's USP Thyroid Tablets, but rather was their Thyroid *Strong* Tablets, a product that is labeled to contain 1½ times the USP potency.

The particular sample of thyroid tablets, tested by the FDA was indeed within our labeled potency range. A letter of apology from the FDA was later sent to the company.

Another example of failure of analysis in controlling the quality of medicinal preparations can be illustrated by the recall of a lot of tetracycline syrup distributed by a number of generic manufacturers a few years ago.

Tetracycline, as you know, is an antibiotic and subjected to batch-by-batch testing and certification by the Food and Drug Administration.

The recall of the tetracycline suspension involved a problem of subpotency. The question that arises here is—was the test performed by the Food and Drug Administration on the sample *before distribution* adequate to determine this lack of stability? On the other hand, if the product was potent when it left the manufacturer's plant, why did the product lose its potency in less than one year after distribution. The minimum shelflife of this product, as established by regulation, is 18 months.

Analysis at the time of manufacture, therefore, cannot assure that a product will be stable or retain its labeled and tested potency for an extended length of time.

This is another important point which a total quality control program contains. Total quality control manufacturers test and study their products to determine the length of time that their products can be assured to maintain the labeled potency.

Ethical pharmaceutical manufacturers perform definitive stability studies of their products. Not only are they studied in a total quality control system during developmental research and manufacture, but also subsequent to distribution.

Recently, Parke, Davis & Company initiated a study to compare a product originated by the company with several products containing the same active ingredient now available from other firms by nonproprietary and brand names. This study was undertaken to determine whether there are any significant differences between these products and the Parke-Davis product. Preliminary information on this study, available at the writing of this statement, indicates that differences were found between products in commercial distribution. More details on the study will be available shortly. They will be submitted as soon as they are received.

The company which has developed a drug product knows it intimately and is continually learning and studying new information concerning it. Its systems of manufacture and quality control are designed to meet the particular needs or requirements of the specific product. All the control procedures that are needed in duplicating the product as determined during the research phase are rigidly followed.

These methods of control are what make the drug clinically effective, batch after batch.

In summary, Mr. Chairman, analysis has its limitations. There are many factors that can produce errors, and therefore, can produce varying results.

Analysis of a drug product is useful, and in most cases essential, but it should only be used as a guideline in determining if the controls established for the manufacturing and the packaging operations are sufficient to insure the quality of the product.

Analysis alone is insufficient to assure quality. Thus, a rigid program of totally controlling all the steps involved in producing a final product is the only way a manufacturer can assure the clinical effectiveness of his drugs.

General Principles of Total Control of Quality in the Drug Industry

(As approved by P.M.A. Board of Directors on June 22, 1967)

INTRODUCTION AND DEFINITIONS

The quality of a product is its degree of possession of those characteristics designed and manufactured into it which contribute to the performance of an intended function when the product is used as directed. The quality of medicinal and related products is the sum of all factors which contribute directly or indirectly to the safety, effectiveness, and acceptability of the product. Quality must be built into the product during research, development, and production.

Total control of quality as it applies to the drug industry is the organized effort within an entire establishment to design, produce, maintain, and assure the specified quality in each unit of product distributed. The effort should not only establish specifications for product acceptance but should provide procedures and methods for achieving conformance with such specifications.

The large variety of substances used in this industry, the complexity of its products, and the various types of company organization make it impossible to design in detail a single universally applicable system for the total control of quality.

OBJECTIVES

The ultimate objective of a program for the total control of quality in a drug company is the attainment of perfection in meeting specifications for a product of high quality. It is a program designed to assure the professional user or ultimate consumer that every lot of a product conforms to specifications and that each dose distributed will fulfill the representations made in the labeling and will meet all legal requirements and such additional standards as the management of a firm may adopt.

ADMINISTRATION

Total control of quality is a plant-wide activity and represents the aggregate responsibility of all segments of a company. The responsibility for auditing the control system and for evaluating product quality is that of a specific group referred to in this statement as Quality Control. A basic principle in the control of quality is that a production group should not have sole responsibility for final approval of products for distribution. The head of Quality Control should have the authority to release satisfactory lots of products, to reject unsuitable lots, and to recommend the recall from distribution of any lots subsequently found to be unsuitable. He should be responsible to a level of management which enables him to exercise independent judgment. His responsibilities and authority should be clearly defined by management.

BASIC CONSIDERATIONS IN A TOTAL QUALITY CONTROL SYSTEM

A system for the total control of quality should be designed to provide proper personnel, product design, specifications and procedures, facilities and equipment, materials, and records. Provision should be made for the audit, evaluation, maintenance, and revision of the system. The failure of any component is cause for review of the reliability of the system.

I. *Personnel:* Individuals involved in the research, development, engineering, production, and control of any medicinal and related product markedly influence its ultimate quality. These people should be competent in their respective fields of endeavor by reason of academic training, experience, or on-the-job training. Total control of quality can be achieved consistently only through quality-mindedness in each employee and an understanding among all personnel of the part their performance contributes toward product quality.

II. *Product Design:* The quality of a product must be built into it during research, clinical evaluation, development, and engineering. The formulation, the method of manufacture, the tests, the choice of materials, and the packaging and labeling should impart to the product or describe the desired quality characteristics. Effective quality control calls for a continuing quality evaluation and improvement program.

III. *Specifications and Procedures:* Specifications should state clearly the desired characteristics and acceptable tolerances for all raw materials, intermediates, packaging supplies, labeling, and finished packaged products. Procedures should clearly state the necessary steps to evaluate sources, to obtain, receive, test, and accept purchased materials; to produce, store, test, and handle intermediates and products; to provide for checks and audits and such other functions that are necessary to assure products of the desired quality. Specifications and procedures should be recorded and dated to clearly designate the period of their use.

IV. *Facilities and Equipment:* Facilities, buildings, and equipment for manufacturing, testing, and storage should be of such design, size, and construction as to assure the desired quality characteristics of each product. Construction of facilities and equipment should take into account such considerations as ease of cleaning and maintenance and proper location in relation to surroundings in order to help avoid contamination or mix-ups.

V. Materials: Materials used in the manufacture of a product including raw materials, intermediates, packaging supplies, and labeling should be of a level of quality to assure that the final product meets specifications. The method of evaluation of quality characteristics in a material, including identification, sampling, testing, stability, and use in a particular manufacturing operation, should be predicated on the product's intended use and should be sufficient to assure conformance to specifications.

VI. Records: The key element by which administrative control of each lot of product is maintained is the control numbering system and related documentation. This is a system of identifying each product lot and includes marking of each distributed package of the manufactured lot so that the manufacturer can establish the history of the package and its contents, the source of each ingredient, the records of tests made on ingredients as well as on the final product, and the identity of the individual responsible for each of the steps in

the manufacturing process and the individual who checked each key step. Such control numbers and documentation should also relate to records of the packaging operations and the final audit for the total number of packages produced. The control number and documentation also provide a means to facilitate recalls, if necessary.

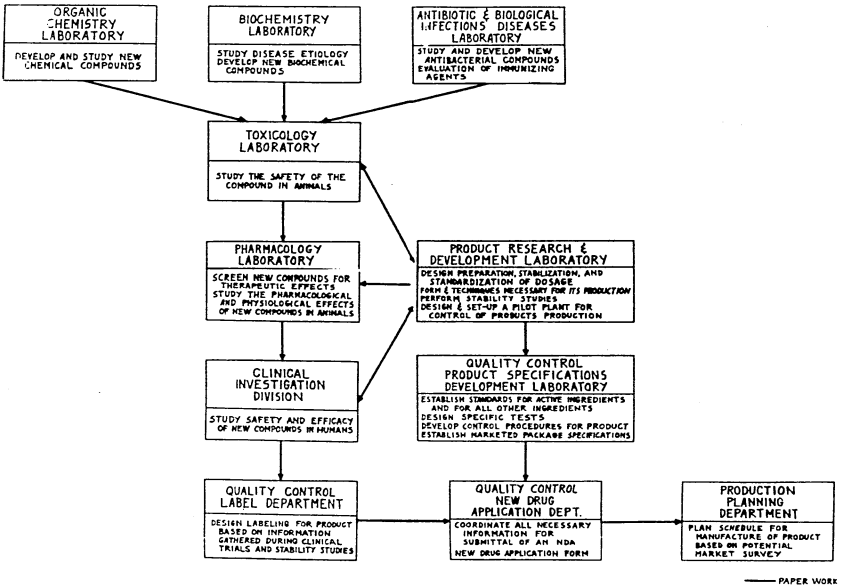
ADDENDUM

In the application of these general principles, consideration should be given, but not necessarily limited, to all of the items mentioned in the P.M.A. Statement on Control of Quality dated May 3, 1961, which are listed below.

1. Buildings for manufacturing, testing, and storage operations are of adequate design, size and construction to:
   (a) provide for proper receipt and storage of raw materials.
   (b) allow proper segregation and identification of material during manufacturing and packaging.
   (c) provide for ease in maintaining cleanliness and for avoiding contamination.
   (d) provide suitable sampling facilities.
   (e) provide adequate laboratory facilities.
   (f) provide proper storage for final products.
2. Equipment is:
   (a) properly located.
   (b) adequate for the required operations.
   (c) constructed to facilitate cleaning.
   (d) properly maintained.
3. Raw materials are controlled by:
   (a) establishment of suitable specifications.
   (b) development of adequate test procedures.
   (c) specific identification markings.
   (d) proper storage conditions.
   (e) adequate sampling.
   (f) appropriate testing.
   (g) requiring compliance with specifications.
   (h) providing for Quality Control release.
   (i) maintaining records and samples whenever appropriate.
4. Manufacturing operations are controlled by:
   (a) use of a suitable batch numbering system.
   (b) preparation of formula or batch records.
   (c) checking of ingedients; identity, weight and measure.
   (d) maintaining identity during processing.
   (e) checking quality during processing.
   (f) checking yield against theory.
   (g) adequate sampling and testing.
   (h) requiring compliance with specifications.
   (i) maintaining appropriate records and samples.
5. Packaging and finishing are controlled by:
   (a) establishment of specifications for packaging and packaging operations.
   (b) a formal procedure providing for the inspection and issuance of packaging materials including labels and labeling.
   (c) providing for the proper disposition of unused labels and labeling.
   (d) use of suitable batch, lot or control numbers.
   (e) maintaining identity of product before and during packaging.
   (f) checking yield against theory.
   (g) sampling and checking for compliance with specifications.
   (h) providing for release by Quality Control.
   (i) maintaining appropriate records and samples.
6. Finished stock quality in maintained by:
   (a) providing proper storage conditions.
   (b) collection and review of stability data.
   (c) investigation of all significant complaints concerning quality of products.
   (d) providing for the disposition of returned goods.

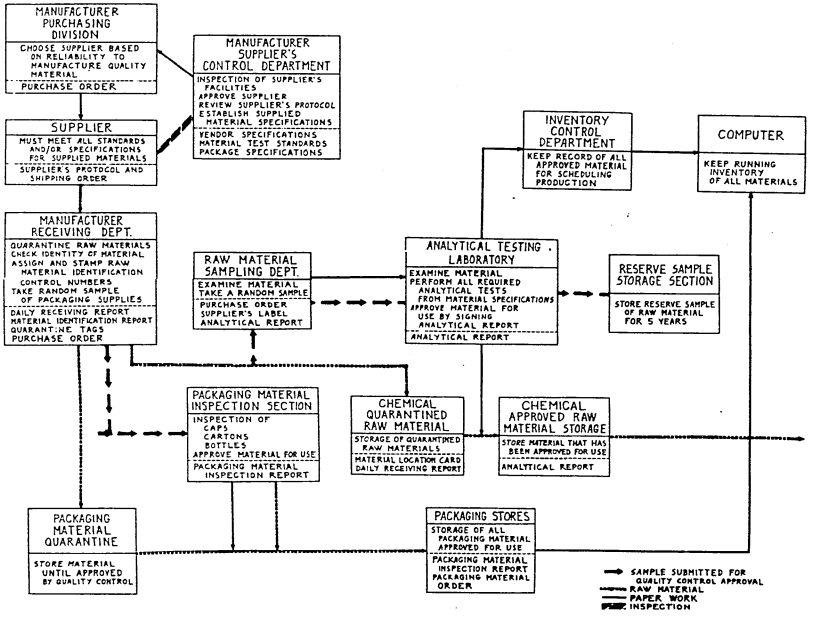
ADDENDUM I

DESIGN PHASE
RESEARCH



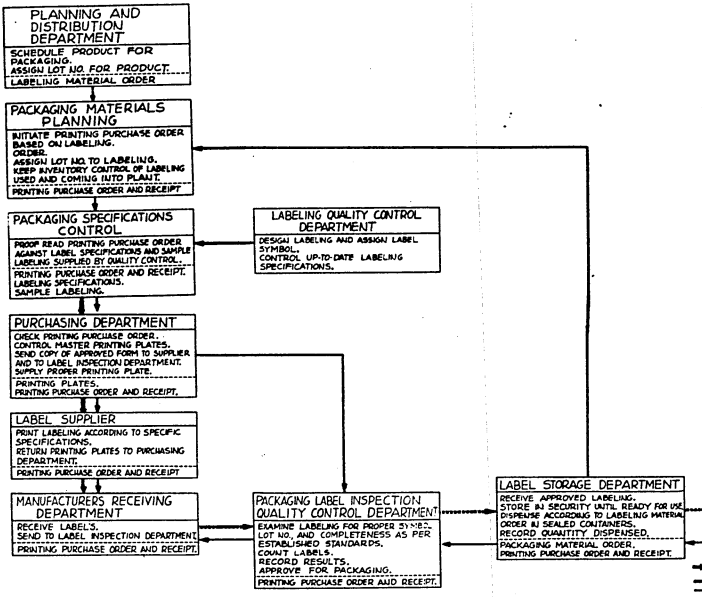
ADDENDUM II

CONFORMANCE PHASE
CONTROL OF INCOMING RAW MATERIALS



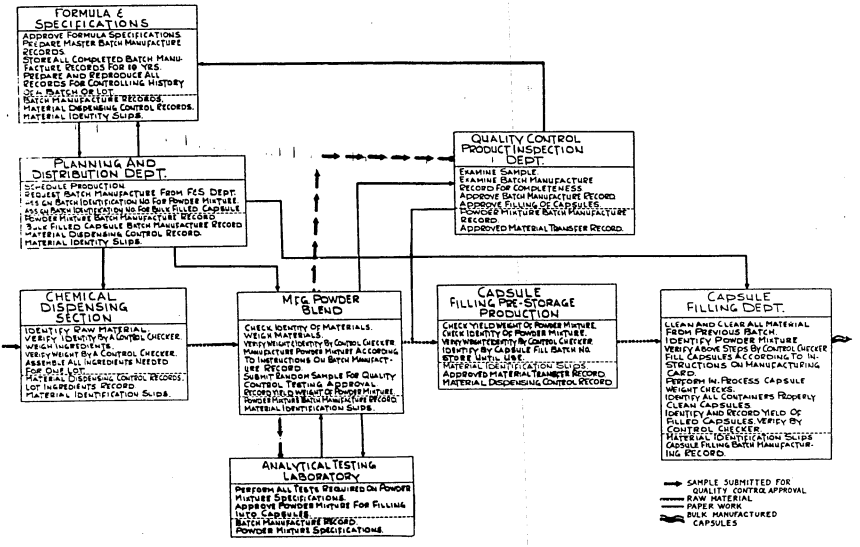
ADDENDUM III

CONFORMANCE PHASE
CONTROL OF LABELING OF PRODUCT



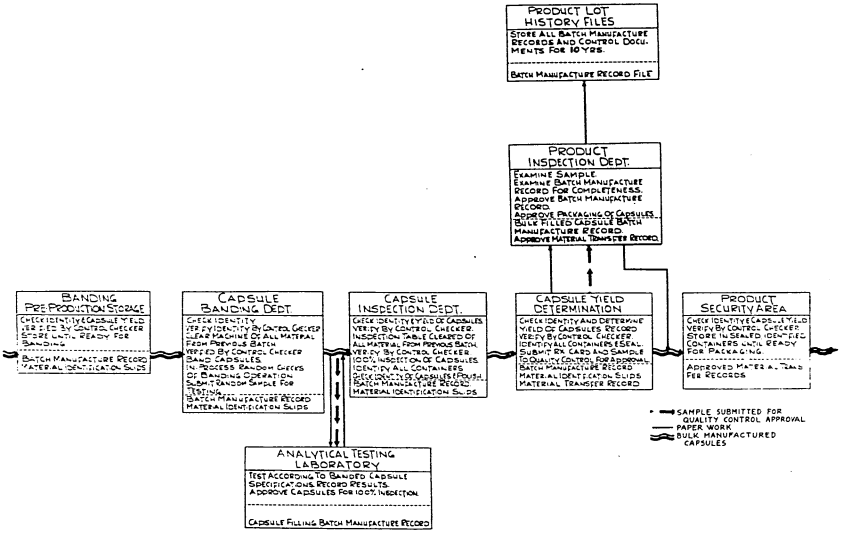
ADDENDUM IV

CONFORMANCE PHASE
CONTROL OF MANUFACTURED BULK CAPSULES I



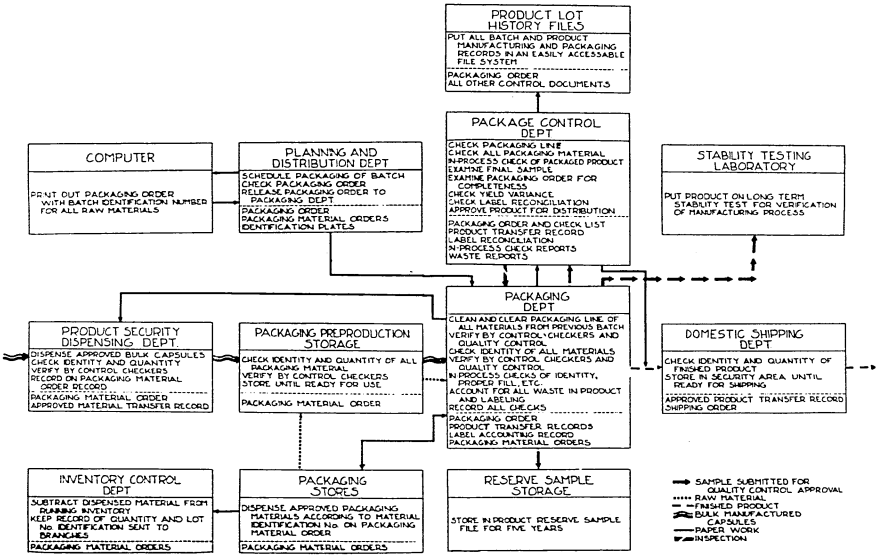
ADDENDUM V

CONFORMANCE PHASE
CONTROL OF MANUFACTURED BULK CAPSULES II

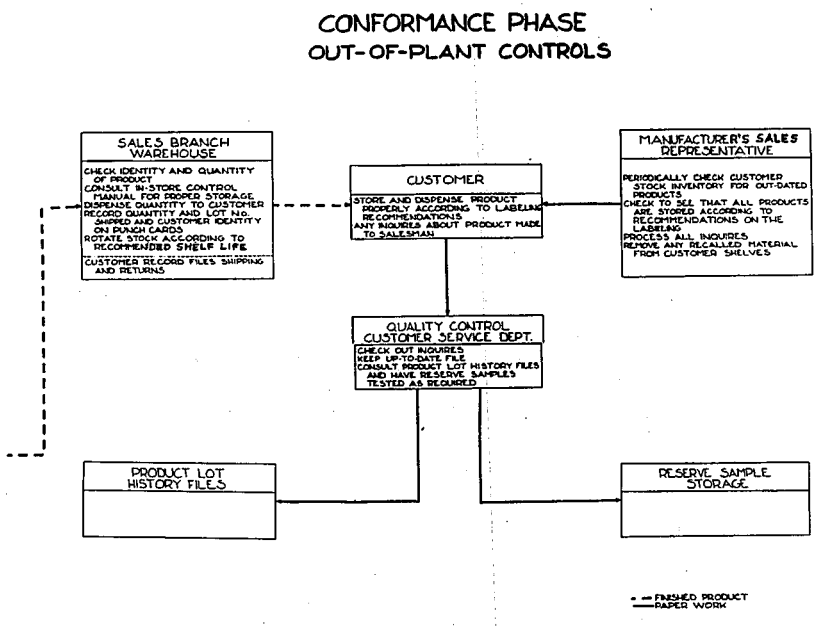


ADDENDUM VI

CONFORMANCE PHASE
CONTROL OF PACKAGING OF CAPSULES



ADDENDUM VII



Senator NELSON. Dr. Slesser is the next witness, I understand.

STATEMENT OF A. E. SLESSER, PH. D., ASSOCIATE DIRECTOR OF QUALITY CONTROL, SMITH KLINE & FRENCH LABORATORIES; ACCOMPANIED BY LLOYD N. CUTLER, SPECIAL COUNSEL, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, D.C.

Dr. SLESSER. Mr. Chairman, if it is satisfactory with you and the members of the subcommittee, I would like, in the interest of saving time, to read a brief statement summary. I had submitted to you in the fall a statement for the record as of November 6. I certainly will entertain questions on that statement should you wish to ask them.

On the other hand, this is a brief summary which is an excerpt, really, from that statement submitted earlier. I will be very happy to tell you what portion of the statement this relates to as I go along, if that is satisfactory to you.

Senator NELSON. I want to do whatever will speed the hearing because I know you were inconvenienced the last time when we did not get through our agenda. I have promised Mr. Stetler that we would get through today.

How long is your summary, how many pages?

Dr. SLESSER. About 10 or at the most, 20 minutes.

Senator NELSON. Let's try it. Ordinarily that procedure does not shorten testimony, because I have to go back to the original testimony which I have marked and repeat portions of it, but I will try.

Dr. SLESSER. Mr. Chairman, first of all, I would like to express my appreciation for your permitting me to appear and giving me the opportunity to supplement Mr. Stetler's statement on the matter of therapeutic equivalency of drug products.

Through my activities in the pharmaceutical industry, I know something about the factors that can affect drug performance.

Senator NELSON. We will print in the record Dr. Slesser's full statement.

Are we talking about the statement that is called supplementary?

Dr. SLESSER. Mr. Chairman, I did not have one that says supplemental testimony before the subcommittee. I think the original one had the wrong caption as far as committee identification is concerned.

Mr. CUTLER. That was when he was going to supplement Mr. Stetler's. That is his original statement.

Senator NELSON. What are we dealing with, then?

Is this the one he is making an abbreviated statement on?

Dr. SLESSER. Yes. I am trying to find a spare copy for you.

Senator NELSON. I would ask that that statement be printed in full in the record. Then we will take his summary statement and we will ask questions. If you have a copy of the summary, I can probably follow you more easily.[1]

Dr. SLESSER. I do have a copy of this brief summary, Mr. Chairman, which I do not believe you have, which we will find very shortly.

Senator NELSON. Go ahead while they are finding it.

Dr. SLESSER. Control of the quality of the medicinals prepared from today's drugs is a complicated operation. It is simply wrong, in the light of the present state of the art and science of pharmaceutical manufacture and the inadequately manned FDA, to contend that all drug products of like generic name are equal.

Even if we make the incorrect assumption that all manufacturers are capable of passing an FDA inspection, we are still in no sense out of the dilemma of therapeutic equivalence.

There is the matter of conforming to USP or other standards. The question is not whether drug products should conform but whether each batch and each tablet, capsule and dose of every drug product does conform. The fact that standards exist and that companies put "USP" or "NF" on drug labels does not establish that, in fact, the companies actually have adequate control procedures or that they follow them. In short, the real question is, do drug products conform to the standards they claim to meet?

Now, I would like at this point to stress the fact that the USP and the NF are indispensable compendia. There is no question about the importance of the standards that appear in these compendia. However, this is only part of the story. Actually, the USP itself points out on page XVII that the problem of providing objective standards and methods for USP drug products to measure physiological availability, which means the extent to which the active ingredient is taken up by the body in a useful form, "remains in the exploratory stage at this time" and adds, "Progress has been slow in developing such standards that would be suitable for U.S.P. use."

[1] The complete prepared statement and attachments submitted by Dr. Slesser for presentation on Nov. 16, 1967, begins at p. 2271, infra.

The NF, on page XLIII, echoes the essence of the USP statement under the caption "Therapeutic Authority Disclaimed," as follows:

> The inclusion of a drug in the N.F. is not intended as an endorsement of its therapeutic value.

Total quality control, Mr. Chairman, involves much more than any compendium can cover. Not too long ago, the chairman of the NF Committee of Revision, Dr. Edward G. Feldmann, discussed natural limitations of the compendia as follows—this is a direct quotation and we have copies here for you:

> Many people in pharmacy have the mistaken notion that if a product meets all the specific tests and requirements detailed for that article in the U.S.P. or N.F. monograph, then that particular product *has* to be perfectly satisfactory.

The word "has" was italicized.

To continue with the quotation:

> While I wish this were true, I am sorry to say it is not and the nature of the problem is such that we can never hope to develop compendia monographs which will give complete assurance of any product's absolute suitability.

The detailed specifications that are needed to produce a quality drug product under good control procedures are so extensive and so all-encompassing as to defy inclusion in compendia of any sort. Quality control measures, records, and reports used in leading drug firms for each batch of even the simplest drug product are massive. These begin with the raw materials and end with the consumption of the product. Details of the manufacturing and control procedures utilized for only a few products of a capable manufacturer would constitute a book in itself.

We all know that safety and effectiveness of a drug product are determined by well-designed, properly controlled and correctly executed clinical tests. Such tests are run by the manufacturer on one, sometimes two, rarely on more than two batches of the product. Now, having proved the safety and effectiveness of the product, we must ask ourselves this question: To what factors are the product's safety and effectiveness due? For an answer to that question and an explanation of how quality control functions, I would like for this subcommittee to take a look at a chart that I have prepared for this purpose.

Before doing this, however, let me state, Mr. Chairman, that contrary to common belief, the drug component in most tablet products comprises less than 10 percent of the makeup of the tablet and that the number of components other than the drug itself may vary from two or three to as many as 20 or more. I mention this because this should be taken into consideration when we are talking about a drug versus a drug product, which is the form of the drug which is marketed and administered to the patient. This is the area in which the effect of know-how or lack of know-how can be demonstrated in a very important fashion.

Senator NELSON. You just quoted Dr. Feldmann. In part 1 of these hearings of the Subcommittee on Monopoly of the Select Committee on Small Business, I quote from Dr. Feldmann:

> A good quality control system will minimize the differences between batches of the same drug product. The official compendia standards are designed to enable the testing of the final product to ascertain that a given lot of a drug

product meets the appropriate criteria of identity, purity, quality and strength. Compliance with these standards constitutes generally reliable presumptive evidence that such a drug product will be clinically effective and safe.

Clinically effective and safe.

So I think Dr. Feldmann is saying the same thing about the issue with which we have been in dispute with the drug companies. If drugs meet the USP standards, it is presumed they will be clinically safe. That is the heart of the issue on which we differ, but a substantial body of authority in this country does agree with Dr. Feldmann's presumption.

Dr. SLESSER. Dr. Feldmann presumes this to be true and certainly he has a right to make this presumption. I think the body of scientific evidence would take issue with this presumption and I hope to bring that out more thoroughly as I proceed with the balance of my statement.

Senator NELSON. I just wanted Dr. Feldmann's statement in the record in proper juxtaposition.

That is a rollcall. Do you have any objection if Mr. Gordon sits and listens while you present your statement, or do you want to wait until I get back?

Dr. SLESSER. I would be happy to wait.

Senator NELSON. I have read your testimony so I know what is in it, and I have a few questions on it. I will do whatever you prefer.

Dr. SLESSER. I prefer to wait.

Mr. CUTLER. If it is just as short as the others, Mr. Chairman, why not wait?

(Short recess.)

Senator NELSON. The hearing will resume.

Dr. Slesser, go ahead.

Dr. SLESSER. Thank you, Mr. Chairman.

Senator NELSON. It appears we will have a continuous series of rollcalls. So I guess we had better move along.

Dr. SLESSER. That is perfectly all right.

Senator NELSON. Is that going to be part of an exhibit you have in your testimony?

Dr. SLESSER. Yes.

Senator NELSON. When you get to it identify it for the record.

Dr. SLESSER. This is chart No. 3, Mr. Chairman.[1]

Now, I think that a brief, a very brief presentation on how clinical effectiveness is established is probably worth while before going into the rest of the chart.

The capable innovator manufacturer will make sure that for the research and development formula, the pilot formula, or formulas, that all tests necessary are run to prove safety and effectiveness. The only way in which this can be done, of course, is by clinical trials on human subjects. So that safety and effectiveness have been established by clinical tests on this particular product.

Now, I think a great deal of misunderstanding about the significance of laboratory testing lies in this particular fact.

It is presumed that—I am using tablets as an example, but they do

[1] Charts 1, 2, and 3 appear as attachments to Dr. Slesser's prepared statement of Nov. 16, 1967, and begin at p. 2275, infra.

not constitute the only type of dosage form by any means—it could apply to any pharmaceutical product.

It is presumed that by applying laboratory tests, whether they are USP, NF, or any other authority, to a certain number of tablets from a batch, or to a certain number of bottles in a shipment of a batch, without knowing anything else, one can then, depending on the results of these analyses, state unequivocally that this product does have safety and effectiveness.

Now, I hope to show wherein the fallacy of this line of reasoning lies.

Quality control, Mr. Chairman, makes sure that what comes out here as a finished batch is a duplicate, insofar as safety and effectiveness is concerned, of what was tested at this particular point.

In other words, I am suggesting that quality control has to be viewed as a chain, that it cannot simply be viewed as beginning and ending in an analytical laboratory, or a testing laboratory wherein, unfortunately, many people believe is the beginning and end of quality control.

So if I may, I would like to show the factors which are responsible for the safety and effectiveness as determined by clinical tests on the prototype formulas.

First of all, the specific components, both the drug and nondrug.

Now, you will notice that I underline "specific" in each case, because this is very important.

The drug itself, we know that such matters as the fineness of the particles of the drug—most drugs are crystals or powders—depending on particle size—you may get differences in the rate of absorption, as well as the magnitude.

There are other physical factors that can enter into the behavior of the drug in a drug product. One of them is described as polymorphism, which is simply a difference in the crystalline structure.

If you were to analyze such a drug by the formal chemical tests, Mr. Chairman, you could not differentiate polymorphic form A from polymorphic form B or polymorphic form C. Special types of tests are necessary, such as infrared spectrometry or X-ray diffraction—and there again is a fallacy in relying upon simple laboratory tests. And, of course, the significance of this is polymorphic form A, B, or C may very well show differences in physiological availability of the drug and the drug product.

Now, the nondrug components. They are also important. The capable, qualified manufacturer is just as interested in who supplies these components as he is in how they test in a laboratory. And he takes precautions to make sure that he deals only with capable, reputable vendors, with whom he has had a history of successful quality in the past.

Specific specifications are set up for drug and nondrug components. Written directions for sampling each incoming shipment exist. These are updated and precautions taken to make sure they are followed.

The ratio of the drug to the nondrug components, and of the nondrug components to one another is important.

Then we are talking about a specific formula. USP clearly indicates that the formulas and methods for manufacturing the dosage

forms which are official in the USP are not a function and cannot be—included in the monographs for the official products that are listed therein. So that with a given drug, a manufacturer who may use the same drug or active ingredient—but then varies in some other respect, and does not use the specific formula—could alter the safety and effectiveness of the resulting drug product.

Specific manufacturing procedure—this is extremely important. A statement has been made that it does not matter—or there is a feeling that exists, that it does not matter how a drug is made as long as it meets standards. This is certainly not true of the pharmaceutical industry. The pharmaceutical industry knows from experience, and the FDA knows, too, that you cannot rely upon the doctrine I don't care what the kitchen looks like, as long as the soup tastes good. This is not at all valid, and there is a very definite relationship between the kitchen and how it looks—namely the pharmaceutical plant, the capability of the people who work there, the facilities with which they work, the know-how, the physical plant itself, and the quality of the product.

Now, throughout the course of every batch, specific in process tests, assays, checks, and inspections are done. Mr. Chairman, these number literally in the hundreds for each batch, and sometimes may number a thousand or more. And it is important that these be done because these are an important part of the chain of quality control which will insure that on a batch-to-batch basis, every batch will be the same in safety and effectiveness a the initial batches which were tested in the clinic.

And finally, other specific in-process controls—one function of which is to make sure that these other four links in the chain have actually been executed, have been effective, have been properly conducted. One function takes the form of a stack of finished reports of data, results of inspections, tests, analyses, and so forth, which for even a single batch may number a great many pieces of paper. They show the complete history of the manufacture of that batch.

Now, once a knowledge of the control of all these things—these links in the chain—is known, then and only then do the laboratory tests have meaning, because if the batch has been made with the links of this chain under control and unbroken, then we know that the finished batch will meet all the USP or NF or other required tests.

So what I am trying to say, Mr. Chairman, is that if this chain has actually been effectuated, and has been capably applied, then the finished batch will meet USP tests. However, I want to emphasize this—the reverse is not necessarily true. In the absence of knowledge that this chain was in fact operative, capably applied and so forth, laboratory tests to establish that the finished batch or a sample of it is safe and effective may not be meaningful.

Now, that is the crux of the basis for the concept of total quality control. Lest there be any misunderstanding that this is solely something which the industry is trying to use as a smokescreen, I would like to quote Dr. Earl Meyers who for many years was in the new drug branch of the Food and Drug Administration—in a speech that he made before the American Pharmaceutical Association, at the fifth

annual Federal Service Pharmaceutical Seminar here in Washington, on November 10, last year—Dr. Meyers made this statement:

It also becomes important to establish the reproducibility of the dosage form of a drug from batch to batch if the clinical studies are not to be biased by an unknown variable.

He says:

A break in the control procedure—

This is specifically an endorsement of what I have just presented—

A break in the control procedures may be just as disastrous as the occurrence of unexpected toxicity.

Then finally—and I quote directly from his talk—

Evidence establishing the safety and effectiveness of one or more batches of a drug under investigation has no significance—

What he means is a drug product—

with respect to the safety of subsequent batches of the drug unless they can be shown to be the same as to identity, strength, quality, purity, with the batches studied.

Dr. Meyers, more recently in an appearance on November 28, at the APhA, Academy of Pharmaceutical Science—made this statement:

The active ingredient in a dosage form of a drug is probably not the sole determinant of its pharmacological effectiveness.

And Dr. Meyers also said that the physiological response may be a function of the formulations of the dosage as well as the active component.

Here is a very significant comment from this very experienced man in the Food and Drug Administration:

Regulations and guidance do not establish product quality. Assurance of product quality begins in exploratory research when the future product is nothing more than a gleam in the chemist's eye.

Mr. Chairman, what I am trying to portray in this chart, and with additive comments, is that generic equivalency does not necessarily denote therapeutic equivalency. I am reading from page 7:

The importance of particle form and size in antibiotics, like chloramphenicol, and in sulfadiazine and the anti-fungal agents, comes to mind. Variability in response to different formulations of the blood anticoagulant tablet, bishydroxycoumarin, are so significant that the choice of manufacturer source is clearly as important as the choice of the agent itself. The fineness of the drug in the tablet and how well the drug particle size is controlled by one manufacturing source as compared to another may very well determine whether dangerous clotting is prevented or serious internal bleeding occurs after ingestion of the usual dose. There are many examples of this sort.

Mr. Chairman, I have a notebook here which contains 211 references, which relate directly to this matter of pharmacological equivalency, to the science of biopharmaceutics, which seeks to explore the ways by which physical and chemical differences in the drug and nondrug components in drug products can affect the therapeutic safety and effectiveness of the drug products.

Now, the question has been raised, or the statement has been made

or has been implied, that because there are 18 or 20 known instances of so-called generic equivalent products, those which meet specifications by USP or NF which are not therapeutically equivalent, that that number is the full total that is known about—and that for this reason we are talking about a small percentage of the total drugs in use.

I disagree with that wholeheartedly.

I think the fact that there are 211 references, that are related to factors, which, can affect the therapeutic effectiveness and safety of products scientifically, shows that there are many more than 18. The only reason the 18 have been acknowledged is in retrospect, because they were so dramatically obvious that it was unmistakable to overlook them. I think this whole problem is more like an iceberg, where nine-tenths of it is below the surface. And I think we have only scratched the surface. To the extent that we study this problem in more detail, more in depth, I think we will find there will be a lot more than 18.

Mr. GORDON. Dr. Slesser, I would like to ask you a couple of questions. With regard to your 211 references of published literature on the effect of drug formulation on therapeutic activity—one, how many are duplicate studies, two, do they cover 211 different drugs? And, three, over how long a period of time were the studies published?

Dr. SLESSER. They do not cover 211 different drugs.

Mr. GORDON. How many drugs are actually discussed?

Dr. SLESSER. I do not know exactly how many are discussed. I am going to make this available to the committee, a copy of these references, if it has not already been available to the committee. But the interesting thing about it, Mr. Gordon, is that one cannot help but be impressed by the effect on the activity, therapeutic activity of a product by differences which are rather subtle—particle size, crystalline structure, PH, additive materials of various kinds, and so forth. And I would like to use this as an example.

You very often hear a negative statement made. "We have not in our experience found that there was any difference between a series of, let's say, generically equivalent products when we have used them."

Here is a hypothetical situation which I think—I think anyone familiar with medicine knows that there are patients who do not respond to certain drugs. The body builds up a tolerance, or there is a certain idiosyncrasy, and they fail to respond.

Let's create a situation here.

We have a patient who is seriously ill, and he needs a certain medication. That medication is supplied to him. The patient dies.

Now, I think without question the verdict would be—even though the death may be due to a failure in the quality of that product, its inability to perform as it should—I think more than likely the verdict would be the patient failed to respond to the drug.

Here is a case where it would not even be recognized for what it is. And I am sure the fact that this can happen, that we have seen dramatic instances where it has happened, certainly is good inference that it is very likely to happen and will continue to happen.

Mr. GORDON. I do not think my question has been answered.

Dr. SLESSER. If you repeat it, I will be glad to answer it, sir.

Mr. GORDON. Are any of these duplicate studies? How many drugs are involved? You said, I think, that there are not 211 drugs involved although you refer to 211 studies. Now, they may be concerned with only one, two, three, or four drugs.

Dr. SLESSER. No—they are concerned with a lot more than one, two, three, or four. I do not know the exact number. But I can tell you they are not duplicate studies. They may be on the same drug in some instances. There may be some on the same drug, yes. But exploring different facets of this particular drug.

In other words, there will not be two that have to do with the fineness of division of drug X let's say in a particular product.

Mr. GORDON. But you do not know offhand how many drugs are actually covered in the 211 studies?

Dr. SLESSER. I have not counted them. Do you know, Dr. Adams?

Dr. ADAMS. Well over 25.

Mr. GORDON. Now, how many are based on clinically controlled double blind studies?

Dr. SLESSER. I do not know the number, Mr. Gordon. I will state this. It is not always necessary to run a so-called double blind study. If you are comparing a drug—for example, in the type of study that Parke, Davis conducted on their Chloromycetin versus so-called generic equivalent chloramphenicol products, this need not be done in a double blind fashion.

Mr. GORDON. You do not know how many are based on controlled clinical double blind studies. Is that correct?

Mr. CUTLER. Could Dr. Van Riper answer that question?

Mr. GORDON. Surely—anybody.

Dr. VAN RIPER. Mr. Chairman, the importance of a double blind study depends on the drug that you have under study. One does not do a double blind study in a situation where he may have a fatal illness, where you would be giving a placebo, a blank.

Now, in this particular instance—I am not familiar with these studies, but the possibility and the probability is that these are run as therapeutic equivalents—one drug is studied against another, in a blind method, whereby the clinician who is doing the study is not aware of whether he is giving drug A or drug B. But he does know that both drugs under study are active.

Mr. GORDON. I can understand that. But I am asking about the 211 studies. Do you know how many of those are of the type you just mentioned?

Dr. VAN RIPER. I do not.

Mr. CUTLER. Mr. Chairman, could we offer these 211 studies for the record? They are all from published medical literature, as I understand it. And then they will speak for themselves.

Senator NELSON. All right. Depending upon how much value we determine there would be in printing them in the record as such. But you let us have them and we will decide that.[1]

Mr. CUTLER. At least the references could be printed in the record.

(Subsequent correspondence between Senator Nelson and Dr. Feldmann re 211 studies follows:)

[1] Retained in committee files.

MARCH 5, 1968.

Dr. EDWARD FELDMANN,
Director, National Formulary,
Washington, D.C.

DEAR DR. FELDMAN: During your testimony on June 8, 1967 before the Senate Small Business Committee's Monopoly Subcommittee you stated that you "would be hard pressed to name more than even a few—less than five—well-conducted clinically acceptable studies which have demonstrated significant differences between two or more products clinically where they have met all the chemical and physical standards as provided by the official compendia."

On November 29, 1967 Dr. A. E. Slesser of Smith, Kline and French submitted a notebook containing 211 references which, he stated, "are related to factors which can affect the therapeutic effectiveness and safety of products," and which show that there are many more than the small number of cases you, yourself, mentioned. Dr. Slesser, however, was unable to tell the Subcommittee how many different drugs were involved in the 211 references; whether they meet USP or NF standards; or to describe the scientific quality of studies which he was supplying.

To complete the record on this subject, I am taking the liberty of sending you the material which Dr. Slesser gave us, and I should be extremely grateful if you would examine its contents to ascertain how valid is the documentation for his position.[1]

Your assistance is greatly appreciated.

Sincerely,

GAYLORD NELSON,
Chairman, Monopoly Subcommittee.

THE NATIONAL FORMULARY,
Washington, D.C., March 13, 1968.

HON. GAYLORD NELSON,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: This will reply to your letter dated March 5, 1968 relative to the notebook or compilation of 211 literature references and reprints entitled "A Measure of the Volume and Content of the Literature Pertinent to the pertinence of its content to its subject title.

In response to your request to me, I have examined this compilation and have evaluated it in a general way from the standpoint of its scientific character and the pertinence of its content to its subject title.

The preface statement in this compilation describes the division of the material contained therein into five sections identified as items A through E. From my examination of these five sections, it is my conclusion that items B, C, D, and E are largely supplemental to the information provided in item A. This conclusion can be drawn from the fact that item B principally draws upon many of the same references as those listed in item A. Item C is a chapter from a textbook, and as such is based principally upon information drawn from the literature—again largely information covered under item A. Item D is an annual review of all areas of research for a specific year in the broad field of the pharmaceutical sciences. As such, the articles in item D of pertinence to this compilation already have been listed under item A. Finally, item E is simply a listing of all periodicals and journals dealing with pharmacy which are published throughout the world.

On this basis then, it appears that greatest attention should be devoted to a consideration of the scientific aspects and pertinence of the material appearing under item A.

As noted in the preface to the compilation, item A consists of a listing of 211 articles (along with the abstracts relating to some of them, and along with photocopies of certain of the other articles). A detailed and thorough examination of these articles would constitute an enormous undertaking. My review of this material has been limited to a general examination of the material as presented in this listing. From this general review and survey, I believe that the following conclusions can be validly drawn:

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[1] Retained in committee files.

1. The literature covered by this survey ("item A") is sufficiently broad to indicate that it represents a reasonably comprehensive review of the subject field. It is rather unlikely that any significant areas have been overlooked in assembling this compilation.

2. The periodicals and journals which are cited as references constitute recognized and respected publications in the medical, pharmaceutical, and related professional or scientific fields. As such, they are appropriate sources for the collection of information on the subject topic of the compilation.

3. Of the 211 references, the first group of 102 references—according to the preface statement—pertain to *in vivo* clinical observations, which is the subject of greatest interest to the question that the compilation attemps to answer. *On this basis, the succeeding observations will be limited to references from this first group of 102.* However, it appears that this first group of references is quite analogous to the second group of references in all other respects, so that the same general observations could be validly drawn regarding the source of the information, the applicability of the studies, the scientific veracity of the conclusions, etc.

4. The absence of either abstracts or reprint copies of a substantial number of the references cited makes it difficult to evaluate the conclusions or pertinency of such articles without consulting the original literature. Certain of the articles listed by title only appear to be of questionable pertinency to the topic of this compilation; for example, references number 37 and 71.

5. A number of the references appear to pertain to isolated case histories or other types of casual observations which were not conducted in a scientific manner—nor were they intended to be. Such articles are equivalent to testimonials and while interesting, are usually regarded as almost meaningless by trained scientists and experienced clinical investigators. A few examples of this type include references number 13, 14, and 19.

6. A few of the references do not appear to be appropriate for inclusion in this listing since the titles and/or abstracts of the articles indicate that the study involved is concerned only with the pharmacology of the drug under examination and not in any way with dosage forms or matters of formulations; for example, reference number 35.

7. Somewhat along the same vein, certain references appear only to compare entirely different routes of administration of a drug rather than different dosage forms or formulations to be administered by the same route. It is obvious to all that a drug administered by injection will be physiologically available more promptly than virtually any oral dosage form. Examples in this category include references number 24, 25, and 97.

8. Many of the studies compare entirely different types of oral dosage forms—for example, a drug in the form of tablets or capsules in contrast to the drug substance in some liquid dosage form such as an elixir of suspension. Selection of the optimum dosage form is important and unquestionably can have an effect on the therapeutic effectiveness of the drug involved. However, I am unaware of any suggestion or claim that "therapeutic equivalency" exists between completely different types of dosage forms. This is quite another matter from comparing the tablets made by one firm with the tablets made by another firm. Therefore, references of this nature do not seem appropriate for inclusion in this compilation on "generic equivalency"; some examples include references number 7, 10, 12, 89, and 98.

9. By the same token, certain drugs are *purposely formulated* in a manner to provide slow or gradual release of the drug. Studies comparing such timed-release or sustained-release preparations with drug products intended for regular drug release should not be included in this listing. Since such products are purposely intended to have different properties or characteristics of drug release, it does not seem appropriate or valid to include such references in this listing. It is implied that the listing consists of references demonstrating differences observed in drug products where no such differences were intended. Examples of some of the references which should be excluded on this basis are numbers 4, 21, 32, 48, 70, 76, 84, 85, and 90.

10. Many of the articles cited appear only to compare completely different compounds. It is quite obvious that formation of a water-soluble salt of a water-insoluble organic compound will result in a new compound which is more

readily soluble in aqueous body fluids. For this reason, different salts and esters are regarded by the FDA, the official compendia, and the scientific community as entirely different drugs, since in fact they are entirely different compounds. It is inappropriate, therefore, to include in this listing studies which principally appear to compare different compounds rather than different formulations of the same drug entity. This would exclude, for example, references number 27, 30, 34, 41, 72, 73, 80, 86, and 96.

11. Certain references appearing on the list are duplicative of others already included on the list. The duplicative references include editorials, review articles, and general statements which are based on studies already included in the listing. Consequently, inclusion of these latter references could be misleading since their presence suggests a larger number of original reports in the literature than actually exists in fact. References in this category which appear to provide no new data include, for example, numbers 22, 26, 38, 45, 51, 53, 58, and 66.

12. Several of the references referred to appear to be inconclusive or borderline regarding the conclusions which are drawn as to existence or nonexistence of therapeutic equivalency. Such references include numbers 5 and 31.

13. A number of the references cited indicate that current standards are satisfactory to assure quality drugs. See, for example, references number 57 and 65.

14. Several of the references listed appear to constitute articles in which the conclusions of the respective authors show that drug product variation was *not demonstrated* on the basis of the particular study reported. The references which appear to support therapeutic equivalency include numbers 61, 62, 63, and 77. Moreover, references 61 and 77 specifically refute other articles appearing on this list which apparently report clinical differences among drug products.

15. None of the examples of questionable references listed in the above paragraphs are duplicative. Furthermore, in each instance the references cited above are just some examples chosen at random to illustrate each of my points; hence, additional references probably could be similarly disqualified if a closer scrutiny were made. Consequently, significant question exists concerning the pertinency or appropriateness of including a large proportion of the references tabulated. Moreover, it appears that a substantial portion of the remaining references may in fact support the idea of "therapeutic equivalency" of drug products rather than refute it.

16. After eliminating the above-mentioned questionable, inappropriate or refuting references, a limited number of references still remain which appear valid as documentation to demonstrate instances in which "therapeutic equivalency" may not exist. It should be noted, however, that these remaining references do not all pertain to studies on different drugs. In other words, some of them constitute confirmatory studies regarding certain drugs discussed in other reports on this list. Hence, while it is appropriate to include these confirmatory references in this listing, the number of drugs concerning which non-equivalency of some sort has been observed is substantially less than the total number of references which remain after excluding the invalid or inappropriate reports. For example, references 18, 32, 42, 43, 49, and 67 all pertain to enteric coated aspirin tablets.

17. Your letter to me dated March 5, 1968, quoted a statement by Dr. Slesser explaining that the compilation contained references which "* * * are related to factors which can affect the therapeutic effectiveness and safety of products."

After eliminating the inappropriate studies, some of the remaining references do appear to provide some support to Dr. Slesser's statement. It should be noted, however, that his statement says that these considerations are *"related to factors,"* and that the factors *"can affect"* effectiveness and safety. This broad generalization does not really answer the basic question implied during the Subcommittee hearings; namely, "Does the scientific literature reveal many studies showing that a significant clinical difference (effectiveness or safety) has been demonstrated in comparing two drug products which meet applicable official compendia standards?"

In conclusion, it appears from the above point-by-point evaluation, that this compilation actually supports and substantiates the testimony presented by me and a number of other witnesses during the hearings of the Senate Subcommittee on Monopoly during 1967. In my testimony before your Subcommittee on June 8, 1967, I stated under conclusion number 6:

"Information available in the published literature reveals only isolated case histories, and very few scientifically performed studies, which demonstrate sub-

stantial differences in 'therapeutic equivalence' between two comparable drug products (also referred to as generic or brand equivalence). Consequently, while we must recognize that this factor exists, currently available evidence indicates that only very seldom is there a difference in clinical performance if the official compendia standards are met by both drug products."

In subsequent testimony both FDA Commissioner Goddard and USP Director of Revision Miller, among others, also commented to the effect that differences do exist in the case of some drug products, but that there are relatively few documented cases in literature references,, indicating that from a clinical standpoint this problem has been greatly exaggerated. In your March 5, 1968, letter to me you also quoted from my statement made to your Subcommittee that:

"* * * I would be hard pressed to name more than a few—less than five—well-conducted clinically acceptable studies which have demonstrated significant differences between two or more products clinically where they have met all the chemical and physical standards as provided by the official compendia."

The references which remain after eliminating those that are inappropriate may include a few such studies, but the number certainly does not exceed five and probably is even smaller than five.

Consequently, it appears that the above-quoted statement from my testimony is actually confirmed by a review of the compilation of references which you supplied to me, and concerning which you requested my evaluation and opinion from a scientific viewpoint.

Sincerely,

EDWARD G. FELDMANN, Ph. D., *Director.*

Mr. GORDON. How many of the drugs in the 211 studies you cited did not meet the required standards set for them by the USP or the National Formulary?

Dr. SLESSER. Mr. Gordon, I do not know the answer to that question. But let me state this.

The existence of USP or NF standards does not by any means assure that every product on the market will meet them. The fact of the matter is there are products on the market that do not meet U.S.P. and NF tests, and there probably are a great number of them. The evidence is certainly in that direction

There are products that do meet the USP and NF tests which do not function properly therapeutically. And these are covered, of course, either directly or indirectly by scientific literature in these 211 references.

Senator NELSON. Do you know of any drugs on the market that do meet USP standards or NF standards and do not function appropriately therapeutically which are not on the list of the 14 or 15 to which Dr. Miller and other witnesses testified? In other words, do you know of more than the 14 or 15 that are cited as exceptions by Dr. Miller and other pharmacologists and experts in the field?

In other words, if you know of some that ought to be added to the list, we ought to have the USP advise us about them, because they are not aware of any more than 15 or so.

Dr. SLESSER. Senator, perhaps in this connection you might be interested in inviting to some future session of this committee—I do not know whether he will consider this as an honor or not—my recommending him, I am talking about—not appearing before this committee—but Capt. Solomon Pflag who is Chief of the Technical Operations Division, Director of Medical Materiel, the Defense Supply Agency. In a talk he made on November 20, a little over a week ago—perhaps you are interested in what the military feels about this particular point.

Let me read very briefly from his talk.

Senator NELSON. I assume when we get to the area of Government procurement of drugs, we will hear testimony from the appropriate person from the Defense Supply Agency. Go ahead.

Dr. SLESSER. This on page 10, Mr. Chairman.

I will read his direct words.

In our quest for quality pharmaceuticals, we found that we had to go one step further—

He is talking about a 10-step program which he described nine steps of, one of them involving laboratory testing—

we had to go one step further to complete our ten point quality assurance program. Therefore, a few months ago the Department of Defense approved the concept of requiring proof of pharmacological equivalency. The literature is replete with studies of factors, both biological and physiological, chemical, influencing the biological activity of drugs and drug products. This includes dissolution rates, disintegration rates, comparison of dosage forms of the same drug, and particle size as they affect biological activity, and blood tissue levels, absorption rates, and metabolism and excretion rates for drugs. This plus our complaint history on a score of select pharmaceuticals indicated a dire need for pharmacological equivalency testing. In essence DPSC will formulate a proposed testing procedure with the cooperation of government personnel, universities, or industry. This procedure will be submitted to the DMMB—

Which is the Defense Medical Materiel Board—

for professional evaluation and approval. The DPSC will include the pharmacological equivalency testing procedure in the specification. We will also document the bidders or offerors method of manufacture, specifications, procedures, and quality control for the production of the specific lot of materiel subjected to the testing required in the specification.

Now, this, of course, is over and above U.S.P. or N.F., because I think you can easily see that no compendium, irrespective of its nature, can cover all those links in the quality-control chain—the essential links— in order to make sure that each batch is safe and effective—when you consider the differences in the selection of nondrug components, differences in formula, in manufacturing procedure—the quality control differences and so forth.

Senator NELSON. If I understood correctly what the captain was saying, he was reciting careful procedures which must be followed to assure that U.S.P. standards were met, is that not correct?

Dr. SLESSER. No. He was in effect stating the inadequacy of U.S.P. or N.F. standards, because he found it necessary to convince the DSA policymaking people that another specification was necessary—namely, proof of pharmacological activity.

Senator NELSON. This puzzles me a little bit.

Today Dr. Lueck testified that the U.S.P. standards are the highest in the world, if I understood him correctly.

Dr. SLESSER. That is correct.

Senator NELSON. A week or so ago, the president of one of the major pharmaceutical corporations said that the U.S.P. was the highest standard in the world. Does this captain know of standards higher than those we have in this world?

Dr. SLESSER. No standard, Mr. Chairman, can suffice in lieu of or instead of the test for safety and effectiveness on human beings in a clinical study.

Senator NELSON. What we are talking about—the captain, and you—

in terms of quality control, I take it, are procedures to assure that U.S.P. standards are in fact met. Isn't that what we are talking about?

Dr. SLESSER. What we are talking about, Mr. Chairman, is this. That quality control, properly exercised, begins at the R. & D. stage, and that when properly exercised on a batch-to-batch basis—the only way a manufacturer can assure that every batch that he makes and every tablet and every capsule in that batch is as safe and effective as the original clinically tested batches, is by the implementation and the execution of this chain of quality control in the manufacture of each batch. So in effect, quality control serves as a substitute for the clinical test on a batch-to-batch basis.

Now, this is really what quality control is, and what it does, after you have done clinical testing. If you have not done the clinical testing, I state it is a scientific fact that laboratory test results alone may mean absolutely nothing.

Senator NELSON. Well, I hope we are not running around in a circle. But the U.S.P. standards are the highest in the world, and the U.S.P. consults people from the industry, as well as the best clinicians in the country from all the various specialities, to set the standards. It seem to me all you are talking about in quality control is that you must have a first-rate method of assuring that you really come out meeting those standards. If you know of some drugs that meet the U.S.P. standards but are not therapeutically effective, I would like to have the names of them, because Dr. Miller has given us the names of all those he knows, 15 or so known among all the drugs on the market. Now, do you know of drugs in addition to those that Dr. Miller knows about that meet U.S.P. standards and are not therapeutically effective?

Dr. SLESSER. Mr. Chairman, the fact of the matter is that there are such drugs on the market.

Senator NELSON. What kind of drugs do you mean?

Dr. SLESSER. There are two categories. There are drugs which do not meet U.S.P. and N.F. specifications.

Senator NELSON. Those, we will all agree, should not be on the market and are not at issue here at all.

Dr. SLESSER. There is another category of drugs that do meet these specifications, but are not clinically effective.

Now, the U.S.P.—Dr. Miller certainly has something to do with the U.S.P. On the page that I referenced, he stated that there is no—at the present state of knowledge, the monograph specifications cannot assure pharmacological availability. And that is what we are talking about. That is the guts of this issue. And the Defense Department recognizes this, and therefore they are going beyond U.S.P. or N.F. specifications. And I suggest that Captain Pflag could probably reveal reasons why they had to go to this particular kind of activity.

Senator NELSON. There wouldn't be any reason for you to be aware of this, but I believe I have asked every industry witness that has appeared, "Do you know of any drugs that meet U.S.P. standards that are not therapeutically effective?" They do not give me any examples.

Now, what amazes me, just absolutely astonishes me, is that I say this week after week after week, but witnesses merely give me a lot of other material that is peripheral.

I will give you the names of the drugs that Dr. Miller gave us, and then will you give me a list of those proven cases that you know of where drugs meet U.S.P. standards but are not effective. Dr. Miller does not know of more than 14 or 15 cases. No witness from the industry knows of additional examples. I think I asked the PMA for examples when they testified for the first time and I did not get any. I am anxious to have it in the record. We are trying to do a fair job here. It would seem to me if you assert that certain drugs meeting U.S.P. standards are not therapeutically effective or equivalent, that you are bound to name them.

Dr. SLESSER. Mr. Chairman, I would respectfully suggest that the reverse is true. Before we can market a drug, we must test to make sure——

Senator NELSON. Just a minute, Doctor. You asserted this yourself. Now, if you make such an assertion, you must base it on some knowledge.

Will you give me the specific cases that you know, from your experience, or anybody else's experience, of drugs meeting U.S.P. standards that were not therapeutically effective beyond the list of drugs of a dozen or so that Dr. Miller and many other witnesses have talked about. You name me one.

Dr. SLESSER. Captain Pflag refers to a score or so.

Senator NELSON. Does he name them?

Dr. SLESSER. I think he can.

Senator NELSON. Really, I must say, Doctor—this is your business, this is your industry. I have been asking this question for weeks.

Dr. SLESSER. I will be happy to call him if you like.

Senator NELSON. If you assert that it is the case that drugs meeting U.S.P. standards are not therapeutically effective, I would think you would be prepared to say on what basis do you draw that conclusion, and name the case, the drug, the example. You are a scientist. I am not. But just as an ordinary lawyer putting in evidence, I would not make that assumption if I did not have the evidence to back it up. I could not sit there and say "This is the case, and you people prove it is not true."

Mr. CUTLER. Mr. Chairman, no one drug company has conducted these tests on every other product.

Now the Defense Department has conducted a number of tests. Captain Pflag—they said he has found a score or more. He would certainly respond to this committee.

Senator NELSON. I did not hear him say, "I found a score or more that met U.S.P. standards that were not therapeutically effective." Did he say that?

Dr. SLESSER. What he said is, "This, plus our complaint history on a score of select pharmaceuticals, indicated a dire need for pharmacological equivalence testing."

Mr. CUTLER. In other words, testing that goes beyond the U.S.P. tests.

Senator NELSON. Well, you did not answer the question I raised.

Mr. CUTLER. Sir; we do not know how to answer that question. Dr. Goddard can help answer it, the Defense Department can help answer it. We have given you 211 medical literature references, some of which

refer to the drugs meeting U.S.P. tests. Those doctors are available to testify. And their findings are reported in medical literature.

Senator NELSON. Name me one of the 211 that met U.S.P. standards and was found not to be clinically effective.

Dr. SLESSER. Chloramphenicol.

Senator NELSON. That is on the list. We know about that one. Name some in addition to the dozen or so that Dr. Miller has mentioned, and Dr. Feldmann has mentioned, and that have been in the literature.

Dr. SLESSER. I do not know the ones they have mentioned. I have not seen them in the testimony.

Senator NELSON. If anybody has combed that record better than the industry, I would be very surprised.

Dr. SLESSER. I read their complete testimony before your committee, Senator, and I have not seen any names.

Mr. GROSSMAN. Dr. Slesser, has the PMA ever made any efforts to deal with the U.S.P. standards? Are you trying all the time to upgrade these standards? We have heard so much about how the standards may not be adequate. What are you doing about it?

Dr. SLESSER. The industry has been for many years, Mr. Grossman—the industry has been—PMA has been cooperating with the compendium officials, with Food and Drug Administration, through the quality control section, which meets twice a year, for the specific purpose of establishing standards and specifications for drug products.

Mr. GROSSMAN. Let us pin this down a little bit. Do you think the U.S.P. standards are adequate, as far as quality control? In other words, we have heard so much talk—let us have a yes or no.

Dr. SLESSER. They are adequate for pharmaceutical—in a pharmaceutical sense, Mr. Grossman, not in a clinical sense.

Mr. GROSSMAN. I am a lawyer. Could you explain that to me?

Dr. SLESSER. Well, there has to be some proof of biological effectiveness.

If you look at any monograph in the U.S.P.—these are the tests and specifications for the U.S.P. and N.F. products—and if you examine each of the tests which are stipulated in those monographs, you will find, except for insulin, where there is a fasting rabbit blood sugar level lowering test—that there will be no test for therapeutic performance. It is simply assumed, erroneously by many, because there are disclaimers in the U.S.P. and N.F. to this effect—nevertheless it is assumed that so long as a product meets these tests, ergo, U.S.P. or N.F. test—ergo it has to be therapeutically effective. This is disclaimed by the compendia themselves. If you are asking me do I know of a substitute for a clinical test, the answer is no.

Mr. GROSSMAN. The U.S.P., then, is not doing enough. I mean yes or no?

Dr. SLESSER. Insofar as therapeutic—I can only answer your question this way. I am not trying to be difficult, believe me.

Insofar as spelling out clinical performance, there is no such specification—except in the one instance that I mentioned, in the U.S.P. or N.F.

Mr. GROSSMAN. Now, on another matter, you make a very, very strong allegation on page 11 of your testimony where you say, "The inability of the FDA to assure even the competence of all drug firms,

let alone the clinical quality of their products, is too longstanding to brush aside. And the possibility of that situation soon or ever changing is extremely remote." Frankly, that is about as strong a charge as anybody could come before this committee and make. And then you come up here—and I was waiting for these 211 examples of doctors' reports—I don't know whether you have read them, but, when you are asked any questions about them, frankly you cannot answer them—do they meet U.S.P. standards.

I would think you would come up here and have fairly accurate and detailed knowledge about these 211 cases, or at least be able to say of the 211 half of them did this or that. But it just seems like you are throwing 211 things that you want everybody to read, and you know nobody is going to read.

Dr. SLESSER. Mr. Grossman——

Senator NELSON. I have to answer another rollcall. You may continue with your questions.

Dr. SLESSER. Mr. Grossman, I would simply like to repeat a comment that I made earlier, and I think certainly it is one that is factual. And that is no matter what tests you may have in the U.S.P. or N.F., you have many marginal and incapable manufacturers of pharmaceuticals in this country today. And irrespective of the legal requirements—after a product has failed to do a job it is supposed to do and there is a casualty as a result of the—in tolbutamide, it was easily recognized after the tablet passed through the GI tract without dissolving it did not meet standards. The fact of the matter was it was on the market, available, prescribed and taken. The same thing, I am sure, happens many times. The fact that I personally do not know about them is simply an indication of the fact that this kind of a thing is not the kind of a thing you are apt to see in the scientific literature.

Mr. GROSSMAN. I am assuming none of these firms are members of PMA that you are talking about. Is that safe to say?

Dr. SLESSER. They may be. I do not say being a member of PMA means one is perfect. I think PMA members make mistakes, too. But I think their batting average is far better than those who are much more poorly qualified.

Mr. GROSSMAN. It just seems to me—and again I waited to see what evidence you would present—that—and Mr. Cutler, as a lawyer—when you come into court or a committee, that if you have 211 cases, that they are just not thrown at us and say "Here are 211 cases." I would like to know what they all mean. When you were asked whether they were below U.S.P. standards and so on—there was no answer.

Dr. SLESSER. Mr. Grossman, I said there were 211 papers that dealt with the subject of biopharmaceutics, which indicated the vast and profound effects that can occur in drug products depending on particle size of the drug, depending on the crystalline form of the drug, depending on certain additives that are present, pH, and so forth.

Mr. GROSSMAN. Have you yourself made efforts to study the various 211 articles, whatever they are, to decide how many say this and how many say that, and whether they refer to the same items, are they duplicative.

Dr. SLESSER. They are not duplicative pieces of work. Some of them—more than one may involve a certain drug. But I would say some different aspect.

Mr. GROSSMAN. I want you to say that if you believe that the U.S.P. standards are not adequate, and that we should increase the minimum quality standards, why isn't the PMA pressuring the U.S.P. to do it. You have people on the U.S.P. that are members of PMA.

Mr. CUTLER. Mr. Grossman, what we have tried to say, and what the U.S.P. itself says, and the publisher, the editor of the N.F. himself says, is that laboratory tests of the type that those two formularies or documents prescribe will not determine pharmacological availability or therapeutic effectiveness.

Now, we cannot conjure up a test that will determine that in the laboratory. What we are trying to say is you can only determine that by clinical testing of the drug product itself.

Mr. GROSSMAN. And the U.S.P. does not at present——

Mr. CUTLER. The U.S.P. does not purport to establish clinical testing. It attempts to establish certain laboratory tests to detect the presence of an active ingredient in a drug.

Mr. GROSSMAN. Do you, as a consumer, feel safe when you take a drug that has a U.S.P. standard?

Mr. CUTLER. The consumer does not select his drug. He goes to a doctor.

Mr. GROSSMAN. You, yourself, sir—are you concerned when you take a drug that has supposedly met U.S.P. standards, that you are not getting the proper quality control?

Mr. CUTLER. I don't have an idea in the world whether it met U.S.P. standards. I do not know how I would know. I get a prescription from a doctor on whom I depend, I go to a pharmacy that he recommends, and I get a drug.

Mr. GORDON. On page 3 you discuss the great care exercised by manufacturers in insuring that the correct amount of ingredients is in each tablet. This is your statement.

At this point I would like to insert into the record a list from the latest issue of Clin-Alert on recalls of products from major companies. I might mention Diamox Sustets, put out by Lederle Laboratories; Coumadin, put out by Endo Laboratories; Panwarfin, Abbott Laboratories. These are all members of the PMA that produced drugs which could not meet U.S.P. standards.

(The document referred to follows:)

[From Clin-Alert, Nov. 3, 1967]

DRUG RECALLS

LABELING ERRORS

A. *Diamox Sustets (acetazolamide-Lederle Laboratories)*: Approximately 700 bottles of 500 mg. Diamox Sustets (the export name for Diamox Sequels) were recalled due to a labeling error. According to FDA's weekly report of drug recalls (Sept. 27 thru Oct. 3), the recall was initiated September 27, 1967 by telephone.

B. *Coumadin (warfarin sodium-Endo Laboratories)*: Approximately 30 million tablets recalled nationally. Tests showed that the tablets were above, and in some cases, below the stated potency levels on the labels. Variations were greater than those permitted to ensure safety. According to news releases (public announcement of the recall was made by FDA's New York Office) a spokesman for the food and drug agency warned that the overstrength tablets could be fatal to some patients. Later, Dr. Goddard, Commissioner of the U.S. Food and Drug Administration, was quoted as stating that lives would not be imperiled by taking the drug.

C. *Panwarfin (warfarin sodium-Abbott Laboratories)*: Approximately 4 million, 5 and 10 mg. subpotent tablets recalled. This FDA-initiated action was announced to retail pharmacists by letter dated October 10, 1967.

Mr. GORDON. Also you remember that some time ago we put into the record a list of major recalls, some of them including millions of tablets, from Squibb, Abbott, Roche, Pfizer. I cannot understand why you are making such a big deal about going beyond U.S.P. standards, when many of your own companies cannot even meet U.S.P. standards.

Dr. SLESSER. Dr. Scheele, are you going to talk about recalls?

Mr. GORDON. Also, I would like to call attention to a list of recalls, which I will put in the record, where the following companies, members of the PMA, could not even meet the current good manufacturing practices provisions of the Kefauver-Harris Amendment of 1962. For example, Squibb & Sons, "Various drugs manufactured without satisfactory controls." Abbott Laboratories, "Various drugs manufactured without satisfactory controls." Wyeth Laboratories, "Aludrox manufactured without satisfactory controls." Charles Pfizer & Co., Inc., "Several drugs mislabeled because of inadequate controls."

(The document referred to follows:)

[From the Pink Sheet, July 26, 1965]

(Excerpts—Drug Recalls—Oct. 1, 1962, to June 30, 1965, p. 18)

ACTIONS INVOLVING "CURRENT GOOD MANUFACTURING PRACTICE"—SECTION CITATION CASES

Firm	Charges	Present status or case
E. R. Squibb & Sons, New York, N.Y.	Various durgs manufactured without satisfactory controls.	Hearing held. Case placed in permanent abeyance by FDA Headquarters on Mar. 11, 1965.
Abbott Laboratories, Inc., North Chicago, Ill.	....do....	Hearing held. Case placed in permanent abeyance by FDA's district office on Mar. 16, 1965.
Wyeth Laboratories, Inc., Philadelphia, Pa.	"Aludrox" manufactured without satisfactory controls.	Hearing held. Case placed in permanent abeyance by FDA's district office on Dec. 1, 1964.
Chas. Pfizer & Co., Inc., New York, N.Y.	Several drugs mislabeled because of inadequate controls.	Hearing held. Case placed in permanent abeyance by FDA's district office on May 25, 1965

Mr. CUTLER. Mr. Gordon, you are only proving our point—that even the best companies make mistakes occasionally. If you go over those drug recall lists, you will find that the frequency of drug recalls for the non-PMA member companies that make only 5 percent of the drugs is far higher for any volume unit of production you want to take than the frequency of recalls of the PMA members who make 90 to 95 percent of the drugs.

The fact that even the best companies are not perfect helps to establish our point—that doctors simply must use their own experience and their own judgment based on what has happened to their patients when particular drugs of particular manufacturing sources were prescribed.

Now, if, as Senator Nelson indicated earlier, he also favors identifying manufacturing source, I do not suppose we have any disagreement. That is all we are trying to say.

Mr. GORDON. Now, on page 4, you stated:

We all know that effectiveness and safety of a drug product are determined by well-designed, properly controlled and correctly executed clinical tests.

It is my understanding that most clinical tests are poorly executed. For example, in the Journal of the AMA, November 6, 1967, an article entitled "Studies of Drug Usages," pages 406 to 510, a review of over 200 papers reporting on the efficacy of many of these agents—that is, drugs most used in hospitals—revealed that very few studies were well controlled. This is on page 510 of the Journal of the AMA.

I ask this article be inserted in the record at this point.

(The article referred to follows:)

[From the Journal of the American Medical Association, Vol. 202, No. 6, Nov. 6, 1967]

STUDIES OF DRUG USAGE IN FIVE BOSTON HOSPITALS

(Ivan Borda, MD, Hershel Jick, MD, Dennis Slone, MD, Barbara Dinan, RN, Barry Gilman, and Thomas C. Chalmers, MD)

A study of drug usage was conducted in five hospitals: two hospitals for patients with acute diseases, two for patients requiring long-term care, and one pediatric hospital. Partially due to the increased length of hospitalization, more drugs were used in long-term hospitals. The number of different drugs used to treat the same problem varied greatly. For some therapeutic indications, one particular drug was widely accepted by most hospitals; in others, there was a wide variance. More than one drug of the same pharmacological action was often prescribed for the same patient. Older patients and women received more drugs. Antibiotics were used in a high percentage of all hospital patients. There were many incomplete prescriptions and discrepancies between drug orders written by doctors and records of medications administered by nurses. These results indicate the need for an epidemiologic approach to therapeutics.

During the past few years the medical community has become aware of the need for more and better information concerning drug efficacy and adverse drug reactions. The importance of obtaining more data in these areas appears to be well recognized in England where the National Health Service has gathered statistics concerning the prescribing habits of British physicians over a four-year period (1959 to 1962). The British Ministry of Health is keeping records of all general practitioners, and these records are periodically checked for "over-prescribing." (1, 2) Public health authorities in West Germany and Canada show an increasing interest in drug epidemiology and have established agencies responsible for studies on drug use and adverse reactions. (3–5) The great majority of publications as well as the structure of the existing programs indictate that investigators are focusing their attention mainly or entirely on the problem of adverse reactions to drugs. (6–10)

However, an adverse reaction program requires the denominator factors for a meaningful interpretation of the numerator data. (11) More specific information may be obtained if adverse drug reactions are correlated with the vital statistics (age, sex, race, etc) of the study population. In a hospital study, the recording of these factors together with characteristics of the hospital itself, such as whether the hospital cares for patients with acute or chronic diseases, whether it is a private or municipal hospital, the number of ordering physicians, and the type of hospital formulary will provide what may be called the "drug profile" of a hospital.

The prescribing habits of the physicians involved should also be studied. It is estimated that in 1963 between 700 and 800 million prescriptions were written in the United States, approximately 12.8 prescriptions for each family.[12] This speaks for the enormous importance of collecting relevant data in regard to drug usage.

A drug survey was conducted in five hospitals in order to describe current drug practices and to point out some aspects of drug use which require further investigation in depth.

METHODS

Randomly chosen records of patients who were discharged or who died between Sept. 1, 1964, and Aug. 31, 1965, were studied in five hospitals in the Boston area. A total of 682 charts were reviewed. One of the hospitals cares for patients with chronic diseases (average stay, 307 days), one for patients requiring intermediate-

length care (average stay, 42 days), two are general hospitals for patients with acute diseases, and one is a pediatric hospital. Table 1 shows age data and diagnoses.

TABLE 1.—AGE AND DIAGNOSIS

Age group, years	Number of patients in hospitals					
	Chronic	Intermediate	Acute 1	Acute 2	Pediatric	Total
Less than 15	0	3	6	8	154	171
16 to 40	2	27	68	58	0	155
41 to 54	5	35	30	31	0	101
More than 55	71	84	46	54	0	255
Total	78	149	150	151	154	682
DIAGNOSIS						
Diabetes	18	21	12	8	1	60
Stroke	24	10	0	6	0	40
Rheumatic heart disease	3	5	2	1	2	13
Hypertensive cardiovascular disease	9	5	6	5	1	26
Myocardial infarction	5	4	5	3	0	17
Heart failure	4	4	3	5	2	18
Arteriosclerotic heart disease	12	15	6	9	0	42
Neoplasm leukemia	19	47	8	8	4	86
Upper respiratory tract infection	0	0	3	1	33	37
Chronic bronchitis emphysema	7	16	4	2	0	29
Pneumonia	2	3	4	1	8	18
Genitourinary tract infection	2	6	7	3	10	28
Meningitis	0	0	0	0	5	5
Abscess	1	1	1	3	2	8
Peptic ulcer	0	1	4	4	0	9
Headache	0	0	1	5	0	6
Seizure disorders	0	2	1	0	6	9
Pregnancy	0	0	0	24	0	24
Rheumatoid arthritis	2	7	0	1	0	10
Anemia	1	10	7	2	6	26
Skin diseases	1	6	8	3	2	20
Cirrhosis	0	11	1	2	0	14

A study card was used for recording the following data copied from the physician's order sheet, the nurse's notes, and the face sheet of the chart: (1) complete list of drugs ordered during the patient's last hospitalization; (2) dose, frequency, and route instructions for each drug ordered; (3) vital statistics; (4) admission and discharge dates; and (5) discharge diagnoses. Each drug was recorded only once. Neither orders to discontinue or restart nor changes in dosage or route were recorded. The data were transferred from the study cards to punch cards and were processed in a computer system. The output of this computer system was in the form of tabulations.

RESULTS

Table 2 shows the basic working data in each hospital. More than twice as many orders were written per patient in the two long-term hospitals as in the two acute hospitals and almost twice as many orders in the chronic hospital as in the intermediate hospital. In order to estimate the role which length of hospitalization played in the observed differences between long-term and acute hospitals, a separate analysis was carried out. Since the average duration of hospital stay in the acute hospitals was ten days, we compared drug usage for this period in the two types of hospitals. Thirty randomly chosen records from each long-term hospital were examined. There was no significant difference between the number of drugs ordered in long-term and acute hospitals during the first ten days after admission.

The frequency with which the various drug categories, ie, groups of drugs with similar pharmacological activity, were used is shown in Table 3. Only anticholinergic agents were used more frequency in the acute than in the long-term hospitals. All other drug categories were ordered more often in the two long-term hospitals. Order ratios of long-term to acute hospitals include the following: antibiotics, 3:1; vitamins, 4:1; tranquilizers, 2:1; diuretics, 4:1; cardiac stimulants, 2:1, antihistamines, 3:1, ointments, 6:1, expectorants, 3:1; corticosteroids, 2:1; antiseptics, 4:1; hematinics, 5:1; and vasopressors, 5:1.

TABLE 2.—BASIC WORKING DATA

Hospital	Number of records reviewed	Number of drug orders		Average number of drug orders per patient		Average duration of hospital stay, days	Number of admissions/ year
		Total	During 1st 10 days	Total	During 1st 10 days		
Chronic	78	1,430	644	18	8	307	332
Intermediate	149	1,543	570	10	4	42	2,000
Acute 1	150	860	----------	6	----------	12	3,000
Acute 2	151	1,083	----------	7	----------	8	5,100
Pediatric	154	563	----------	4	----------	13	2,800

TABLE 3.—DRUG USAGE BY CATEGORIES

	Number of times ordered in each hospital							
	Total	Chronic	Inter-mediate	Total long term	Acute 1	Acute 2	Total acute	Pediatric
Analgesics	963	175	278	453	196	289	485	25
Hypnotics sedatives	783	108	207	315	211	189	400	68
Antibiotics	558	189	134	323	51	54	105	130
Laxatives	539	96	197	293	112	111	223	23
Anticholinergics	259	34	29	63	47	88	135	61
Vitamins	204	102	43	145	15	23	38	21
Decongestants-bronchodilators	192	38	45	83	20	16	36	73
Tranquilizers	131	41	40	81	5	34	39	11
Diuretics	130	62	37	99	12	12	24	7
Cardiac stimulants	116	45	32	77	14	19	33	6
Antihistamines	113	27	48	75	10	14	24	14
Antiemetics	107	35	30	65	11	29	40	2
Ointments (including eye ointment)	83	46	23	69	4	6	10	4
Expectorants	93	23	38	61	17	5	22	10
Corticosteroids	87	16	37	53	8	14	22	12
Antidiabetics	79	23	26	49	14	13	27	3
Antiseptics	56	24	17	41	6	4	10	5
Hematinics	51	26	12	38	6	1	7	6
Vasopressors	37	22	9	31	3	3	6	0

There was a great variation in the number of different drugs used for treating the same problem. Table 4 shows the number of individual drugs used within each drug category. A greater variety of drugs within each category was used in the long-term hospitals. The greatest variety was found in the hospital for patients with chronic diseases; 31 antibiotics, 21 vitamin preparations, 11 tranquilizers, 13 diuretics, 13 cardiac stimulants, 22 ointments, and 22 analgesics were used.

TABLE 4.—NUMBER OF DIFFERENT DRUGS USED WITHIN THE DRUG CATEGORIES

	Type of hospital				
	Chronic	Intermediate	Acute 1	Acute 2	Pediatric
Analgesics	22	19	13	21	6
Hypnotics-sedatives	11	10	6	10	5
Antibiotics	31	26	18	13	17
Laxatives	12	11	6	11	7
Anticholinergics	8	6	6	7	3
Vitamins	21	9	6	9	9
Decongestants-bronchodilators	7	6	4	6	13
Tranquilizers	11	7	3	8	5
Diuretics	13	8	3	5	3
Cardiac stimulants	13	6	3	5	3
Antihistamines	7	4	3	5	2
Antiemetics	4	2	2	3	2
Antacids	6	4	2	5	2
Ointments	22	14	2	6	4
Expectorants	6	5	2	4	3
Corticosteroids	7	10	3	8	5
Antidiabetics	5	3	4	5	3
Antiseptics	10	7	4	3	3
Hematinics	5	4	4	1	2
Vasopressors	3	3	2	1	0

Table 5 indicates which particular drug within each category was used most frequently in each hospital. The data shows that in several categories the same drug was chosen most often in all adult hospitals. These were prochlorperazine (antiemetics), penicillin (antibiotics), atropine (anticholinergics), diphenhydramine hydrochloride (antihistamines), digoxin (cardiac stimulants), prednisone (corticosteroids), aminophylline (therophylline ethlylenediamine) (bronchodilators), ferrous sulfate (hematinics), milk of magnesia (laxatives), bacitracin (ointments), and metaraminol bitartrate (vasopressors).

TABLE 5.—LEADING DRUGS IN EACH DRUG CATEGORY

	Chronic hospital	Intermediate hospital	Acute hospital 1	Acute hospital 2	Pediatric hospital
Analgesics	Meperidine hydrochloride	Propoxyphene hydrochloride	Propoxyphene hydrochloride	Meperidine hydrochloride	Morphine sulfate.
Antacids	Magnesium hydroxide-aluminum hydroxide mixture	Dried aluminum hydroxide gel	Dried aluminum hydroxide gel	Magnesium hydroxide-aluminum hydroxide mixture.	Dried aluminum hydroxide gel.
Antidiabetics	Insulin in ection	Tolbutamide	Tolbutamide	Insulin injection	Insulin injection.
Antiemetics	Prochlorperazine	Prochlorperazine	Prochlorperazine	Prochlorperazine	Prochlorperazine.
Antibiotics	Penicillin	Penicillin	Tetracycline	Penicillin	Penicillin.
Anticholinergics	Atropine	Atropine	Atropine	Atropine	Scopolamine hydrobromide.
Antihistmines	Diphenhydramine	Diphenhydramine	Diphenhydramine	Diphenhydramine	Dipnenhydramine.
Antiseptics	Hydrogen peroxide solution	Hexachlorophene	Hexachlorophene	Hexachlorophene	Hexachlorophene.
Bronchodilators	Aminophylline	Aminophylline	Aminophylline	Aminophylline	Phenylephrine hydrochloride.
Cardiac stimulants	Digoxin	Digoxin	Digoxin	Digoxin	Digoxin.
Corticosteroids	Prednisone	Prednisone	Prednisone	Dexamethasone	Prednisone
Diuretics	Mercaptomerin sodium	Meralluride injection	Hyrochlorothiazide	Chlorothiazide	Meralluride injection.
Expectorants	Cough mxiture	Glycerl guaiacolate	White pine syrup	Diphenhydramine hydrochloride.	Glyecryl gualacolate.
Hematinics	Ferrous sulfate	Ferrous sulfate	Ferrous sulfate	Ferrous sulfate	Ferrous sulfate.
Hyponotics	Chloral hydrate	Chloral hydrate	Secobarbital	Pentobarbital sodium	Pentobarbital sodium.
Laxatives	Milk of magnesia	Milk of magnesia	Milk of magnesia	Milk of magnesia	Bisacodyl.
Ointments	Bacitracin	Bacitracin	Bacitracin	Bacitracin	Lanolin.
Tranquilizers	Promazine hydrochloride	Chlordiazepoxide/ hydrochloride.	Chlorpromazine hydrochloride	Chlordiazepoxide hydrochloride.	Hydroxyzine hydrochloride.
Vitamins	Multivitamins	Multivitamins	Vitamin and Minerals	Multivitamins	Pyhtonadione.
Vasopressors	Metaraminol bitartrate	Metaraminol bitartrate	Metaraminol bitartrate	Metaraminol bitartrate	

In all hospitals several drugs within a given category were often prescribed for an individual. Individual patients received as many as 12 antibiotics, seven analgesics, six diuretics, five hypnotics, seven laxatives, six tranquilizers, and 11 vitamin preparations.

Table 6 shows the use of drug categories in different age groups. The data are expressed as a ratio of the observed (actual number of times the drug category was given) to the expected (number of times the drug category would have been given if the drug categories were equally distributed in each age group). In the adult hospitals drugs were prescribed most often for those over 55 years of age. Particularly striking were the ratios in the following categories: cardiac stimulants (70:16), diuretics (58:31), and vitamins (81:49). Hypnotics, anticholinergics, and analgesics were given more often to patients in the middle-age groups. The youngest age group (0 to 15) presents higher observed than expected figures in decongestants (43:32), antibiotics (65:60), and anticholinergics (68:60).

TABLE 6.—USE OF DRUG CATEGORIES IN DIFFERENT AGE GROUPS [1]

	Age group, year			
Proximum	<15 0.2507	16–40 0.2273	41–54 0.1481	>55 0.3739
Analgesics	23/95.8	109/86.8	84/56.6	166/142.8
Antacids	5/23.6	20/21.4	18/13.9	50/35.1
Antibiotics	65/60.4	34/54.8	34/35.7	108/90.1
Antidiabetics	2/12.5	2/11.4	7/7.4	39/18.7
Antiemetics	2/22.8	22/20.7	18/13.5	49/34
Anticholinergics	68/59.9	71/54.3	37/35.4	63/89.4
Antihistamines	15/25.1	16/22.7	16/14.8	53/37.4
Antiseptics	6/10.5	7/9.5	8/6.2	21/15.7
Cardiac stimulants	6/23.3	3/21.2	14/13.8	70/34.8
Corticosteroids	12/16	6/14.5	10/9.5	36/23.6
Decongestants	43/31.6	10/28.6	16/18.7	57/47.1
Diuretics	6/20.6	2/18.6	16/12.1	58/30.7
Expectorants	12/19.1	9/17.3	15/11.3	40/28.4
Hematinics	6/19.1	1/17.3	5/11.3	30/28.4
Hypnotics	68/129.6	137/117.5	94/76.6	218/193.3
Laxatives	22/89.2	82/80.9	68/52.7	184/133.1
Ointments	4/13	8/11.8	4/7.7	36/19.4
Tranquilizers	10/23.3	17/21.1	15/13.8	51/34.8
Vitamins	21/33.1	9/30	21/19.5	81/49.4
Vasopressors	0/8	2/7.3	6/4.7	24/12

[1] The data are expressed as a ratio of the observed (actual number of times the drug category was given) to the expected (number of times the drug category would have been given if the drug categories were equally distributed in each age group).

Table 7 presents the different drug categories prescribed for male and female patients. The form of this table is similar to Table 6, i.e. observed figures are compared with expected (number of times the drug category would have been given if equally distributed by sex). In 15 of 20 categories orders were written more frequently for the female than for the male patients. Bronchodilators, expectorants, cardiac stimulants, hypnotics, and laxatives were used more often in males.

TABLE 7.—DRUG CATEGORY ORDER DISTRIBUTION IN MALE AND FEMALE PATIENTS [1]

Proximum	Males 0.570	Females 0.430
Analgesics	95/120	117/92
Antacids	4/6	6/4
Antibiotics	68/76	65/57
Antidiabetics	10/11	10/9
Antiemetics	6/8	8/6
Anticholinergics	8/9	8/7
Antihistamines	3/6	8/5
Antiseptics	3/5	5/3
Cardiac stimulants	10/10	8/8
Corticosteroids	8/9	8/7
Decongestants and bronchodilators	31/27	17/21
Diuretics	12/17	18/13
Expectorants	12/10	5/7
Hematinics	2/5	6/3
Hypnotics-sedatives	119/114	80/85
Laxatives and stool softeners	68/69	53/52
Ointments	6/10	11/7
Tranquilizers	12/16	16/12
Vasopressors	1/3	4/2
Vitamins	14/27	34/21
Total number of patients (682)	385	297

[1] The data are expressed as a ratio of the observed (actual number of times the drug category was given) to the expected (number of times the drug category would have been given if the drug cateogries were distributed equally by sex).

In the 682 patients reviewed, 585 antibiotic orders were written. The most frequently used antibiotics are shown in Table 8. Penicillin is followed in order of overall usage by sulfonamides, chloramphenicol, tetracyclines, and neomycin.

TABLE 8.—USE OF ANTIBIOTICS

Type of hospital	Tetracyclines	Penicillins	Chloramphenicol	Sulfonamides	Neomycin-paromomycin sulfate
Chronic	6	78	20	22	0
Intermediate	13	41	13	14	8
Acute 1	11	24	1	3	1
Acute 2	3	27	6	8	1
Pediatric	7	56	4	25	1
Total	40	226	44	72	11

We have found a high percentage of incomplete prescriptions in all four adult hospitals. Instructions for route of administration were missing in 35% to 60% of all prescriptions. In contrast, at the pediatric hospital only 29 (5%) of the prescriptions failed to specify the route of administration.

Comparing the physician's order sheet and the nurses' files, we frequently found that the drug order as written by the physician was not charted by the nurse as having been given as specified. Whether the nurse had forgotten to chart the medication given or the patient had actually not received it, could not be determined in retrospect.

COMMENT

This study is a descriptive one and is not intended to lead to any definite conclusion. It documents certain characteristics of therapeutics practiced in five hospitals. The following findings merit emphasis since they help to define areas which require study in depth.

Our data confirm observations (10, 11, 15, 16) that the large quantities of drugs administered to patients are related to the length of hospitalization. Patients with chronic disease stay in the hospital longer than patients with acute disease and receive more drugs during hospitalization. Within any adult hospital, patients in the older age groups receive more drugs in almost all categories. These findings are not in themselves startling, but they serve to point out the need for careful evaluation of drug effects in older patients in general and in those with chronic disease in particular. More information is needed in such areas as drug interaction and drug effects in older patients. (13, 14)

Drug effects are not only related to age but also to sex. The fact that more drugs are ordered for women than for men may partially explain the observations that more adverse reactions are reported in women than in men. (15) Other studies have shown a direct relationship between frequency of drug reactions and the number of drugs used. (10, 16) The proportionately greater use of bronchodilators, expectorants, and cardiac stimulants in men is probably accounted for by a higher incidence of chronic pulmonary disease in this sex.

The use of antibiotics is exceeded only by analgesics and hypnotics in the study hospitals. Antibiotic orders were repeatedly changed in regard to both dose and specific drug. The same antibiotic was often ordered more than once for a given patient. Various antibiotic combinations were used. The leading antibiotic was penicillin in all hospitals. The usage frequency of other antibiotics showed marked variation in the different hospitals. Overall, sulfonamides were used more often and tetracyclines less often than chloramphenicol. The extraordinary frequency and variability of antibiotic drug practice points out the need and importance of further studies.

The following four drug categories stand out in terms of usage frequency in the pediatric hospital: (1) antibiotics; (2) decongestants-bronchodilators; (3) hypnotic-sedatives, and (4) anticholinergics. Seizure disorders and surgical procedures probably account for the frequent use of hypnotic-sedatives and anticholinergics. Antibiotics are the most frequently used drugs in the pediatric hospital.

Certain specific drugs within their respective categories were preferred in all of the adult hospitals as shown in Table 5. A review of over 200 papers reporting on the efficacy of many of these agents revealed that very few studies were well controlled. Therefore, it would appear that general acceptance of a given drug is frequently based on personal experience.

Muller has reviewed the importance of proper prescription writing. (17) Physicians who write prescriptions which lack precision and have poor style and incomplete instructions are unintentionally adding more variables to the problems of drug usage. (18) The present study documents the fact that improper prescription writing included omission of route and frequency orders. While this study is descriptive and is not intended to lead to any objective conclusions, it does document the need for more studies of multidrug therapy, and more care in the writing of drug orders.

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Generic and trade names of drugs

Bisacodyl—*Dulcolax.*
Chlordiazepoxide hydrochloride—*Librium.*
Chloramphenicol—*Chloromycetin, Cylphenicol, Tega-Cetin.*
Chlorpromazine hydrochloride—*Thorazine Hydrochloride.*
Chlorothiazide—*Diuril.*
Dexamethasone—*Decadron, Dexameth, Gammacorten, Hexadrol.*
Diphenyldramine Hydrochloride—*Blenadryl, Valdrene.*
Dried aluminum hydroxide gel—*Alkagel, Amphojel, Creamalin.*
Hexachlorophene—*G–11, Germa-Medica, pHisoHex, Septisol.*
Hydrochlorothiazide—*Esidrix, Hydrodiuril, Oretic.*
Hydroxyzine hydrochloride—*Atarax, Vistaril.*
Meperidine hydrochloride—*Demerol, Hydrochloride, Pro-Meperdan.*
Meralluride injection—*Mercuhydrin.*
Mercaptomerin sodium—*Thiomerin, Sodium.*
Metaraminol bitartrate—*Aramine, Pressonex Bitartrate.*
Paromomycin sulfate—*Humatin.*
Pentobarbital sodium—*Nembutal Sodium.*
Phenylephrine hydrochloride—*Aquamephyton, Konakion, Mephyton, Mono-Kay.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort.*
Prochlorperazine—*Compazine.*
Promazine hydrochloride—*Sparine.*
Propoxyphene hydrochloride—*Darvon.*
Secobarbital—*Seconal.*
Tetracycline—*Achrocmycin, Tetracyn.*
Tolbutamide—*Orinase.*

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Mr. GORDON Now, in discussing the variability in response to different formulations of bishydroxycoumarin, you stated that the source of manufacture is as important as the choice of the drug itself. Evidence already in the hearing record, which was brought out in an article by Dr. Gerhard Levy, shows that bishydroxycoumarin tablets have shown a major variation in clinical response between two separate lots of that drug produced by the same manufacturer. Consequently, while there may be some evidence that a very few drugs such as this one you have mentioned are sensitive to variations in their formulation, even two lots from the same manufacturer may not be exactly the same.

I would like this to be part of the record, too.

(The document referred to follows:)

(Excerpts from Competitive Problems in the Drug Industry, Part 1, Page 438)

PHARMACEUTICAL FORMULATION AND THERAPEUTIC EFFICACY

(Gerhard Levy, Ph. D., Buffalo and Eino Nelson, Ph. D., San Francisco)

There is a mistaken belief among many that the active constituent as a chemical entity is the sole basis for the pharmacological effectiveness of a pharmaceutical product. It is the purpose of this review to show that the physiological response to the administration of a given drug product is frequently a function of both the pharmaceutical formulation of the particular dosage form as well as of the active ingredient. Certain variables related to pharmaceutical formulation will be discussed with respect to the manner in which they may modify therapeutic response in the hope that the examples cited may lead to the recognition that the choice of dosage form and of brand can be just as important as the choice of the actual therapeutic agent.

In general, differences in therapeutic efficacy among different generically identical drug products, while sometimes caused by lack of stability or by contamination, are most frequently due to differences in the rate at which the active ingredient or ingredients become available for absorption. This may modify the onset intensity, and duration of the desired physiological response. Furthermore, the efficiency, the biological availabliity (e.g., the completeness of absorption), as well as the incidence and intensity of side effects and toxic reactions from he drug may be affected.

A dramatic example illustrating differences in intensity of action of a drug as a result of dosage form modification has been given by Lozinski. His company found it desirable to increase the physical size of their bishydroxycoumarin (Dicumarol) tablets to facilitate breaking the tablets for administration of half doses. Patients who switched from the smaller to the new larger tablets required larger doses in order to maintain prothrombin levels in the therapeutic range. Laboratory studies undertaken to explain this difference indicated that

the dissolution rate of drug from the large tablets was slower than from the old tablets. The tablets were reformulated to increase this rate, and these were then used to replace the stocks of older tablets in retail and hospital pharmacies. A surprising turn of events occurred. It became apparent that some patients who had their prescriptions refilled with the newest tablets showed prothrombin levels below the therapeutic range and, in some, bleeding occurred. The company alerted all physicians concerning the more intense therapeutic effect of the new bishydroxycoumarin tablets and urged that all patients on anticoagulant therapy with their brand of bishydroxycoumarin tablets be retitrated for their requirements. It is quite likely that no 2 manufacturers' brands of bishydroxycoumarin tablets will act alike in therapeutics, and it is conceivable that a change from a slow release brand to a fast release brand might even result in death if the necessity for retitration is not recognized.

Mr. CUTLER. Mr. Gordon—are you in agreement that doctors would be well advised to identify the manufacturing source rather than simply prescribing by a generic name?

Mr. GORDON. I think so.

I do not have any more questions.

Mr. CUTLER. I do not have any more questions, either.

Mr. GORDON. I would say I would go along with that.

Mr. GROSSMAN. I do.

Mr. CUTLER. Then I think we have closed a very large part of the gap between us.

Mr. GORDON. This is only my opinion.

Mr. CUTLER. Senator Nelson earlier disclaimed any recommendation that doctors should prescribe simply by the generic name, and leaving it to the pharmacist to pick out any old drug product meeting that generic name. If we are in agreement on that, I think we have closed the gap a good deal, and we might close in, then, on the next issue.

Mr. GROSSMAN. I would like to turn to another aspect of this.

Would you say that different PMA members—I assume you would—perform different quality controls?

Dr. SLESSER. Yes; I think there are variations in the type.

Mr. GROSSMAN. That you have mentioned here.

Dr. SLESSER. You can have different approaches to accomplish the same thing. And I think the magnitude of the quality control system will be directly related to the number of products and the number of people, and things of that sort; yes.

Mr. GROSSMAN. Would you say that some of your members are better at quality control than others?

Dr. SLESSER. I think they all do the best job they can. I do not think they knowingly—any of them knowingly slight quality controls.

Mr. GROSSMAN. But would you say probably that the leaders—I won't define it, because we do not define leaders—perform essentially similar quality controls?

Dr. SLESSER. Yes.

Mr. GROSSMAN. In other words, that the top firms would produce just about the same drug if they were given it from the beginning, if they had the same ingredients? Is that true?

Dr. SLESSER. I think they would all make sure the product behaved in the clinic the way it was supposed to, and then do whatever is necessary to make sure each batch resembled in its clinical effectiveness the prototype clinically tested batch.

Mr. GROSSMAN. Let me give you a hypothetical situation.

Suppose, for example, that Squibb produces a brand-name drug, and

that Lilly produces a generic, the same drug. Would you say that the quality controls would be different?

Dr. SLESSER. I don't think they would be. As I said, there may be minor differences in the approaches. But I think one would be as effective as another, and they would both accomplish essentially the same thing.

Mr. GROSSMAN. Are there, or do you know of any examples, then, of drugs such as I have just mentioned where there is a trade name—a brand-name drug and a generic both produced by the leaders, so to speak, where there is a great deal of price differential between the two? I am not talking about——

Dr. SLESSER. Mr. Grossman, I am not too well informed about prices. I have no price-determination function in my capacity with my company.

Mr. GROSSMAN. Are there any of you that could answer that? Are there cases where a generic and a trade-name drug, both produced by leaders, the prices vary to a great extent?

Mr. CUTLER. I do not have a specific answer for you, Mr. Grossman, but I think we can assume there are some such cases.

Mr. GROSSMAN. I am informed we have prednisone $17 by Schering and $2 and some odd cents by Merck.

Mr. CUTLER. Those are both sold under brand names. But still you can go ahead and make your assumption. There may be there are cases where they are sold under generic names.

Mr. GROSSMAN. As a doctor, how would you make a distinction between those two? This is very basic—but I think sometimes we have gotten away from the very basic. In other words, how is a doctor going to make his distinction?

Dr. SLESSER. Mr. Grossman, since you brought up prednisone, and since the Medical Letter has been cited frequently in the course of these hearings—referred to, I should say—I would like to point out the significant statement that appears in this very same Medical Letter that so far has not been aired. And I will read it:

Disintegration test—

Which is a U.S.P. test—

measures only disintegration and not physiological availability. There is nothing, however, either in reports of clinical trials or in the experience of Medical Letter consultants to suggest that variations in formulation are causing any problems in the treatment of patients.

Now, here again there is a double negative, which proves nothing.

Mr. GROSSMAN. Would you be able to tell me, then, that a doctor should choose the Schering product as opposed to the Merck product, for any reason—except his own—for some reason he likes one?

Mr. CUTLER. Mr. Grossman, I think the only answer we can make to that is that if the doctor, based on his clinical experience with his patients or other clinical experience in which he has faith, concludes that those two drugs are substantially equivalent therapeutically, then as Dr. Slesser says, he ought to prescribe the cheaper one. And the AMA has urged doctors to take price into account.

Mr. GROSSMAN. How does a doctor find out about price?

Mr. CUTLER. About price?

Mr. GROSSMAN. Yes. In other words, where does he find this out?

Mr. CUTLER. The detail men inform him about price. Pharmacists will tell him, I suppose, if he asks about price.

Mr. GROSSMAN. Would you agree that there should be something available to doctors to show pricing policies of all drugs—in other words, should there not be something? I think there should be something that—so that a doctor would be able to look at something and say Merck is $2-some-odd cents, and Schering is $17, and maybe I better think twice before I do it.

Mr. CUTLER. Mr. Stetler testified the other day that he thought a doctor should have whatever information, meaningful information, can be provided to them about manufacturers' prices. Now, you do have problems in equating manufacturers' prices, of course, because those are not the prices at which the drugs are sold in the drugstore. And it may be more meaningful for him to have drugstore prices.

Mr. GROSSMAN. Is this ever going to be resolved? Are we going to continue to discuss this?

Mr. CUTLER. We would favor having it resolved.

Mr. GROSSMAN. What steps are we taking to resolve it? Or are we going to resolve it?

Mr. CUTLER. You now have directed HEW to make studies, at least with respect to the medicare problem.

Mr. GROSSMAN. We discussed this at the end of Mr. Stetler's testimony last week. Aren't we faced with this unending process again?

You know when FDA makes that study—I don't know—but there is going to be a lot of problems with the study, and you have the Parke, Davis study on the other side, and you can go on and on—this is with regard to equivalency. I am sure we can have the same discussions about compendia. In other words, we can go on and on and on about all these things.

Mr. CUTLER. Mr. Grossman, I agree. But we suffer from some of the limitations of a trade association, one of which is that the member manufacturers cannot talk together about their respective price policies, or how they will communicate prices to any class of customer. This may well be a governmental function.

Mr. GROSSMAN. Thank you.

Senator NELSON. I have only a couple of questions, Doctor.

How many companies would you guess meet the stringent quality control procedures that you suggest in your testimony should be followed?

Dr. SLESSER. I wish I knew how many companies there were.

Senator NELSON. I meant in the Pharmaceutical Manufacturers Association.

Dr. SLESSER. How many of the PMA member firms? I would say most if not all of them—most of the time. I do not think any company is perfect.

Senator NELSON. I do not mean that they always get that result, but how many follow a procedure that you approve of as an expert?

Dr. SLESSER. I beg your pardon?

Senator NELSON. You testified very extensively about the kind of quality control procedures that you feel are necessary to produce a quality drug. In your judgment, how many companies in the PMA do you think meet this standard?

Dr. SLESSER. I think most of them do most of the time, Senator.

Senator NELSON. Well, it is not really much of a problem, then, in this country, since PMA member firms produce 95 percent of the prescription drugs sold in this country. And if some of the 5 percent

that do not belong meet the standard, we do not really have much of a problem, do we?

Dr. SLESSER. If we take 1,500 as a round number—and I think a part of this problem arises from the fact that no one actually knows how many manufacturers, and I am talking about manufacturers—there are, then you are talking about 1,364 firms, and only 136 of the 1,500 PMA member firms—5 percent of the drug supply in this country can be meaningful if the products are given to people who are seriously ill and need effective medication, and they happen not to be.

Senator NELSON. But in any event, as I understand it, the members of the PMA manufacture about 95 percent of the prescription drugs. If they meet the standards, we do not have a quality control problem as to 95 percent. Then of that 5 percent who do not belong to the association, there are certainly some who meet the standards. So you are down to a situation where a very small percentage—it could be 2 percent, or 1 percent—of the drugs on the market are not meeting the quality control standards that you suggest.

All I am saying is that this big problem is not nearly so big as it would appear from your testimony, is it?

Mr. CUTLER. Senator, while you were over in the Senate just recently Mr. Gordon and I reached a meeting of the minds at least on one issue, I think——

Senator NELSON. That probably means I won't agree with you.

Mr. CUTLER. You agreed earlier—namely that doctors would be well advised to identify the manufacturing source of any drug product they prescribe. If we are all in agreement on that, I think we have narrowed the issues considerably. And our thesis is they should identify those sources, because the sources vary in the therapeutic effectiveness of their products, and that is true among PMA members and as between PMA members and non-PMA members.

Senator NELSON. All the expert testimony from pharmacists or pharmacologists or doctors who have appeared and addressed themselves to this question, has stated that prescriptions should all be written in the generic term, and that if the doctor has a preference for a particular brand, then he should name the company or the brand, if he wants. That is the testimony, as I recall it, from the experts we have had.

Mr. CUTLER. How he should write the prescription is a second issue. But if we do agree that he should identify the manufacturing source, then that is something—we have moved that far along. That is really a condemnation or at least a critique of generic prescribing in the normally understood sense of the word, which is just to write the generic name and let the pharmacist pick any product of that generic——

Senator NELSON. I do not know that is what the testimony is. I know they testified that the doctor should prescribe generically, and should be free to name the company or the brand in addition. I think there might very well be some argument from the pharmacists themselves as to their qualification, once you give them a generic name, for being able to select a high-quality generic drug. They may very well be as qualified as a doctor in ordinary circumstances.

Mr. GORDON. I want to make a correction. You asked me whether a doctor should write the manufacturer's name or identify it. What I

meant was that the doctor should have the right to identify it if he desires to do so. That is only my opinion.

Senator NELSON. I have a couple more questions and we can move along.

(At this point in the hearing a short recess was taken.)

Senator NELSON. We will resume the hearings.

Dr. Slesser, on page 11 of your statement, you say,

> The inability of the FDA to assure even the competence of all drug firms, let alone the clinical quality of their products, is too long-standing to brush aside and the possibility of that situation soon or ever changing is extremely remote.

I think you also recited some statistics showing that they made less inspections recently. Was that less inspections this year than last?

Dr. SLESSER. Yes, sir.

Senator NELSON. Would your company support expanded appropriations for FDA so that the agency could do a better job of inspecting?

Dr. SLESSER. Yes, Senator. We certainly have concurred as a member of PMA in the past history of the PMA to do everything they could to encourage maximizing the budget for the Food and Drug Administration so that—so as to increase its staff, including inspectors.

Senator NELSON. Has your company ever appeared before the Appropriations or other committees in behalf of more staff for the FDA?

Dr. SLESSER. I do not know, Mr. Chairman.

Dr. SCHEELE. If I can answer. It has not been the practice of the Appropriations Subcommittees of the House or Senate to hear outside witnesses on such matters.

Mr. CUTLER. I am sure we have written letters, Senator Nelson, supporting appropriations for FDA.

Senator NELSON. I think it is a very serious matter that FDA does not have an adequate number of personnel in the field for better inspection and better enforcement to assure higher quality. I am sure from all the testimony we have had that certainly there is no member of the PMA who objects to that.

But in order to do something about it, I am wondering if the members of the PMA or the PMA itself is prepared to appear before Appropriation Committees and strongly endorse an expansion of FDA personnel for purposes of testing, inspection, and enforcement of higher standards in the manufacture of drug products. Can you answer that?

Mr. CUTLER. I believe, Senator, we have supported all of FDA's requests for appropriations, and we are on record and were on record in 1962 as supporting more frequent FDA inspections.

Senator NELSON. Good. I think that is very important. I am hopeful that we will be able to do something constructive about it in the near future, because I do not think it is any economy to economize on quality in this field.

One more question.

We had testimony yesterday from Dr. Helen Taussig. She testified in the same way as some other expert witnesses we have had respecting the labeling of bottles that go to patient from the pharmacist. This is not your responsibility, of course. She testified, as have some other witnesses, that she thought it was very important that the bottle that goes to the patient from the pharmacist have on the label

the generic name of the product, excepting, of course, in cases where a doctor has a specific reason for instructing that the generic name not be on the bottle.

Does the PMA endorse that idea?

Mr. CUTLER. That is the recomendation as I understand it of the AMA, and the PMA supports that proposal. The PMA also thinks that the manufacturing sources should be identified and the brand name when there is one in addition to the generic name.

Senator NELSON. You have no objection to the appearance of the generic name?

Mr. CUTLER. No, sir.

Senator NELSON. That concludes all the questions I have, Doctor. I appreciate very much your testimony. It was very constructive, very informative, and useful to the committee.

Dr. SLESSER. Senator Nelson, thank you so much for allowing me to appear.

(The complete prepared statement and attachments submitted by Dr. Slesser for presentation on November 16, 1967, follows:

STATEMENT OF A. E. SLESSER, PH. D., ASSOCIATE DIRECTOR OF QUALITY CONTROL, SMITH KLINE & FRENCH LABORATORIES

Mr. Chairman and Members of the Committee, I am pleased to have the opportunity to supplement Mr. Stetler's statement on the matter of therapeutic equivalence of drug products.

Through my activities in the pharmaceutical industry I know something about the factors that can affect drug performance. There was a time when pharmaceutical manufacturing, like many other industries, was relatively simple. During that era there was a bare handful of drugs, few of them of known composition or specificity in treatment of disease. However, now we have a great number of highly sophisticated drugs, many of which are chemically complex and quite specific in disease treatment. As a consequence, the technology of manufacturing consistently safe and effective medicines today is not simple.

Control of the quality of the medicinals prepared from today's drugs is a complex operation. There was a time when quality control pretty much began and ended in an analytical testing laboratory. But, Mr. Chairman, that time is long past.

It is simply wrong, in the light of the present state of the art and science of pharmaceutical manufacture and the inadequately manned government agency, to contend that all drug products of like generic names are equal.

I submit we are not likely to have that assurance soon despite the efforts of all involved. Recent figures on FDA inspections, for example, do little to encourage optimism in this regard. The Agency made 3,651 inspections of drug plants in 1966; impressive as that figure may seem, it is 150 inspections less than the 1965 figure, and 341 less than the number for 1964. I do not recite these figures to criticize the FDA, Mr. Chairman. Their inspections of necessity are becoming more complex and time-consuming, and FDA personnel shortages are persistent. Nevertheless, fewer inspections are being made, not more. It seems to me, therefore, that it would be imprudent to rely heavily or solely on this mechanism as "the method" of assuring drug quality.

Even if we make the incorrect assumption that all manufacturers are capable of passing an FDA inspection, we are still in no sense out of the dilemma of therapeutic equivalence.

There is the matter of conforming to USP or other standards. The question is not whether drug products should conform, but whether each batch and each tablet, capsule and dose of every drug product does conform. The fact that standards exist—and that companies put "USP" or "NF" on drug labels—does not establish that in fact the companies actually have adequate control procedures, or that they follow them. In short, the real question is, do drug products conform to the standards they claim to meet?

In all candor, as one who has long followed and participated in the work of the USP and NE, I must also note that the standards of the USP and NF do not

pretend to include all the specifications and tests that a highly skilled, conscientions manufacturer requires his product to meet before he will put his name on it.

Mr. Chairman, the chart which I have here (chart #1 attached) provides a dramatic illustration of the potency of some of the pharmaceuticals manufactured today and the importance of pharmaceutical know-how in manufacturing and quality control technology. It shows the proportionately small amount of drug that is contained in 100 tablets of this product. This small amount of drug creates a serious problem—that of making certain that each tablet in the batch contains exactly the correct fractional amount of the total quantity of drug used. This requires technological and control know-how. Furthermore, if an error occurs during manufacture and some tablets have too little drug while others have too much, the consequences to the patient could be serious—yet the cause of the error could not be identified by USP or NF tests. In other words, unless quality and uniformity are built into the batch, laboratory tests may very well not reveal the defect, nor can all the testing in the world of the batch after it is made instill quality into the batch.

The fact is that the detailed specifications needed to produce a quality drug product under good control procedures are so extensive and so all-encompassing as to defy inclusion in compendia of any sort. Quality control measures, records and reports used in leading drug firms for each batch of even the simplest drug product are massive. These begin with the raw materials and end with the consumption of the product. Details of the manufacturing and control procedures utilized for only a few products of a capable manufacturer would constitute a book in itself.

What I am saying is that conformance to compendial standards like those of the USP and NF, while of unquestioned importance, represents only part of the story. Total quality control involves much more. Mr. Chairman, with your kind permission I would like to call your attention to chart #2 (copy attached) to demonstrate what quality control is, what it does, and how it does it.

We all know that safety and effectiveness of a drug product are determined by well-designed, properly controlled and correctly executed clinical tests. Such tests are run by the manufacturer on one, sometimes two, but rarely, on more than two, batches of the product.

Having proved the safety and effectiveness of the product, we must ask ourselves this question: "To what facts are the product's safety and effectiveness due?"

I have indicated the five factors on chart #2. First, the specific COMPONENTS used—drug and non-drug components. Let me state, Mr. Chairman, that contrary to common belief, the drug component in most tablet products comprises less than 10% of the makeup of the tablet and that the number of components other than the drug may vary from two or three to as many as twenty or more.

The capable manufacturer makes sure that components all have pertinent, significant specifications and that these are in writing; that the components are purchased only from known, reputable vendors; that written, detailed instructions describing the manner and method of sampling incoming shipments of components exist and are followed; that all analytical test methods are written, are complete, up-to-date, available to the analysts, and are followed for establishing compliance with the written specifications. For example, an apparently trivial characteristic such as particle size of a component, whether the component is the active drug or not, may very well be a significant specification for which a test may be required prior to approving it for use in manufacturing a batch of the drug product.

The second factor is the formula. Neither the USP nor the NF lists the formula of the products contained therein and for good reason as we shall see later. The formula must list each component and the amount that is to be used. The master formula should be checked by no fewer than two capable, competent people, independently and individually, for correctness. Each batch formula derived from this master formula is produced by a process which assures against errors in transcribing, so that each batch formula will have to be correct if the master formula itself is correct.

The third factor is the Manufacturing (or Compounding) Procedure. Now, again, these are written, extremely exacting, detailed descriptions of every step of the manufacturing operation, including directions denoting the specific type of equipment to be used in each instance.

Fourth, are the various Analytical Tests, Inspections and Checks that must be carried out at certain stages during manufacture of the batch. These are in-process controls and they are important; they must be written, they must be detailed; there must be a lot of know-how in deriving the tests, inspections and checks to be followed at the various stages of the manufacturing operation—

with respect to raw material components, intermediates, and at the finished product stage.

Finally, we come to what can be called Other In-Process Controls, one important function of which is to assure that all of the preceding four factors were, in fact, operative and correctly so. Thus the required records, reports, data, signatures, analytical and inspection test results on each batch would comprise an important segment of this factor.

Now, Mr. Chairman, let us assume that we have confirmed the safety and effectiveness of one or, at most, two or three batches of the product. However, when we get down to the matter of day-to-day, batch-to-batch production of the product, we obviously cannot clinically test each batch before releasing it to the marketplace. Such tests are extremely time-consuming and costly. Yet we must be sure that each batch is the clinical counterpart of the prototype batch(es).

Here, Mr. Chairman, is where the capably exercised Quality Control function comes into play. Quality control, by *locking into* each batch manufactured subsequently to the clinically tested, prototype batch(es) the five factors responsible for the product's safety and effectiveness, *services as a substitute for the clinical tests on a batch-to-batch basis!*

In other words, Mr. Chairman, quality control must be visualized as a chain, as shown in chart #3 (copy (copy attached). Thus, the manufacturer who has capably applied the chain throughout the batch's manufacture can be reasonably certain that compliance with the laboratory test results at the end of the manufacturing operation assures the safety and therapeutic effectiveness of the batch. However—*and this is important*—laboratory test results obtained on a sample of a batch or a shipment of tablets, without knowledge as to whether the quality control chain was applied at all or how effectively, may not be at all significant in evaluating the safety and therapeutic effectiveness of the batch or shipment.

Dr. Lueck will present specific evidence to support the inadequacy of apparent compliance with typical laboratory specifications to assure therapeutic performance. In other words, generic equivalency does not necessarily connote therapeutic equivalency.

The importance of particle form and size in antibiotics, like chloramphenicol, and in sulfadiazine and the anti-fungal agents, come to mind. Variability in response to different formulations of the blood anti-coagulant tablet, bishydroxycoumarin, are so significant that the choice of manufacturer source is clearly as important as the choice of the agent itself. The fineness of the drug in the tablet and how well the drug particle size is controlled by one manufacturing source as compared to another may very well determine whether dangerous clotting is prevented or serious internal bleeding occurs after ingestion of the usual dose. There are many examples of this sort.

A few examples of the steps over and above standard procedures or official standards taken by a quality manufacturer to improve his product and distinguish it from competing products are the following:

(a) To lessen pain on injection. As you know, the injection of some drugs is painful. We are constantly striving to lessen such pain and some of us have learned that by the addition of certain ingredients we can produce a product that causes less pain on injection. This does not happen by accident.

(b) To produce medications, particularly injections, which lessen the liability of allergic reactions, which are sometimes not just troublesome but, on occasion, fatal. Much can be done to exclude as far as possible ingredients suspected of causing such reactions. Again, such procedures are sometimes costly, but the manufacturer who values his identity and reputation will constantly strive to attain higher levels of purity. The manufacturer who is interested only in "generic equivalency" may not.

(c) To produce more prompt solution in the stomach and absorption in the blood where this is desired. Variations in manufacturing procedures, differences in the crystal structure or particle size of the active ingredient and its purity, differences in the combination of non-drug components—all may affect the time necessary for the drug to dissolve in the gastrointestinal tract and may distinguish one product from another. Such differences can have a crucial effect on the therapeutic efficacy of the product.

(d) To retard solution in the stomach of a drug that is better absorbed in the intestinal tract, or which performs its function better if it is gradually released. All this is, and can be, influenced by different methods of compounding the product, or (if a tablet) by a different coating, or by the addition of other non-drug ingredients.

(e) To mask bad flavor of an active ingredient which not infrequently causes adults as well as children to resist and even refuse to take the medicine. The problem is getting a child to take a prescribed and oftentimes extremely necessary medicine is something that every mother and every nurse is familiar with. Pediatricians and general practitioners choose their medicines carefully and by specification with this in mind. The importance of palatability, I should note, is important in geriatric medicine as well.

Mr. Chairman. I am happy to submit for the record a PMA publication entitled "The Importance of Manufacturer Identification" which includes additional information on the points just covered. (Copy attached.)

Recently we undertook a careful search of the published literature on the effects of drug formulation on therapeutic activity of drug products. We collected a total of 211 references. Many of them are reports on variations in therapeutic activity observed in human volunteers and patients; the others cover both *in vivo* and *in vitro* (laboratory) experiences. These articles, I should point out, are solely related to the subject of generic and therapeutic equivalence.

In fact, much additional literature on pharmaceutical sciences, published in thousands of articles annually, bears on this question; much of it relates to corollary subjects, such as stability variations, effects of certain non-drug components on the drug's effectiveness or stability, particle size and form, and other significant factors that can and do affect quality. Gentlemen, there is a whole profession, international in scope, with thousands of practitioners who are dedicated to such scientific studies and, in fact, a new scientific discipline, called "biopharmaceutics" has recently arisen because of the importance of such work. The scientific literature output of these scientists has been estimated to be nearly 10,000 articles each year.

Some witnesses who have appeared here would like to eliminate or to curtail therapeutic duplication of drug products. In my opinion, such a step would serve as a devastating setback to medical progress and deprive patients of essential medication. In illness, patients vary in their response to medication. Patients vary in their idiosyncrasies, sensitivities, allergies and tolerances to drugs.

It is, for example, a well known fact that no one or two drugs are suitable for the treatment of all cases of epilepsy. The wide choice of drugs available for epilepsy exists solely because a half century of experience has shown that there is great variability in response by individual epileptics to available drugs. What we need is more and not fewer strings to our therapeutic bow.

The same is true of almost every disease and disability. The broader the therapeutic armamentarium, the better our physicians can care for the sick and suffering. The harm of eleminating one necessary drug far outweighs the alleged burden of too many drugs.

Mr. Chairman, the evidence of variability in drug product performance is too obvious to be ignored. The inability of FDA to assure even the competence of all drug firms, let alone the clinical equality of their products, is too longstanding to brush aside, and the possibility of that situation soon or ever changing is extremely remote. Of one thing I am certain: tying the doctor's hands, binding him in a kind of pharmaceutical straightjacket, will not answer the problem. It will compound it. It will be more constructive to work toward a Federal drug program that will take cognizance of all the realities of medicine and pharmacy today. And in that task we are most anxious to join you.

BIOGRAPHICAL SKETCH OF DR. A. E. SLESSER, ASSOCIATE DIRECTOR, QUALITY CONTROL, SMITH KLINE & FRENCH LABORATORIES

Born: Lafayette, Indiana.

Education: Purdue University, School of Pharmacy, B.S. in Chemistry M.S. and Ph. D. in Pharmaceutical Chemistry.

Experience:

Four years with Burroughs Wellcome & Co. as Chief Research Pharmacist in product research and development, followed by two years with Bristol Laboratories as Head of Production Development.

Seven years with University of Kentucky College of Pharmacy as Professor of Pharmacy, Chairman of the Department, and Assistant to the Dean.

Thirteen years with Smith Kline & French Laboratories as Assistant Technical Director, involved in Quality Control, production trouble-shooting, formula, process and packaging improvement in commercial products. Currently Associate Director Quality Control for SK&F.

Awards, Honors, Memberships:

Eli Lilly & Company postgraduate Fellowship.
Member Society of the Sigma Xi and Rho Chi Society.
Past Chairman, Committee on Inter-Tablet Dosage Variation (a committee of the Quality Control Section of the Pharmaceutical Manufacturers Association).
Author of textbook: "The Pharm-Assist Manual" (C. V. Mosby & Co.—1953).
Registered pharmacist (Indiana and Kentucky).
Member American Pharmaceutical Association's Academy of Pharmaceutical Sciences (Drug Standards, Analysis and Control Section, and Industrial Pharmaceutical Technology Section).
Senior Technical Advisor, Exhibit Committee, National Pharmaceutical Council.

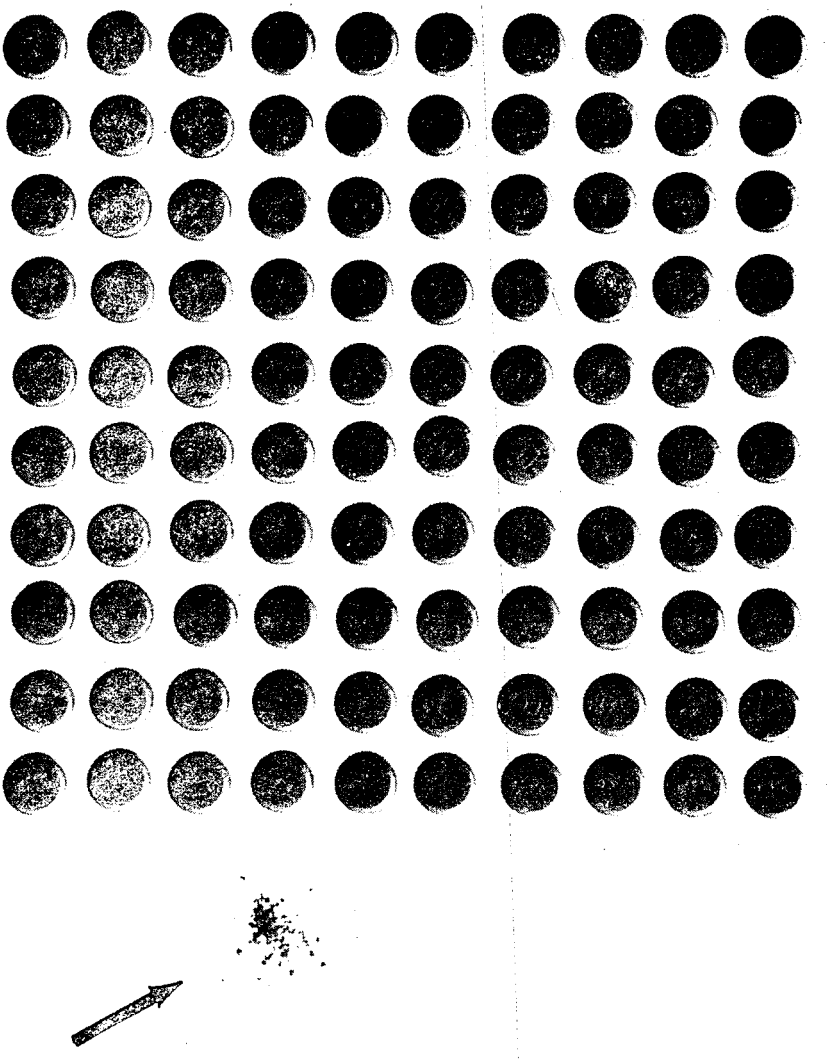

CHART 1

FACTORS DETERMINING SAFETY AND EFFECTIVENESS OF A DRUG PRODUCT

1. Components (Drug and Non-Drug)
2. Formula
3. Manufacturing (Compounding) Procedure
4. Assays, Tests, Inspections, Checks
5. Other In-Process Controls

CHART 2

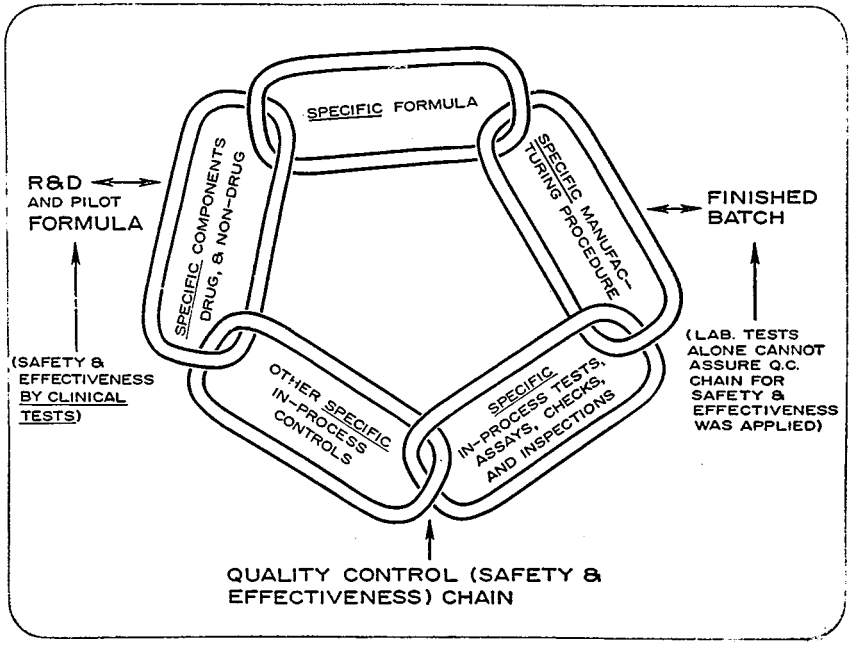

CHART 3

THE IMPORTANCE OF MANUFACTURER IDENTIFICATION

A review of the issue influencing the choice of drug products in the interest of more precise therapy and greater assurance of reliability

(By the Pharmaceutical Manufacturers Association, October, 1965)

I. INTRODUCTION AND BASIC POSITION

The member firms of the Pharmaceutical Manufacturers Association (P.M.A.) believe that competition in prescription drug production and distribution, under a system whereby physicians' prescriptions and drug labeling and advertising prominently identify the source of products by company name or product trademark, accelerates the pace of drug discovery, and encourages the highest standards of safety and effectiveness and the most economical medical care.

This statement outlines the bases for this belief and discusses the public health importance of a drug identification system.

As the statement will show, there are variations in finshed drug products resulting from the different formulations and production methods of individual manufacturers—differences that exist even though the pharmacologically active ingredients may be chemically identical. These differences are not necessarily related to product quality, but they may be. In any event they can affect the therapeutic value and physician or patient acceptance of a given finished drug. The system of using trademarks or brand names is the best known and most effective means of providing *responsible identification* of finished products, thereby giving the greatest assurance of reliability and predictability in drug therapy.

And, for the same reasons that prevail throughout all American industry, the trademark or brand name system fixes the responsibility and the reputation of the manufacturer, causing him to seek ever higher levels of excellence in his total performance.

Modern medical care owes much to pharmaceutical advances. Medical and pharmaceutical scientists have turned one key after another in the search for specific remedies to treat the myriad ills responsible for suffering and premature death. P.M.A. member firms alone have contributed more than $2 billion-worth of research to this quest since 1945.

Thirty years ago, for instance, there was only a small handful of drugs which would safely cure an infection in man. Today there are many, ranging from the broad-spectrum antibiotics to a compound so selective in its action that its use is restricted to a specific virus infection in the human eye.

Around one billion prescriptions are written by the nation's physicians and dentists every year in the United States. Practically all of the products prescribed and used come from the nation's pharmaceutical manufacturing laboratories. Precise dosage forms and formulations usually identified by trademark or brand name are made available to the physician and are dispensed by a pharmacist to his patient.

The proposition that the use of drug trademarks or brand names is in the public interest is based on three principles that are fundamental to the continuance of excellence in drug discovery, production, and therapy. They are:

1. *Therapeutic Control.*—The physician responsible for the care of the patient must determine which drug product is needed in each case. Many important and widely used drug products do not have legal standards. Even when drugs are covered by such standards, there are difference among individual formulations of products of different manufacturers which can be significant for some patients. The physician must decide whether therapeutic precision, reliability, or convenience calls for a particular formulation for a given patient, or the extent to which the selection can be delegated to another member of the health team, e.g., the pharmacist.

2. *Reliability of Product.*—A physician should be in a position to judge and select products on the basis of his knowledge of the reliability of the product and experience with the past performance of the producer. This method gives added protection to the patient—who should be assured that high standards of quality and reliability are being used in prescribing and dispensing pharmaceutical products for his use—and promotes high standards of production and control that go beyond minimal enforceable levels.

3. *Company Total-Value Product.*—The prescription pharmaceutical manufacturing industry is in competition for excellence. Responsible pharmaceutical concerns, under the stimulus of our competitive system commit themselves to expenditures and accomplishments in creative research, reliable production and marketing, and high standards of management. These organizations, who openly and widely identify their products by trademark or brand name, and in so doing identify themselves, are thus motivated to provide excellence in *total quality* of product and service. Such total control of quality of product and service is of significant value to dispensers and consumers of today's prescription medicines, exceeding by far the value of the product's ingredients.

In summary, patients, physicians, and pharmacists can best be assured of therapeutic control, reliability of product, and the value of total company service when the product is designated by trademark, brand name or other *responsible identification* of the people who stand behind it.

II. NAMES, STANDARDS AND REGULATIONS

The issues involved in drug prescribing and regulation cannot be approached intelligently unless certain terminology, references and practices are precisely defined and clearly understood. The following description of drug nomenclature, of the official reference guides to drug standards, and of government regulatory processes are presented here in brief summary.

A. How drugs are named

Most drug products have three names: the *chemical* name, the *established* or generic name, and the *trademark* or *brand* name. The first two names describe the same thing; that is, the chemical composition of the active therapeutic ingredient(s). The first is scientific and precise; the second is more convenient and concise. The relationship is analogous to that of the scientific term, *Homo sapiens*, and the more common and usable term, *man*. The third name—the trademark or brand name, on the other hand, refers to a particular manufacturer's formulation, and identifies the drug product with the originator or manufacturer. So, the completed analog would go like this: Homo sapiens, man, *John T. Jones.*

Chemical name

A therapeutically active compound, like all other matter, is composed of a combination of basic chemical elements. Once created or identified, a drug molecule is named in the laboratory according to standard practice in the field of chemistry.

Here is an example: *6-choloro-3,4-dihydro-7-sulfamoyl-2H-1,2,4,benzothiadiazine-1,1 dioxide.* This is the chemical name of a product compound widely prescribed to decrease excessive fluid content in the body—a diuretic. While long and cumbersome, this name is also precise for it serves as a complete identification of the compound to any trained chemist.

Established (or generic) name

Obviously, a drug compound must also have a shorter, more usable name. Such a name is originated by research or medical authorities involved in the possible therapeutic application of the chemical. The name is then submitted to review committees of the American Medical Association and of two standard drug references, the *U.S. Pharmacopeia* and the *National Formulary.* These three groups function through a coordinating group called the United States Adopted Names Council. If there is any conflict with existng names, or disagreement as to the meaning suggested by the proposed name, further negotiation takes place with the initial sponsor of the name. The Food and Drug Administration has veto power over final selection. If entirely satisfactory, the name is then transmitted to the World Health Organization, which works with the official pharmacopeial organizations of many nations.

Once a name for a drug compound has been approved by the Adopted Names Council, or by a regulatory body it is thereafter known as the "established" name, also referred to as the "generic," "official," or "nonproprietary" name; the most popular of these terms, and the one that will be used in the balance of this paper, being, "generic".

In the case of the compound illustrated earlier, the established or generic name adopted is *hydrochlorothiazide.* Still quite a mouthful, but much easier than: *6-coloro-3,4-dihydro-7-sulfamoyl-2H-1,2,4, benzothiadiazine-1,1 dioxide.*

The generic name is a shorthand way of referring to a specific chemical substance. It does not describe some of the therapeutically significant physical attributes of the substance; i.e., it does not tell if it is amorphous, crystalline, coarse, or fine. Neither does it describe its degree of purity beyond minimum legal standards.

For these and other reasons, the often-used phrase "generic drug product" is no more than a misleading term.

The term "generic name," properly used, refers only to the pharmacologically active chemical ingredient of a finished product, and not to the finished product itself. To be dispensed and used, the chemical ingredient must be combined with other carefully selected substances and embodied in a finished product (dosage) form such as a tablet, an ampule, or a suppository. Therefore, in the case of finished drugs (dosage form), application of the same "generic" name to two or more products does not and cannot mean that they are necessarily identical.

The brand name or trademark

Pharmaceutical companies generally adopt brand names or trademarks to identify their products. No official rules control this nomenclature. The objective is to coin a name which is useful, dignified, easily remembered, and individual or proprietary.

After it is finally put into use in interstate commerce, the brand name is generally registered with the U.S. Patent Office.

To continue the example cited above, one manufacturer of a product based on hydrochlorothiazide gave its finished produce the brand name, HydroDiuril, suggesting partly the chemical name and partly its diuretic properties. Another manufacturer, for other reasons, chose to name its product containing hydorchlorothiazide Esidrix; a third, Oretic.

These names are quite different, which is proper since they are intended to identify different products produced by different companies. But in order to avoid confusion and simplify the physician's and pharmacist's task of remembering the main therapeutic ingredient of the many products on the market, the generic name of the principal ingredient appears on product labels in advertising and in other communications about the product. Hence, the names mentioned above may be referred to this way in written communications.

HydroDiuril (hydrochlorothiazide)
Esidrix (hydrochlorothiazide)
Oretic (hydrochlorothiazide)

There is the alternate method of using the company name, initials, or symbol along with the generic name. The following examples, based on a fictitious John Doe Drug Co., illustrate the method:

hydrochlorothiazide, Doe
or
hydrochlorothiazide, DDC

B. Legally acceptable and other standards

For more than 100 years, drug standards established by non-governmental bodies have played a major role in the continuing effort to obtain uniformity in therapeutic agents. Their existence, however, does not *guarantee* therapeutic uniformity of products from manufacturer to manufacturer. But since these standards have frequently been cited as a readymade foundation for a system of so-called generic name prescribing, it is important to understand their exact coverage and function.

The *Pharmacopeia of the United States* and *National Formulary* are "official" publications of the U.S. Pharmacopeial Convention and the American Pharmaceutical Association respectively. They are recognized as registers of legal standards to which drugs and some ingredients used in making medicines should conform. These lists are specified by the U.S. Government under the Food and Drug Act, as amended, as setting minimum standards. Lists are periodically compiled by other organizations, too, each designed to serve specific needs.

Pharmacopeia of the United States (U.S.P.).—This compendium was the first of two published in the 19th century covering the broad practice of pharmacy, to guide pharmacists and drug manufacturers. The first edition of U.S.P. was printed in 1820 under the auspices of the U.S. Pharmacopeial Convention, a private assemblage of physicians, pharmacists, chemists and others. It is an authoritative source of minimal standards for therapeutic substances "the utility

of which is most fully established and best understood." U.S.P. is now revised every five years by a committee representing the nation's schools of medicine and pharmacy, certain government agencies, medical and pharmaceutical societies, and other professional organizations.

National Formulary.—Because the U.S.P. was selective in its inclusion of drugs, restricting its coverage of those drugs the utility of which the committee considered the "most fully established," many other valuable and widely-used drugs were not included. To cover these, the American Pharmaceutical Association, a professional association of pharmacists, began publishing in 1888 the *National Formulary* (N.F.). The N.F. also has served as a guide to drugs sometimes before they appear in U.S.P., and frequently after they are removed from U.S.P.

The monographs of the U.S.P. and N.F. have been recognized in every federal law pertaining to drugs, starting with the Food and Drug Act of 1906, as legal standards. Drug products containing ingredients conforming to the criteria in these compendia have permission to carry the designation "U.S.P." or "N.F." on their labels and packages.

It is important then to understand just what these standards guarantee as well as what they do not guarantee:

1. In general, the information in these compendia is descriptive only of the chemical properties of active ingredients and adjuvants and the laboratory procedures required to demonstrate substance identity and allowable limits of purity. Significant as this information is, the chemical tests and specifications do not by themselves give full information on the pharmacologic or microbiological activity of the substances listed. Additional studies of a given drug product are still necessary to reveal the presence of certain physical characteristics such as particle size, crystal form, surface properties and other attributes which influence the biological availability of the pharmacologically active compound in question. Only an extensive and integrated physical-chemical-biological research program can determine the ultimate pharmacological action of the compound along with the characteristics which must be controlled to guarantee safety and efficacy.

Moreover, it is rare to find an active drug compound used *by itself* in therapeutic treatment of a patient. Frequently, the finished product will contain other materials to facilitate or augment the action of the principal ingredient. Often the complete preparation contains more than one active ingredient. The selection of these active ingredients and ancillary materials—in terms of their purity, function, concentration and appropriateness—is of central importance to achieve maximum efficacy and safety.

In short, the complete formulation of a finished product for use by a patient involves much more than is covered by the information in these compendia.

2. U.S.P. and N.F., stemming from an era in which the pharmaceutical formulation of active ingredients was largely performed by the local pharmacist, contain some occasional information on simple compounding. But they do not cover the complex processes of modern mass production, and they give relatively little guidance to standards in this area. Neither do they cover other considerations of great importance to modern production and distribution, such as long-term stability.

Many of these things are not covered, because in fact they cannot be reduced to precise standardization that would be meaningful with respect to all manufacturers alike. Production of quality pharmaceutical products is not entirely a science; it is also an art and craft involving experience and know-how and professional pride. The experienced industrial pharmacist calls upon skills and a background of knowledge unique to him.

3. Because of the prodigious effort required of so many authorities working on U.S.P. and N.F. revisions, these compendia are revised only at five year intervals with supplemental addenda published occasionally in the interim. However, numerous new drug products may be introduced without being included in either compilation for several years. The regulatory agencies, of course, do not depend solely on the compendia for establishing standards, and new products are monitored from the start on a product-by-product, company-by-company basis (see below). But, until a consensus is worked out within the U.S.P. and N.F. mechanism, there is no set of standards for these new items.

AMA New Drugs.—In view of these limitations, it is understandable that regulating bodies and large purchasing groups have set up other reference standards.

The Council on Drugs of the American Medical Association began to publish in 1906 detailed information on the chemistry, pharmacology, clinical utility, and safety of some new drugs in a reference guide, until recently titled *New and Non-Official Drugs.* This book has been redesigned, changed in form and text, and first published in 1965 as *New Drugs* (N.D.). The N.D. does not establish standards at all, as U.S.P. and N.F. do, but rather serves as an annual collection of monographs for the guidance of the practitioner. Like the U.S.P. and N.F., this volume does not provide criteria from the chemical-physical-pharmaceutical subtleties of drug product manufacture and control.

Selected groups depend on other sources for guidance regarding drugs for use in their fields, for example the dental profession generally refers to *Approved Dental Remedies* as a source of information. The Medicare Act (P.L. 89–97) accepts the above four compendia as well as the *Homoeopathic Pharmacopoeia* as lists of drugs qualifying, without further action, for reimbursement under the program.

New Drug Application Specifications.—The Federal Food and Drug Administration (FDA) requires that each new drug application (NDA) include detailed data on the process and control procedures under which the product is to be manufactured. Thus, the new drug application covers a broad range of information and standards not included in the U.S.P. and N.F. For obvious competitive reasons, much of this information is not published. But, even if it were, it is important to note that each manufacturer filing an NDA must include his own production specifications. Therefore, approval of one company's product does not carry with it the assumption that a second or third company's version will be approved or will be identical. In point of fact, the techniques of production and complete formulation inevitably differ. This is further recognized by the FDA's requirement that clinical trials and data are required from each company for each product version as assurance that every formulation is safe and effective.

So, even though all new drugs come under FDA control and there are detailed standards applied to the production of these products, these standards are not and cannot be regarded as *general* across-the-board standards, applying to a group of products with the same generic name.

Purchaser Specifications.—Finally, standards are sometimes applied by purchasing groups having the facilities and staff to prepare and enforce specifications in a more detailed way. Large hospitals, government agencies and other such volume purchasers may consult with suppliers and draw up detailed, but practical, specifications as a guide to competitive bidders for supplies of drug products.

C. Regulation—Enforcement and "voluntary compliance"

Regulation of any private enterprise in this country, of necessity, is composed of two elements—direct enforcement and voluntary compliance. It is impractical to expect the government or any outside agency to observe and then rule over every action of a large industry. Neither is it in the public interest to allow products affecting human health to be made and distributed without regulation. Obviously, the best situation consists of a proper balance, a harmony of purpose between official regulations and private initiative. Our brand name system actively serves to promote this goal, which has been called "voluntary compliance."

As it is, the U.S. prescription drug industry is one of the most intensively regulated industries in the country. Numerous laws affecting the industry are administered by the U.S. Food and Drug Administration, the Division of Biologics Standards of the National Institutes of Health and other federal bodies, as well as state and local agencies.

A proposed drug product is monitored by the government from the time an experimental project is designed through its emergence from the laboratory ready for trial and its marketing for treatment of human disease. Monitoring does not stop here. It continues as long as the product is on the market. A new drug cannot be offered for sale without express approval; its production, promotion and marketing methods must also be approved.

These laws stem from the Pure Food and Drug Act of 1906, which was aimed at barring adulterated or misbranded foods and drugs from interstate commerce. The Food, Drug and Cosmetic Act of 1938 added provisions requiring that the FDA pass on the safety of new drugs before their commercial in-

troduction. The Kefauver-Harris Amendments of 1962 added the pre-marketing requirement of proof of product effectiveness, increase government control of production and quality control procedures, required the registration of all drug manufacturers, increased the inspection powers of FDA and gave FDA greater control of labeling and promotion.

Despite increased legislation and regulation, both the Food and Drug Administration and the industry recognize that the principle of voluntary compliance has remained a key part of the philosophy of federal regulation. This principle gives rise to positive stimulation of responsibility within the industry, so that federal enforcement activities can be held to reasonable, workable limits.

In the field of quality manufacture and control, the techniques and patterns set by pharmaceutical industry leaders have tended over the years to be codified into government regulations. But it is important to recognize that under our system of voluntary compliance, it is neither intended nor practical for a government agency to assume the fundamental responsibilities of production and distribution. For instance, the law calls for inspection of every production facility at least once every two years. Clearly, this infrequency places the greatest share of the burden of maintaining good manufacturing practice upon the producer.

In this area, as in so many others, the competitive nature of American business serves the interests of the public well. For the reliable manufacturer there is a built-in desire to excel in product quality as a competitive measure. The FDA picks up products from distribuiton channels to spot-check contents and labeling. But there are thousands of products in interstate distribution, and hence there is a real responsibility of the manufacturer to guard against the distribution of sub-standard products. Furthermore, spot-checks of product contents and labeling are made after products have been in the channels of distribution for some time. The services performed by brand name manufacturers supplement the regulatory activity of FDA. Their record-keeping, returned goods policies, and inventory checks by their sales representatives help to maintain fresh stocks of quality products on retailers' shelves.

Then too, some FDA powers extend only to products in *inter*state commerce. In many states, separate regulations apply to *intra*state commerce in drugs. Some states have statutes almost identical to the Federal Food, Drug and Cosmetic Act; in others, consideration is being given to laws comparable to federal provisions. Realistically, however, the state rules covering production and sale of drugs within a state's boundaries are, and are likely to remain uncertain and varied for years to come; and the capacity of state governments to carry out an effective enforcement program to back up their laws varies considerably.

Here again, the importance of voluntary compliance is evident. In view of the limitations of enforcement, the public interest is well served by our system of trademark or supplier identification. The well-identified product and producer must excel in product quality as a matter of probity, as well as competitive necessity. By creating a proprietary interest in the performance, reputation, and hence usage of branded products, this system gives a strong stimulus to private responsibility, which together with practical regulation and enforcement, can provide the public with maximum assurance of safe and effective medicines.

III. THERAPEUTIC CONTROL

A fundamental principle enunciated by this paper is that the physician responsible for the care of the patient must determine which drug product is needed in each case. Many important and widely used drug products do not have legal standards. Even when drugs are covered by such standards, there are differences among individual formulations of products of different manufacturers which can be significant for some patients. The physician must decide whether therapeutic precision, reliability, or convenience calls for a particular formulation for a given patient, or the extent to which the selection can be delegated to another member of the health team, e.g., the pharmacist.

Finished pharmaceutical products can differ, even though their principal active ingredients are identical in the generic sense. For some patients these differences can have significant therapeutic consequences.

Under a *compulsory* generic system, which would suggest that all products bearing the same generic designation are equal and could be interchanged, the

physician would prescribe by indicating, without regard to the producing source, only the generic name of the drug and the dosage form he wanted his patient to have. This would introduce the possibility of a number of variables which could affect the course of treatment of some patients.

For one thing, the physician would not know, unless he made a later check, exactly which one of any number of preparations the patient actually received from the pharmacy. Since different products purporting to contain the same ingredients may have different effects, the physician could not properly judge the patient's responses.

Not only may products which purport to contain the same active ingredients have *therapeutically* significant differences, there are significant differences between such products at least in terms of patient convenience and acceptance. If a medication is relatively pleasant and "easy to take", the patient is more likely to follow the regimen outlined by the physician.

Then too, most patients and most physicians, under ordinary circumstances, prefer to avoid the potential uncertainties of generic prescribing. The long-range trend of drug therapy has been the search for precise treatment—matching the particular therapy to the individual patient and disease. Even with the same finished form of the same drug, there are variables in patient response. Further unnecessary variations in the drugs themselves only serve to reduce the control of the physician over the circumstances he seeks to correct or prevent.

The members of P.M.A. do not contend that all patients would in every instance be adversely affected by "bline" generic name prescribing nor that the physician should never elect to govern his choice of product by price differences in cases where they exist. However, the fact that variations occur in products purporting to contain the same active ingredients makes it advisable that only in exceptional circumstances should the physician fail to designate by trademark or manufacturer's name the source of the product he intends for his patient.

A. Product differences

Here, in brief, are selected aspects of drug formulation that affect the action or patient-acceptance of drug products.

Liquids.—Among drug preparations administered as liquids, by injection, ingestion, or application to sensitive tissue membranes, there can be distinct variations in particle size, stability, sterility, surface tenson (which determines wetting or spreadability), and viscosity (which controls resistance to flow, or adherence).

Solids.—Important variables among tablets include the maintenance and effective release of potency; absorption characteristics of ingredients; tablet disintegration and dissolution rate characteristics; uniformity and biological behavior of delayed and sustained release compositions.

Lotions, creams, ointments.—Factors important to therapeutic effectiveness and patient tolerance include skin permeability, ease of application and removal, and lack of local irritation.

Other therapeutic variables.—For certain types of patients, specialized formulations provide significant elements of safety or tolerability. The allergenicity of the additive (filler or binder) substances in some brands of a pharmaceutical preparation may be reflected in undesirable reactions on the part of sensitive patients. Also, a quality manufacturer will design his formulation, if possible, to be compatible with other medications that may be added to it or taken with it.

Subjective factors.—A patient's acceptance of a drug preparation is also important. If the product is in some way obnoxious or uncomfortable to the patient, he will tend to avoid taking the prescribed medication. Liquids require palatability, freedom from nausea, pleasant "feel", freedom from grittiness and ease of swallowing. Odor and flavor can be of considerable importance, particularly when medications must be used over long periods of time.

Packaging.—Pharmaceutical products are frequently in direct contact with their containers for long periods of time. The choice of proper grades and types of glass, plastics, meal, rubber foil and other materials to prevent interaction with the components of a drug preparation, and to provide adequate protection for the contents requires specialized tests and skills of the highest competence.

Stability.—A drug product should be compounded to maintain its labeled potency throughout the expected period between its production and consumption by the patient. Care must be taken to assure reasonable shelf stability when

the drug is at the pharmacy and in the patient's medicine cabinet. Responsible producers will generally accept for credit out-of-date goods returned by a pharmacist.

B. Therapeutic consequences of product differences

Clinicians, pharmacists and others have reported the significance—in some cases, the hazard—of changing to different brands or formulations of so-called generically identical drugs. No complete scientific study of the entire problem has been made, but published findings are persuasive indications of the risks involved in generic prescribing.

The dissolution rate of a compound may be influenced by the finished formulation, as with dicumarol tablets reported by Levy-Nelson (*Journal of the American Medical Association*, September 9, 1961) and others. Levy has also cited differences in absorption rate of spironolactone, leading to a fourfold overestimation of proper oral dosage. Similar experiences with formulations of, cortisone, prednisone, and other steroids have been reported, as well as with the antidiabetic tolbutamide in certain tablet preparations.

Probably the most telling review of this issue was that recently published by Sadove, Rosenberg and Shulman of the University of Illinois Hospital and Hines VA Hospital (*American Professional Pharmacist*, February 1965). Their experience is presented from the viewpoint of hospital staff members who are not always informed of changes made in the hospital's inventory of drugs, and who have found therapeutic variations later traced to switches among so-called "generic equivalents". They cite the marked irritancy resulting from switching to an erythromycin preparation containing a different salt; the decreased shelf life of a soluble barbiturate preparation using a different vehicle; the effect of buffering agents on local anesthetics, with marked differences in irritation, onset, and duration; the irritating consequences of a new container which used a closure high in heavy metal content; a case of idiosyncratic reaction to a test drug that unexpectedly caused a thrombophlebitis because of a different vehicle used in its preparation; and so on.

In commenting on the proposal to obtain drugs from different sources at lower cost through "generic" prescribing, they say:

"The specifications of . . . two products were identical. The clinical results were entirely different . . . in many instances it is physically impossible to compare two similar products without extensive, carefully-controlled laboratory and clinical trials. Though it is admirable to keep the cost of drugs to a minimum and it is admirable to know and prescribe drugs generically, the generically-similar product exerts, in many instances, a very different reaction from the one anticipated.

"It is practically impossible for one not skilled in the area of clinical pharmacology to know what is—and what is not—a real 'equivalent'.

"Above all, the lack of available data would preclude substitution without prior equation of the many factors which could materially alter apparent equivalency."

Their conclusion was "that generic equivalency is frequently a fable without basis in fact; chemical equivalency of the primary agent or agents is *not* necessarily clinical nor pharmacologic equivalency".

IV. RELIABILITY OF PRODUCT

The Basic principle presented here is a physician should be in a position to judge and select products on the basis of his knowledge of the reliability of the product and experience with the past performance of the producer. This method gives added protection to the patient—who should be assured that high standards of reliability are being used in prescribing and dispensing pharmaceutical products for his use—and promotes high standards of production and control that go beyond minimal enforceable levels.

Except in large and exceptionally well-equipped institutions and consulting laboratories, facilities for providing independent and reliable assays of drug quality do not exist. The resources of the average physician, pharmacist or hospital are not adequate for comparing physical qualities of competing products. Under these circumstances, the system of *responsible identification* by trademark or brand name plays an important role. It enables the physician to judge quality of product on the basis of its producer's established reputation. And since respon-

sible producers know that their products are so judged, they strive to achieve and maintain the best possible reputation for quality. The physician and his patients obviously benefit greatly from this system in which the needs of medical care are matched by the aspirations of the producer.

Standards and legal enforcement, as a practical matter, can concern themselves only with certain major aspects of product specification. Only through the active desire and efforts of the producer to excel can the principle of "voluntary compliance" give the assurance of quality that the public must have. This desire to excel is a built-in feature of the responsible identification system.

The P.M.A. defines quality control as follows:

"Control of quality in the formulation, manufacture, and distribution of pharmaceutical, biological, and other medicinal products in the organized effort employed by a company to provide and maintain in the final product the desired features, properties, and characteristics of identity, purity, uniformity, potency, and stability within established levels so that all merchandise shall meet professional requirements, legal standards, and also such additional standards as the management of a firm may adopt." [1]

Testing a finished pharmaceutical product for quality is a difficult and complex laboratory problem, because quality is often a hard-to-trace feature that must be built in—during production, from raw materials to formulation, through in packaging and all intervening operations up to the delivery of the products to the consumer. As an example, long-range stability is a feature of quality made possible by careful research, formulation, and production. The only completely valid test of this feature is time. Any short cut or lack of skill during manufacture that results in deterioration of the product months later often cannot be detected until the weakness appears. And only fortuitous spot-checking would pick up the inadequacy before many patients have received the faulty medication.

For these reasons, federal regulations are now stressing standards of good manufacturing practice, even though such standards are difficult to enforce unless the company itself it motivated to meet them.

The storage facilities for raw materials; the facilities for bulk formulation; the layout of the plant; the work-flow process; the precision of the equipment; the training and experience of supervisors and workers; the standards and disciplines of internal quality inspectors; the attention to quality control technology; the searching for solutions to, rather than avoidance of troublesome problems; the willingness to assume the costs of detecting and correcting error; the intelligence of information flow, and record keeping—these are among the elements of responsible, quality production.

These elements are recognized by most experts in drug production. However, they emphasize the difficulty encountered by an individual physician or pharmacist in making quality judgments without the advantage of relying on the producer's known reputation. The drug standards regulatory system (see pages 7 to 14) is clearly not designed to replace private manufacturing responsibility.

It is therefore clear that the system of competitive stimulation to quality, through responsible product identification, provides a service of inestimable value.

V. THE VALUE OF TOTAL COMPANY PERFORMANCE

The third positive value of the brand name system, which goes beyond reliability of product, has been expressed in this way:

Company Total-Value Product.—The prescription pharmaceutical manufacturing industry is in competition for excellence. Responsible and identified pharmaceutical concerns, under the stimulus of our competitive system commit themselves to expenditures and accomplishments in creative research, reliable marketing and production, and high standards of management, personnel and comprehensive service. These organizations, who openly and widely identify their products by trademark or brand name and in so doing, identify themselves, are thus motivated to provide excellence in *total quality* of product and service. Such total control of quality of product and service is of significant value to dispensers and consumers of today's prescription medicines, exceeding by far the value of the product's ingredients alone.

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[1] General Principles of Control of Quality in the Drug Industry, adopted by the Board of Directors of the P.M.A., May 3, 1961.

Encouraged by the stimulus of a system built around *responsible* identification of products and their source, the private-enterprise method of drug development and supply impels companies to seek continually rising levels of total performance. Spurred by competition, and vulnerability to criticism if products or services are lacking on any count, companies seek constantly to surpass others and to improve their own record in quality performance that extends into all operations.

The physician and pharmacist gain added assurance of excellence when a company undertakes quality performance, for dedication to quality is a long-term commitment. A quality operation requires the assembling of capital and skills and a background of experience that cannot be readily shifted from one business to another. Manufacturers without these long-term commitments are risking relatively little in producing cut-rate products of questionable quality. They can seek short-term gains, with little to prevent their shifting to a different field when difficulties arise.

And the consumer-patient also gains because commitment to quality generates what might be called *"total quality."* To provide top-notch facilities and personnel for excellence in production and distribution, the company must make a commitment over the long-term suffcient to attract investment money and high-caliber technical people. These factors stimulate pressures for growth in performance and service that motivate the other activities or potential activities of the company—enterprising marketing of products to new geographic areas or new fields of medical practice; enterprising search for products improvements leading often to totally new products and services; more efficient management and administrative and legal operations to back up the broadening product line and numbers of personnel.

In short, quality performance in research, in development, in production and control generally does not operate in a vacuum, but accompanies or creates a broader range of company service that supplies the professional and consuming public with what can be termed *"total-value product."* This total value extends from the creation and marketing of the product to its production, distribution and service as part of an industrial organization with a broadening role to play in the city's, state's, nation's or world's economic and social progress.

Elements of total company performance

Here, in brief summary, are some of the most important activities adding up to total quality performance in the prescription drug industry. Note that quality of product *per se* is not one of the items listed, since this has already been covered adequately.

1. The importance of *research for new products* is so obvious that it requires no explanation. It is enough to say that three-fourths of the drugs taken by patients today did not even exist in 1950, and that all too many diseases causing premature death and untold suffering today cannot yet be controlled.

2. The *continued testing and improvement* of existing products is another obviously necessary and ongoing activity of responsible pharmaceutical companies.

3. *Availability* of product, regardless of distance or population density, is important in a nation such as ours which happily considers the health of a person in a remote rural area just as significant as that of a man living within easy distance of a major medical center.

4. The care and completeness with which *records are kept* can make a considerable difference in many situations. Being able to trace a suspected product problem throughout the entire distribution operation can ease the worry from an unexpected occurrence and provide a course of action otherwise less certain.

5. Under unusual circumstances, if *recall of a shipment* of products is necessary, a reliable company can perform the task with speed and thoroughness.

6. At any time, when a physician anywhere has *questions* concerning the use or effects of a drug a staff of experts is on hand to respond with all the available information.

7. A quality company provides *complete product information* to prescribing physicians and pharmacists; as well, it hires and trains professional representa tives who personally visit health professionals.

8. In addition to the above, quality companies contribute substantial sums to further the *professional education* of health professionals and to inform the general public on health matters.

9. Quality companies have the facilities and will to move quickly to meet *emergency situations*, which might involve massive shipments to disaster areas or the formulation of a special dosage of a product to treat rare individual cases.

10. Quality companies as a service to physicians and patients frequently *stock lifesaving medicines* for which there is no profitable market, medicines such as an anti-venom for the black widow spider bite.

11. With an established company, the public is assured that there will be *continuity* of its high-quality products, an especially important point for persons with long-term chronic illness helped by a particular medication.

12. With no reference to its contribution to health, an established company usually represents a significant *contribution to the economy*, in terms of employment, purchases, payments of taxes and general desirability of an entire area.

VI. THE ALTERNATIVE TO ABSOLUTE GOVERNMENTAL REGULATION

Earlier sections discussed the limitations of existing standards and government regulation of the pharmaceutical industry. The intent of these sections was to show why these measures alone cannot be relied upon to provide the best medication and the best therapy. Nevertheless, they are an indispensable part of our present productive system. On one hand, they provide restraints against gross actions contrary to the public interest. On the other hand, they represent a base from which competitive companies build toward ever higher levels of total quality performance in production and in service.

In fact, it frequently happens that the companies in the vanguard introduce advanced standards and techniques that are later codified into the regulations. In this way, the regulations keep moving ahead. The ultimate effect of this process may be the virtual elimination of companies in which little or no effort is made to pursue the goal of total quality. For once a company makes a significant commitment to quality performance, as outlined in the preceding section, its course tends to move steadily upward.

It might be argued that, if regulations and enforcement have this beneficial effect, why do we not upgrade all the regulations and increase their enforcement?

To begin with, it has been shown in other sections of this statement that no amount of regulation could possibly cover all the important aspects of drug discovery, production and therapy. In addition to what has been said before, it should be recognized that the complexities of drug production make it not only impractical but completely unfeasible to develop such detailed standards and such complete enforcement as to oversee the the detailed operations carried out in the production process. For instance, raw materials and intermediates for the production of drug ingredients may be collected from a number of sources, the active ingredients manufactured in various stages and even in more than one plant, and incorporated in a number of products and a number of dosage forms of each product. During this process, literally hundreds of laboratory tests may be conducted. The most complete government regulation attempted to date has not been sufficient to oversee all details of production and testing. Government regulation simply cannot substitute for competition in stimulating the achievement of superiority in discovery and production. Unless legal standards set by the government permit the free play of competition such as that evidenced by the trademark system, it could easily result in higher economic costs without providing additional benefits.

Instead of considering ways to place research or production of pharmaceuticals, or any other consumer products, under airtight governmental domination we should work toward further perfection of the present balanced and flexible system which is the foundation of the most inventive, productive and quality-conscious pharmaceutical industry in the world. It is clearly in the interest of everyone concerned to keep it that way.

VII. SUMMARY

In briefest summary, the position of the Pharmaceutical Manufacturers Association with regard to the responsible identification of product and manufacturer in drug therapy, is as follows:

Pharmaceutical products, even those with the same principal therapeutic ingredients, differ from manufacturer to manufacturer in terms of quality and formulation, either of which may influence proper therapy.

Existing standards, controls and enforcement measures contribute importantly to the protection of the public, but they would be inadequate to assure reliability without the incentives and dedication of responsible pharmaceutical companies. Moreover, generic identity of principal drug ingredients is a futile goal, for it does not guarantee uniform therapeutic effect of finished products in all patients.

The quality-minded producer who identifies his products and promotes them under unique names or under his company name has an interest in furthering his reputation and his services to a point that goes far beyond any norms that could reasonably be established and enforced as a general system of governmental regulations, even under complete domination of the industry.

The overall reputation and performance of a company serve as reliable indexes to the quality of its products.

No measures should be instituted that might abridge the physician's prerogative and responsibility to determine the proper therapy and prescribe the type and quality of medication which in his opinion will best serve the needs of his patients.

Senator NELSON. Who is your next witness?

Mr. CUTLER. Our next witness, Senator, is Dr. Leonard Scheele. But before he begins, let me just add in response to a question asked earlier—there is at least one of the references in this book which specifically recites that the drug in question, which happened to be prednisone, did meet U.S.P. standards, and yet was found to be therapeutically deficient. And that is from the Journal of Pharmaceutical Sciences, volume 52, No. 5, June 1963.

Senator NELSON. Mr. Cutler, I am sure you will be pleased to know that is one of the drugs named by Dr. Miller as one of the 15 examples. So you have not yet added to my list. Prednisone is also one.

Mr. GORDON. Mr. Cutler, was that a clinically controlled study?

Mr. CUTLER. It is a study done by Dr. Eino Nelson, and a number of other doctors experienced in this subject.

Mr. GORDON. They are pharmacists, not medical doctors.

Mr. CUTLER. Dr. Campagna, one of the four, is a physician.

Mr. GORDON. Do you know if it is a double blind study?

Mr. CUTLER. I cannot tell you, but I will be glad to hand you the study.

Mr. GORDON. I have a letter on this subject by Dr. Harold Aaron that I would like to submit for the record at this point.

(The letter referred to follows:)

JUNE 12, 1967.

DR. J. A. CAMPBELL,
Department of National Health and Welfare,
Food and Drug Directorate,
Tunney's Pasture,
Ottawa, Ontario, Canada.

DEAR DR. CAMPBELL: Many thanks for your comments on our preliminary draft of "Tests of Prednisone Tablets." Dr. Gerhard Levy made the same comments. If we turn to the articles cited by you and Dr. Levy we find the following: The article by Dr. Campagna cites one case in which a patient with paroxysmal peritonitis did not respond clinically to one brand of prednisone. The dissolution time of tablets of this brand of prednisone was slower than that of the clinically effective tablets. However, there were no *in vitro* determinations of prednisone or its metabolites or conjugates in the blood, urine or other body fluids. Such determinations are generally required to confirm "physiologic availability" and absorption of the drug. Clinical response as a test of adequate dissolution rate and absorption is usually unreliable because of spontaneous changes or remissions in clinical behavior. Such tests can be reliable only when they are double-blind and the number of subjects is large. This is likewise true in the case cited in the second reference, in which a patient with "arthritic pain" failed to respond to one brand of prednisone. In a telephone conversation with

Dr. Levy on May 24, 1967 he agreed that dissolution time of a tablet should be correlated with plasma or urinary levels. It is also noteworthy that Dr. Campagna's study was reported in 1963 on tablets of undefined age and Dr. Levy's article was published in 1964.

Finally, a Food and Drug Administration official was not aware of any substandard prednisone tablets reported to it or determined by the FDA itself. If your department has evidence of substandard prednisone tablets or other preparations we shall be grateful for the information.

One unrelated point—iron and vitamins are considered to be absorbed only in the jejunum. Are any drugs absorbed chiefly in the ileum or even in the colon?

Sincerely,

HAROLD AARON, M.D.

Senator NELSON. Just so I have the record straight, did we put all of Dr. Slesser's statement and the summary in the record?

Mr. CUTLER. Yes, sir.

Senator NELSON. Now, did I put Dr. Lueck's full statement in the record?

Mr. CUTLER. Yes, you did, Mr. Chairman.

Senator NELSON. I thought Dr. Lueck's statement was very professional and very valuable and informative. We are pleased to have it for the record.

I did not know whether I had asked that it be printed in full.

Mr. CUTLER. Thank you very much, sir.

Senator NELSON. Proceed.

STATEMENT OF DR. LEONARD A. SCHEELE, PRESIDENT, WARNER-LAMBERT RESEARCH INSTITUTE, MORRIS PLAINS, N.J.

Dr. SCHEELE. Mr. Chairman, my statement is very brief. With your permission, I will read it.

First, I wish to make a very brief statement concerning my background. I was a career medical officer in the U.S. Public Health Service for 23 years, serving as Surgeon General from 1948 until 1956. Since then, I have been a member of the staff of the Warner-Lambert Pharmaceutical Co. in Morris Plains, N.J., and have devoted the last 5 years primarily to administration of the company's research programs.

I shall devote my statement mainly to new drug research and development as conducted by the research-oriented companies in the pharmaceutical industry.

A recent National Science Foundation study shows that industry supports about 96 to 98 percent of its own drug research. Facing unknown odds against success because the overwhelming majority of chemicals synthesized never become useful drugs, and being self-financed, each pharmaceutical company must draw new research and development money from its own financial resources.

The key organizations for finding urgently needed new drugs for many unsolved medical problems are the research-oriented firms in the pharmaceutical industry. Currently research and development expenditures for a successful new single chemical entity drug product range from $500,000 to $10 million—with an average estimated cost per new drug discovery of about $7 million during the period 1957–66. From the point of discovery it takes from 4 to 10 years to develop and market a new drug product. Obviously, the successful product must pay for the hundreds of costly efforts that failed along the way.

At present the medical research expenditures of research-oriented drug companies average about 11 percent of sales, compared with an average of 2 percent for all types of industry in the United States.

The total PMA member firm expenditures for research and development this year will exceed $460 million. For the 10 years 1958–67, these firms expended nearly $3 billion of their own funds in such activity.

A report entitled "Ethical Pharmaceutical Industry Operations and Research and Development Trends—1960–66"[1] based upon PMA annual surveys of member firms, contains considerably more detail than I have briefly outlined in my statement. A copy of this report is attached for inclusion in the record.

It should be noted that the research-oriented firms in the pharmaceutical industry employ the highest ratio of scientists of all industries. A study done a few years ago by the National Science Foundation showed 156 scientists per 1,000 employees in the drug industry, compared with the next highest of 48 in the chemical industry, 32 in the petroleum industry, and an average of eight for all manufacturing industries. The large number of research scientists in pharmaceutical laboratories attests to the complex problems of biomedicine and fundamental drug research in contrast to the more applied and technical nature of research in other industries.

Drug research progress is complex and slow. The unfinished work hopefully leading to understanding of the biochemistry of health and disease and in new drug development is vast and needs to be pursued more intensively by all sectors of the research establishments in academic and private institutions and in Government and industry.

Mr. GORDON. You say 2 percent of all industry. Does that include manufacturing only, or does that include agriculture and mining? What does it actually include?

Dr. SCHEELE. It is all manufacturing industries.

Mr. GORDON. Only manufacturing, you say?

Dr. SCHEELE. Yes, sir.

Mr. GORDON. All right.

Dr. SCHEELE. These elements of our research force are not separate. They have and need to continue to work together closely for maximum achievement. For example, it was academic-industrial collaboration that brought about the discovery of cortisone and then made it available as a major drug of value in the treatment of arthritis. Later industrial research and good molecular modification led to the finding of other uses and the development of other steroids with new uses, such as treatment of skin problems. In more recent times, still other molecular changes have led to progestational steroids and such steroids, combined with estrogens, provide a useful treatment of women's menstrual disorders. More recently, used together or sequentially, they have become important in spacing pregnancy—family planning. Although great strides have been made with the now classical 20-day regimes, it is certain that, in the not too distant future, altogether new concepts of hormonal modification may be expected, which will control fertility in either sex with specificity and relative lack of side effects. These developments will only be made possible by continuation of the reproductive physiology studies of the past 20 years. The current compounds are playing a role in attacking one of the world's

[1] See p. 2293, infra.

greatest problems—the population explosion. In the future, even newer compounds and newer methods discovered by research-oriented pharmaceutical companies will play an even greater role in population control.

Penicillin, and its availability for use on a mass production basis, and chloramphenicol, a widely used broad-spectrum antibiotic, were also the results of work in government, university, and industrial laboratories. Today the search for soil samples that may contain micro-organisms which will produce as yet unknown antibiotics, useful against viruses and cancer as well as against larger micro-organisms infecting man and animals, is an expensive research operation. The venture capital being plowed into it comes almost entirely from the research-oriented drug firms. In spite of continued large-scale efforts to find new antibiotics, few have emerged in recent years. Nevertheless it is important that these costly industrial research programs be continued.

You have occasionally heard references to "molecular manipulation" and the implication that this is bad and wasteful. It is a rare instance when a company markets a product that doesn't have some superiority over existing ones. There are many instances where molecular modification has led to major advances in medicine. Sometimes the drugs have been useful in new diseases and in other cases new clinical values of such drugs turn up months or even years after they have been marketed.

The discovery of aspirin as an analgesic was the result of attempts to improve the properties of a plant constituent, salicylic acid. The local anesthetic, procaine hydrochloride, was found in attempts to synthesize a simple molecule retaining the structural features of the complex alkaloid, cocaine.

Studies in which attempts were being made to simplify the chemical structure of quinine led to synthesis of Atabrine and other antimalarials. Later studies of pharmacologic properties of the synthetic antimalarials led to observation of an unexpected, new effect which was interpreted as an antagonistic action to histamine. These observations culminated in synthesis of an important new class of drugs, antihistamines. Later observation of the sedative effect of one of these on mental patients in France led to discovery of a very useful tranquilizer, chlorpromazine. This drug has played a major role in decreasing the number of patient beds in use in mental hospitals for 11 consecutive years. Thus, antihistamines and tranquilizers can trace their history to an ancient remedy, quinine, and its molecular modification.

Chance pharmacologic observations on existing drugs led to many important new drugs and to new uses for old drugs.

Today's new drug research is complex. Industry chemists are engaged in large-scale chemical synthesis programs. Various members of the biomedical research team screen these compounds for activity in animals. The promising compounds are then tested for toxicity and if the mass of data from this screening suggests that the compound is safe and may have utility in the treatment of human illness, a "Notice of Claimed Investigational Exemption for New Drugs" (IND) is filed with the Food and Drug Administration.

I do not want to take the time here to describe in detail the complicated processes of research that lead to new drugs; however, Mr. Chairman, with your permission I would like to submit for the record a chart describing the process.

If I may just make one additional—I should say this chart is one of the best graphic presentations I have seen of the flow of activity in research, development, and preparation for manufacture of a new drug and the preparation of a New Drug Application for submission to the Food and Drug Administration. It was prepared by Eli Lilly's research staff and presented at a hearing of a House of Representatives subcommittee studying drug safety, chaired by Congressman Fountain in June 1964. The chart shows the great complexities faced in the creation of a new drug and the assembly of material submitted as a New Drug Application.[1]

I might point out here that the steps are complex, and they are variable. This chart is not the exact course of every drug. These things flow back and forth. A certain finding in one instance may make it go back to something else and flow around. Nevertheless, it is a very complex process.

Strange as it may seem, few new drug products that our industry makes are ever "finished" as far as laboratory and clinical research are concerned. New analytical techniques are continually developed and applied and other efforts to improve absorption, stability, and clinical effectiveness of many old drugs represent a way of life in research-oriented and quality-conscious companies. These usually include more elaborate testing and specifications than appear in the U.S. Pharmacopeia and National Formulary, which are chemical descriptive documents. Clinical research continues to be sponsored by research-oriented companies on many old drugs even though the products have been on the markets for years.

The 1962 amendments to the Federal Food, Drug, and Cosmetic Act have had the effect of increasing greatly the testing required before a new pharmaceutical can be marketed, increasing substantially the risk connected with administrative decisions concerning the continued investigation and marketing of products, and enlarging greatly the period between investments made in research and the beginning of any monetary return—to keep the cycle of research trial going with its many failures and only occasional successes.

If we are to make additional progress, industry must be allowed to continue to fulfill the role it has succesfully performed up to now—namely, synthesizing and experimenting, conducting the long and costly process of screening, the preclinical testing, development of production and quality control procedures, and finally the long clinical trials leading to accumulation of data showing the safety and effectiveness of drug products.

I hope that we will always keep our academic-Government-industry science teams working together, because doing so will lead to major new health benefits.

Dr. Van Riper will follow me and discuss clinical testing. This is his area of specialty.

Senator NELSON. Thank you for your fine statement. I have some notes on questions to be asked. I think what we had better do is get all the testimony in the record and if we have some time we will go back.

(The attachments to Dr. Scheele's statement follow:)

[1] See chart, p. 2352, infra.

ETHICAL PHARMACEUTICAL INDUSTRY OPERATIONS AND RESEARCH AND DEVELOPMENT TRENDS 1960-1966

A Report Based Upon PMA Annual Surveys of Member Firms

Pharmaceutical Manufacturers Association
Office of Economic Research

ETHICAL PHARMACEUTICAL INDUSTRY OPERATIONS AND RESEARCH AND DEVELOPMENT TRENDS 1960 - 1966

This report encompasses key results of a number of PMA analyses of prescription drug manufacturers' operations. Surveys have been conducted annually since 1960, dealing mainly with sales and research and development activities of member companies. The last two reports in the series, "Manufacturers' Sales of Ethical Pharmaceuticals, 1965" and "Pharmaceutical Industry Research and Development Activity, 1965-1966," were distributed to member firms in the fall of last year.

The present study is designed to serve as a link between earlier trend data and projected studies. It summarizes previous findings and incorporates, for the first time, detailed analyses of quality control activities and fields of research. When used in conjunction with forthcoming PMA reports this study should be a useful tool to member company executives in their planning and decision making functions.

In preparation is a more detailed review of 1966 operations, scheduled for release within the next few months.

Prepared by:

Office of Economic Research

Howard L. Binkley, Director
M. Erol Caglarcan, Economist

March 1967

INTRODUCTION

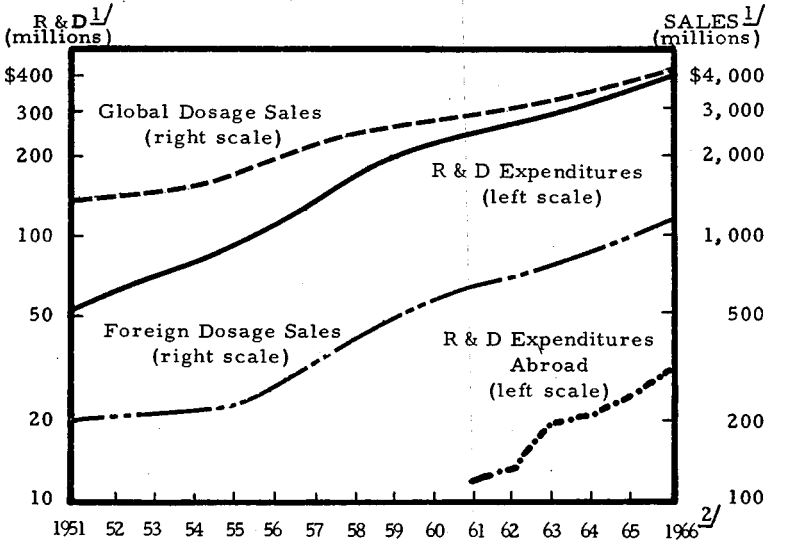
The ethical pharmaceutical industry has experienced a faster growth than many other sectors of the economy. Between 1951 and 1965 dosage sales of ethical drugs grew 35 percent faster than the national output of all goods and services.

New and therapeutically more effective drugs have paved the way for the ethical drug industry's rapid growth. It is estimated that the industry has invested some $7 million in research and development costs for every new and significant drug that has reached the public in the past decade. The industry continually invests in the future. While sales doubled in the 15-year period shown in Chart 1, research and development expenditures increased sixfold.

A significant portion of every sales dollar is devoted to drug research activities. For instance, in 1965 companies sponsoring research allocated 10.5 percent of their U.S. domestic and export sales revenue to R&D activities directed toward the discovery and development of human-use and veterinary-use pharmaceuticals and biologicals.

Chart 1

Growth Picture of Ethical Drug Sales and Research & Development



1/ Plotted on semi-logarithmic grid. 2/ Estimated.

PART ONE: OPERATIONS

HIGHLIGHTS OF 1965 OPERATIONS[1]

Sales: In 1965, global ethical pharmaceutical sales by U. S. firms rose to $4.2 billion, 13.5 percent more than in 1964. Sales in the United States increased 13 percent, while foreign sales of U. S. manufacturers increased 15 percent.

Product Classes: Central nervous system drugs ranked first in dollar sales volume in 1965. This group also registered the greatest increase, $88 million, from the preceding year.

Market Shares: No single company had as much as seven percent of domestic sales of prescription drugs. The 13 largest manufacturers accounted for only 62 percent of the U. S. market.

Customers: Manufacturers sold approximately half of their dosage form products directly to ultimate dispensing outlets and government agencies and the other half via wholesale channels.

Taxes: Producers of ethical pharmaceuticals paid a record $559 million in taxes for 1965, 73 percent of which went to U. S. Federal taxes. Firms averaged an outlay of 13 cents in taxes for each sales revenue dollar.

Employment: 1965 employment of the U. S. industry totaled one hundred ninety-three thousand, 120,500 in the United States and 72,500 abroad.

Quality Control: Quality control operations involved over 7,000 full-time employees and at least $74 million in expenditures in 1965.

Manufacturing Plants: Fifty-two PMA members operated 338 plants throughout the world, 232 abroad and 106 in the United States.

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[1] The following data, unless indicated to the contrary in the text, have been extrapolated to represent the entire industry based on the estimate that PMA member companies account for 95 percent of the ethical drug industry's U. S. sales of dosage form products for human use.

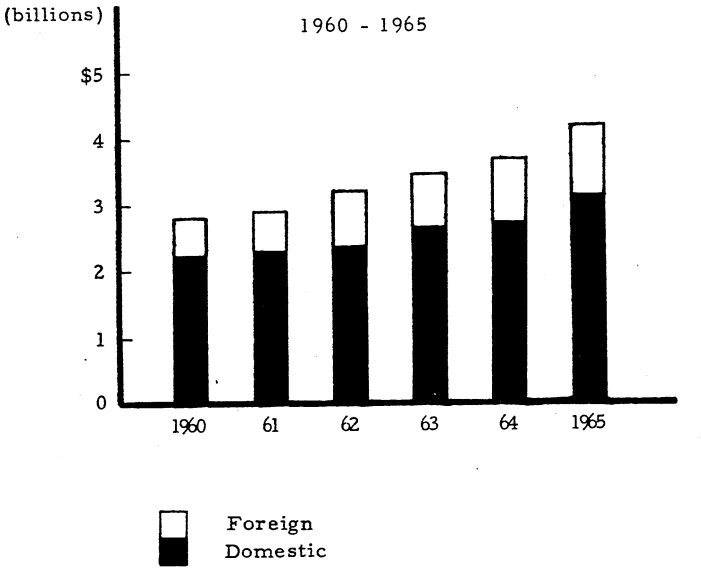
SALES

Prescription product sales have increased annually for the past two decades. Between 1960 and 1965, worldwide sales rose 48 percent (see Chart 2). The increase in 1965 was 13.5 percent.

Chart 2

Domestic and Foreign Sales

1960 - 1965



SIX YEAR GROWTH TREND, 1960-1965

The relatively steep upward trend has been dominated by sales abroad, going up 70 percent in the 1960-1965 period. Thus, foreign sales continued to gain a more prominent share of U.S. companies' global sales, rising from 23 percent of the total in 1960 to 26 percent in 1965. The relative share of exports as percent of total foreign sales declined in every one of the six years between 1960 and 1965, from 13 percent in 1960 to six percent in 1965.

Table 1

MANUFACTURERS' SALES, 1960-1965
(millions of dollars)

Destination	1960	1961	1962	1963	1964	1965
Domestic	$2,201	$2,259	$2,480	$2,604	$2,763	$3,121
Private	2,111	2,147	2,354	2,468	2,614	2,876
Government	90	112	126	136	149	245
Foreign[1]	646	733	756	865	955	1,098
Export	81	79	66	56	62	66
Abroad	565	654	690	809	892	1,032
TOTAL	$2,847	$2,992	$3,236	$3,469	$3,717	$4,219

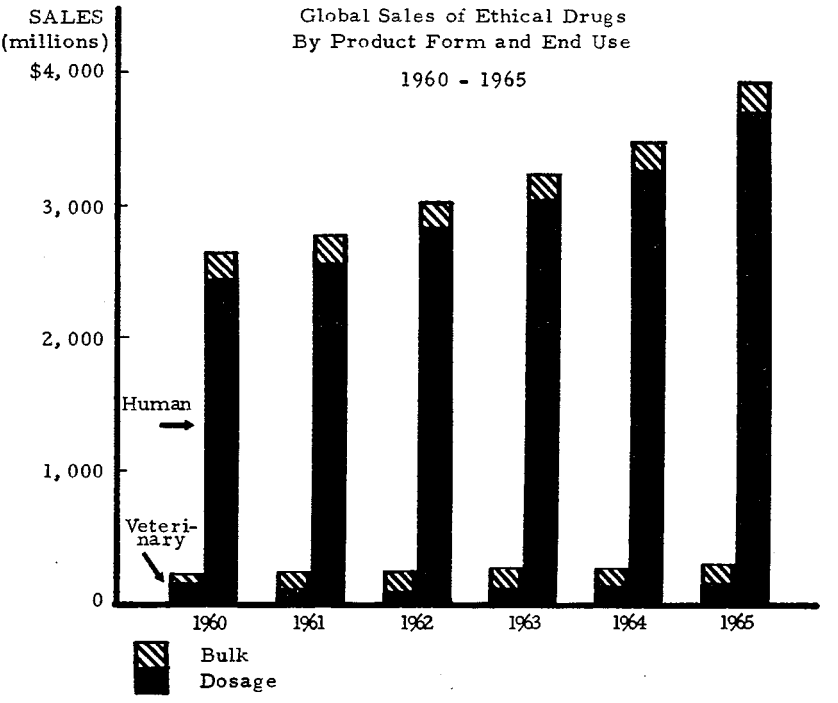
[1] Intra-company exports to foreign subsidiaries (not shown separately in Table 1) are included in "sales abroad". Two-thirds of the 1965 total transfers of $115 million were in bulk form.

PRODUCT FORMS AND END USE

Global Sales: Ninety-three percent of manufacturers' 1965 sales were in products intended for human use. Veterinary drugs accounted for the remaining seven percent. Ratios have remained relatively unchanged in the last several years. Ninety-four percent of the 1965 ethical drug sales for human use were in dosage form. Dosage-form and bulk-form products equally shared the 1965 veterinary drug market.

U.S. Sales: Bulk sales made up 57 percent of the veterinary market in 1965. However, importance of veterinary sales in bulk form increased only in recent years. For instance, while in 1960 bulk products accounted for one-third of total veterinary sales, every year since then they have accounted for more than half. In contrast, during the same period dosage-form products for human use have consistently accounted for 95 percent.

Chart 3



Foreign Sales: Sales abroad made up 94 percent of the foreign sales total in 1965. Exports from the United States accounted for the rest. In 1965, drug products for human use dominated the export sales as well as the drug sales overseas. Most of the 1965 foreign sales revenue was obtained from dosage-form products.

Table 2

ETHICAL DRUG SALES, [1] 1965
(millions of dollars)

Product Form and End Use	Domestic [2]	Foreign [3]	Total
Dosage form: human	$2,779.3	$ 929.8	$3,709.1
Dosage form: veterinary	76.6	55.7	132.3
Bulk: human	161.1	68.7	229.8
Bulk: veterinary	104.1	43.5	147.6
TOTAL	$3,121.1	$1,097.7	$4,218.8

[1] Sales are before deducting cash discounts and other marketing expenses, but after returns and allowances (domestic returns and allowances totalled $86.3 million in 1965). Export sales are f. o. b. port. The majority of the firms reported most sales were made f. o. b. purchaser's location or equivalent.

[2] "Domestic sales" are "gross" at invoice price. For "f. o. b. manufacturers' plant" totals, deduct $81.7 million ($37.2 million transportation out and $44.5 million company branch or field warehousing).

[3] "Foreign sales" refer to exports and sales in a foreign area by subsidiary or other corporate operations.

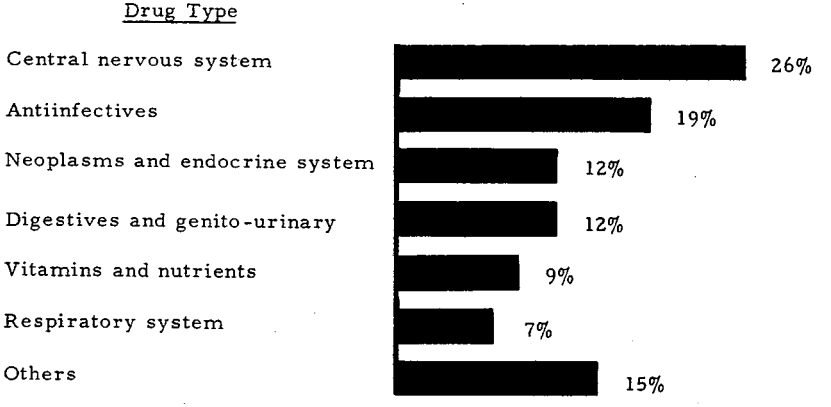
PRODUCT CLASSES[1]

Growth: Fifty-eight PMA members, accounting for 90 percent of the industry's sales, reported a 12 percent sales increase in 1965, a growth rate considerably higher than the eight percent growth between 1963 and 1964. The detailed product data in Table 3 are based on an analysis of these firms' reports.

From 1963 to 1964 the sales volume of drugs affecting neoplasms, endocrine systems and metabolic diseases increased 24 percent. However, the rate slowed down to 5.6 percent from 1964 to 1965. While sales of respiratory drugs rose the fastest in 1965, the greatest increase in sales revenue came from central nervous system products and anti-infectives, $88 million and $65 million respectively. These two product groups accounted for almost half of total sales in 1965 (see Chart 4).

Chart 4

1965 Sales, Product Group Percentages



[1] Unlike most sections of this report, the following analysis does not represent the entire industry and is based on reports received from 58 PMA members.

Competition: For purposes of analysis the entire human use drug market was divided into 11 product classes. Not all firms were active in every product market. The number of companies varied from a minimum of ten actively competing for the diagnostics market to 50 for the digestive, genito-urinary and central nervous systems product classes. Approximately one half of the companies with annual sales in excess of $5 million depended upon one product class for more than half of their annual sales revenues.

Biologicals: Sales of biologicals for human use continued to drop in 1965. There had been a 30 percent decline in reporting members' biological sales between the end of 1963 and 1965. Only 15 PMA members reported continued production of biologicals for human use during 1965. In 1964 the number of producers was 20. During 1965 five companies ceased production of biologicals altogether.

Volume of biological sales dropped from $98 million in 1963 to $74 million in 1964 to $68 million in 1965. Between 1964 and 1965 six companies experienced an $11.3 million drop. When added to the $2.6 million sales production on the part of the five firms that dropped biological production, this amounts to a sales decline of $13.9 million for the year. However, this was partially offset by a $7.8 million revenue gain sustained by seven other manufacturers.

Table 3

SALES BY PRODUCT CLASSES, 1963-1965

U.S. Sales of Dosage Form Ethical Drugs for Human and Animal Use
(millions of dollars)

For Human Use	1963	1964	1965	Growth 1964-65	Number of Firms Reporting 1965 data
(a) Drugs for central nervous system and sense organs	$ 534.5	$ 576.6	$ 664.5	15.2%	(50)
(b) Drugs affecting parasitic and infective diseases	400.0	424.1	489.1	15.3	(43)
(c) Drugs for neoplasms, endocrine system and metabolic diseases	226.6	280.3	296.9	5.6	(41)
(d) Drugs acting on digestive or genito-urinary systems	288.7	290.3	294.6	1.5	(50)
(e) Vitamin, nutrients and hematinic drugs	192.3	215.7	224.1	3.9	(46)
(f) Drugs acting on respiratory system	135.8	148.1	173.9	17.4	(45)
(g) Drugs acting on cardiovascular system	135.0	143.4	168.1	17.3	(40)
(h) Biologicals	97.9	74.0	67.9	-8.2	(15)
(i) Drugs acting on skin	51.4	40.5	45.5	12.3	(43)
(j) Diagnostic agents	*	*	26.8		(10)
(k) Other pharmaceutical preparations	28.1	53.5	66.8	24.9	(26)
TOTAL	$2,090.3	$2,246.5	$2,518.2	12.1%	(58)
For Animal Use					
(a) Pharmaceutical preparations	$ **	$ 52.9	$ 58.2	10.0%	(21)
(b) Biologicals	**	18.3	18.4	0.5	(13)
TOTAL	$ 65.6	$ 71.2	$ 76.6	7.6%	(22)

* In 1963 and 1964 some diagnostic sales were included in other pharmaceutical preparations.
** No breakdown available.

MARKET SHARES

The number of leading ethical drug producers with individual global sales volume exceeding $100 million increased from 12 in 1964 to 13 in 1965. In 1962 this sales class consisted of only ten manufacturers. This expansion in number was reflected in a larger share of the domestic market attributable to this group.

Table 4

MARKET SHARES BY SALES SIZE GROUP, 1965
Percentage

	Sales		
Sales Group	U.S.	Foreign[1]	Total
$100 million and over	61.7%	87.6%	68.5%
$30 to $100 million	21.3	8.7	18.0
$5 to $30 million	13.3	3.5	10.7
Less than $5 million	3.7	0.2	2.8
TOTAL	100.0%	100.0%	100.0%

[1] U.S. firms' sales abroad plus U.S. exports to other companies for sale abroad.

In 1965 wholesalers accounted for 48 percent of manufacturers' domestic sales of ethical drug products in dosage form (see Table 5). The remainder was made directly to retailers, hospitals and other outlets (see Table 6).

Table 5

SALES BY CLASS OF CUSTOMER, 1965
Manufacturers' Direct Dosage Form Sales in the U. S.

Customers	Value (millions)	Percent of Total
Wholesalers	$1,344.5	48.4%
Retailers	840.4	30.2
Private Hospitals	287.9	10.4
State and Local Government Hospitals	138.2	4.9
Federal Government Hospitals	83.6	3.0
Federal Government, Other Than Hospitals	22.1	0.8
Practitioners, Private Medical and Dental	41.0	1.5
Manufacturers and Repackagers	2.6	0.1
All Other Direct Sales	19.0	0.7
TOTAL	$2,779.3	100.0%

Table 6

DISTRIBUTION OF DIRECT SALES, BY SIZE OF FIRM, 1965

Customers	Sales Group over $100 million	$30-$100 million	$5-$30 million	Less than $5 million	Average, All Firms
Wholesalers	$ 35.70	$ 65.60	$ 72.30	$ 66.20	$ 48.40
Retailers	41.70	14.40	9.30	13.40	30.20
Non-Federal Hospitals	16.40	15.30	10.90	12.20	15.30
Federal Government[1]	3.70	4.10	4.40	2.20	3.80
Practitioners	1.40	0.50	2.70	5.40	1.50
Other	1.10	0.10	0.40	0.60	0.80
TOTAL	$100.00	$100.00	$100.00	$100.00	$100.00

[1] Including federal hospitals.

Distribution by Size of Manufacturer: There appears to be an inverse relationship between the size of the firm and its sales via wholesalers. Table 6 shows that in 1965, on the average a manufacturer in the $100 million and over yearly sales group distributed via wholesalers $35.70 worth of drugs for every $100 of manufacturer's business. The remainder was sold directly to various dispensing outlets. Smaller manufacturers sold a greater proportion of their products via the wholesaler (see Chart 5).

Chart 5

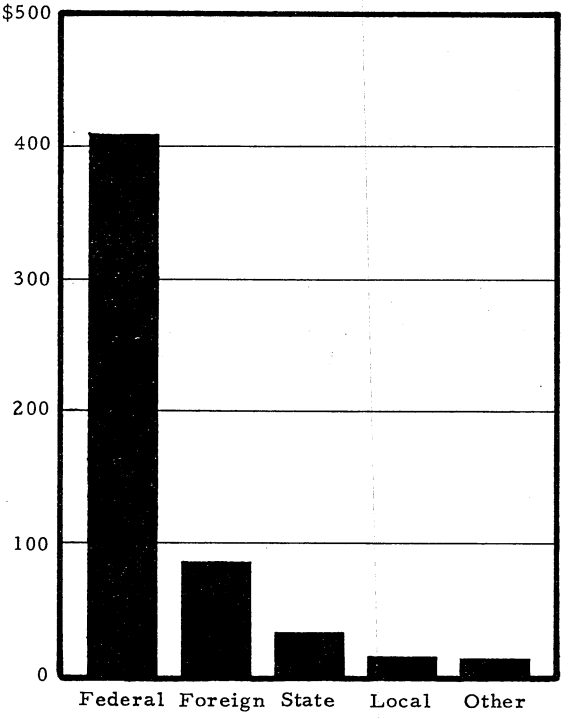
Manufacturers' Direct Sales Market
For Each $100 Sold, By Size of Firm, 1965

TAXES

A total of $559 million was paid in taxes for 1965 by ethical drug producers. Of this sum nearly three-quarters was paid by the thirteen largest manufacturers who produce 62 percent of the nation's total prescription drug output. The Federal Government received 73 percent of all the taxes paid by ethical drug manufacturers for 1965.

Chart 6

Manufacturers' Taxes and Excises, 1965
(millions)



EMPLOYMENT

Global prescription drug manufacturing employment for U. S. corporations and the U. S. -based subsidiaries of foreign companies reached 193,000 during 1965. Approximately one-third of the total was employed abroad. The industry employed 120,500 persons in the United States — three percent over the 1964 figure of 117,500. Production workers comprised 46,200 of the domestic working force.

Table 7

EMPLOYMENT, 1965

United States	120,535
Foreign	72,510
TOTAL	193,045

The 13 firms with more than $100 million in sales employed 60 percent of the working force. Eighteen percent was attributable to concerns grossing between $30 to $100 million in sales. Companies with sales under $30 million employed 22 percent.

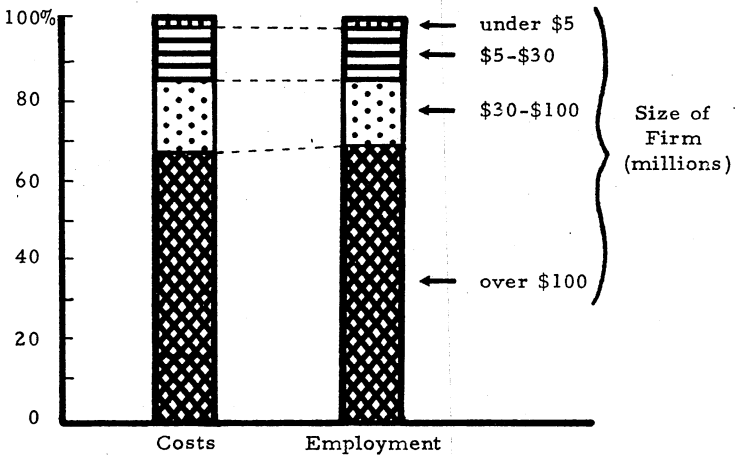
QUALITY CONTROL

Quality control is a vital, continuous process to assure the desired result when the pharmaceutical product is used by the consumer. Quality control is the sum total of all the planning, testing and supervision involved in this process.

Survey data pertaining to the control of physical product quality encompass all employees responsible for sampling and testing of materials as they are received, produced or stored. [1] Investigation of complaints, disposition of returned goods, selecting and weighing of components, proper sanitation, storage of raw and finished materials, and inspection of labels, contents and packages are all fibers of the complex quality control procedures that govern product excellence.

Chart 7

Quality Control
Costs and Employment, 1965



[1] The analysis in this section was made on the basis of data received from 64 major PMA members with 1965 sales volumes in excess of $1 million.

The data reported here includes quality control in production. For a responsible firm, however, quality control goes well beyond this to establish an excellence in quality of operation which has been called "company total-value product". [1] This represents activities designed to assure quality of product and service which surpasses normal standards.

Direct and Indirect Quality Control: "Direct quality control" employment and cost data deal with full-time staff members of reporting companies' quality control departments. But since almost all production employees have some quality control functions incidental to their primary assignments, estimates were solicited from member firms on "indirect quality control" employment and costs. Employment data on such individuals is stated in terms of full-time equivalents, prorated by respondents on the basis of hours devoted to quality control functions as a share of total labor time.

Company Allocations: Table 8 shows that quality control costs during 1965 amounted to at least $73.8 million. Primary quality control accounted for three-fourths of the total cost incurred by all firms. Companies with yearly sales exceeding $100 million were responsible for approximately two-thirds of all quality control costs and employed a higher proportion of quality control workers -- a ratio larger than their share of the market (see Chart 7).

Average Quality Control Costs: As Table 9 demonstrates, average quality control spending per company was $1.2 million in 1965. However, quality control costs were much higher for the leading firms. On the average, responding firms allocated 2.4 percent of their 1965 domestic sales revenue to quality control. However, quality control cost-to-sales ratios ranged up to 7.5 percent.

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[1] Responsible pharmaceutical concerns commit themselves to expenditures and accomplishments in creative research, reliable production and marketing, and high standards of management. These organizations are motivated to provide excellence in total quality of product and service. Such total control of quality of product and service is of significant value to dispensers and consumers of prescription medicines, exceeding by far the value of the product's ingredients.

Table 8

QUALITY CONTROL COSTS BY SALES GROUP, 1965

Sales Group	Number of Firms	Total Cost		
		Direct	Indirect	Total
		(thousands of dollars)		
$100 million and over	13	$38,880	$10,875	$49,755
$30 to $100 million	14	9,355	4,015	13,370
$5 to $30 million	27	7,970	2,300	10,270
Less than $5 million	10	395	15	410
TOTAL	64	$56,600	$17,205	$73,805

Table 9

AVERAGE QUALITY CONTROL EXPENDITURES PER COMPANY BY SALES GROUP, 1965

Sales Group	Number of Firms	Expenditures Per Company		
		Direct	Indirect	Total
		(thousands of dollars)		
$100 million and over	13	$ 2,990	$ 835	$ 3,825
$30 to $100 million	14	670	285	955
$5 to $30 million	27	295	85	380
Less than $5 million	10	40	2	42
Average, All Firms	64	$ 885	$ 270	$ 1,155

Quality Control Employees: In 1965, sixty-four pharmaceutical manufacturers employed more than 7,000 people in their efforts to maintain high product quality. Such duties were the principal concerns of 75 percent of these employees. The other 25 percent had additional responsibilities in conjunction with their quality control work (see Table 10).

Table 10

QUALITY CONTROL EMPLOYMENT BY SALES GROUP, 1965

Sales Group	Number of Firms	Total Employment		
		Direct	Indirect	Total
$100 million and over	13	3,695	1,260	4,955
$30 to $100 million	14	805	390	1,195
$5 to $30 million	27	760	180	940
Less than $5 million	10	55	5	60
TOTAL	64	5,315	1,835	7,150

Ratio of Quality Control Employees to Total Employment: Table 11 indicates that one production employee in eight was directly engaged in the quality control process. Persons connected with this phase of production comprised 17 percent of the manufacturing staff and six percent of the U.S. employment total. The 13 largest firms had higher ratios.

Table 11

QUALITY CONTROL EMPLOYMENT AS PERCENT OF PRODUCTION WORKERS AND ALL EMPLOYEES BY SALES GROUP, 1965

Sales Group	Number of Firms	Percentage of Production Workers Engaged in Quality Control		Percentage of All Employees Engaged in Quality Control	
		Direct	Direct and Indirect	Direct	Direct and Indirect
100 million and over	13	13.6%	18.2%	5.1%	6.8%
30 to $100 million	14	11.0	16.3	3.7	5.5
ess than $30	37	10.3	12.6	4.9	6.1
verage, All Firms	64	12.5%	16.9%	4.8%	6.5%

Average Quality Control Employment: On the average, each of the reporting 64 PMA members had in its employ 112 quality control workers, 83 of whom performed quality control activities as their primary assignments (see Table 12). On the average, a company with annual global sales exceeding $100 million employed 284 full-time persons in direct quality control activities. Their activities were supplemented by many other workers who attended to other responsibilities as well. When prorated, time spent in quality control activities by such part-time people meant an additional 97 full-time workers with quality control functions.

Table 12

AVERAGE QUALITY CONTROL EMPLOYMENT PER COMPANY BY SALES GROUP, 1965

Sales Group	Number of Firms	Employment Per Company		
		Direct	Indirect	Total
$100 million and over	13	284	97	381
$30 to $100 million	14	57	28	85
Less than $30 million	37	22	5	27
Average, All Firms	64	83	29	112

MANUFACTURING PLANTS

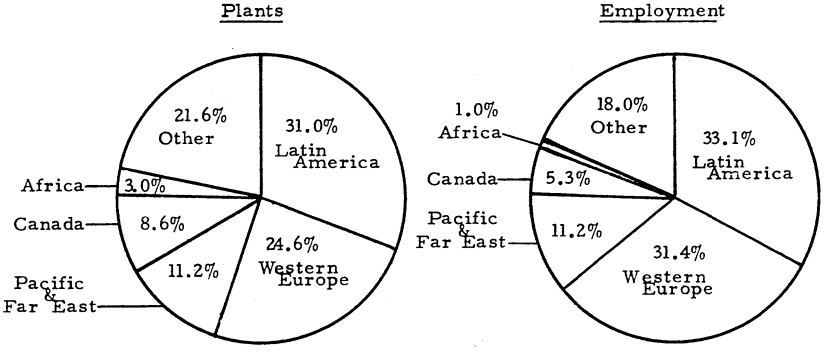
Fifty-two PMA members, accounting for four-fifths of the industry's United States employment and a slightly higher ratio of total domestic and export sales, reported production plant locations and related employment data for 1965. Domestic operations were scattered throughout 27 states. Manufacturers reported 232 plants abroad—more than double the 106 U. S.-based plants.

On the average, one out of every three employees was located abroad. Domestic concerns averaged 345 production workers per plant as compared to 105 for each foreign plant. United States manufacturing plants averaged 625 total employees; overseas plants employed an average of 170 persons.

Foreign Manufacturing Plants: Respondent firms employed 90 percent of all persons working in the U. S. companies' ethical drug facilities abroad. An average of 60 percent of the personnel employed abroad worked in production plants.

Chart 8

Regional Distribution of
Foreign Plants and Employment, 1965



Latin America accounted for almost one-third of the foreign plants (see Chart 8). With 25 percent, Western Europe ranked second. Twenty-six plants were located in the Pacific and Far East region, accounting for 11 percent of the total abroad. Canada and Africa represented nine percent and three percent respectively. The remaining 21 percent is not classified (see footnote, page 26).

Latin America and Western Europe were the leaders in employment among regions with a combined total of 25,560 employees (amounting to 65 percent of the total abroad). The average number of employees per plant in Latin America was 180 as compared to 220 for Western Europe. These averages exceeded the over-all overseas average of 170 per plant site. The Pacific and Far East region equaled the norm of 170. However, Canada with 105 and Africa with 60 employees per plant fell below the median.

Of the individual countries, the United Kingdom had 19 plants and ranked highest for total number of employees (6,415), yet it had one plant less than third-ranking Mexico with total employment of 3,075. Brazil placed second in employment with 4,275 persons, employed at eight plant locations.

Table 13

FOREIGN MANUFACTURING PLANTS OF U. S. FIRMS AND RELATED EMPLOYMENT, 1965[1]

Region and Country	Number of Plants[3]	Employment[2]		
		Production	Other	Total
LATIN AMERICA				
Brazil	8	1,665	2,610	4,275
Mexico	20	1,525	1,550	3,075
Argentina	11	1,670	1,190	2,860
Colombia	10	655	590	1,245
Venezuela	6	245	120	365
Peru	4	135	150	285
Chile	3	140	30	170
Panama	3	55	40	95
Puerto Rico	3	510	70	580
Other[4]	4	110	70	180
Regional Total	72	6,710	6,420	13,130
WESTERN EUROPE				
United Kingdom	19	3,885	2,530	6,415
Germany	9	880	525	1,405
France	9	755	435	1,190
Italy	8	645	490	1,135
Spain	4	1,000	75	1,075
Belgium	3	420	70	490
Other[5]	5	390	330	720
Regional Total	57	7,975	4,455	12,430
PACIFIC & FAR EAST				
Australia	10	990	590	1,580
India	4	1,005	365	1,370
Pakistan	3	220	100	320
Philippines	3	190	120	310
Other[6]	6	530	325	855
Regional Total	26	2,935	1,500	4,435
CANADA	20	1,025	1,090	2,115
AFRICA	7	270	135	405
UNCLASSIFIED[7]	50	5,430	1,685	7,115
TOTAL	232	24,345	15,285	39,630[8]

Footnotes for Table 13 on page 26.

U. S. Manufacturing Plants: Fifty-seven respondents, accounting for four-fifths of the industry employment within the United States, provided statistical information on plant locations and related employment. These firms reported 66,500 employees located in 106 plants, an average of 625 workers per plant. It is estimated that there were an additional 20,300 people employed in numerous smaller plants of companies that did not respond to this survey.

Footnotes for Table 13, page 25:

1/ 52 reporting companies.

2/ Data deal only with respondent firms' employment within manufacturing plants. Sixty percent of total drug industry personnel abroad work in plants. The other 40 percent are housed outside of plants.

3/ Countries are listed by region in descending order by number of employees with the exception of "other" and "unclassified".

4/ Includes plants in Uruguay (1) and other Latin American countries (3).

5/ Includes plants in Turkey (2), Netherlands (1), Ireland (1), and Austria (1).

6/ Includes plants in Japan (2), Thailand (1), New Zealand (2), and Taiwan (1).

7/ Includes 50 plants not specifically classified by country. It is estimated that there are at least 50 additional U. S. owned ethical drug plants in various foreign countries. PMA received only limited data on these manufacturing facilities and was unable to classify them in the above manner.

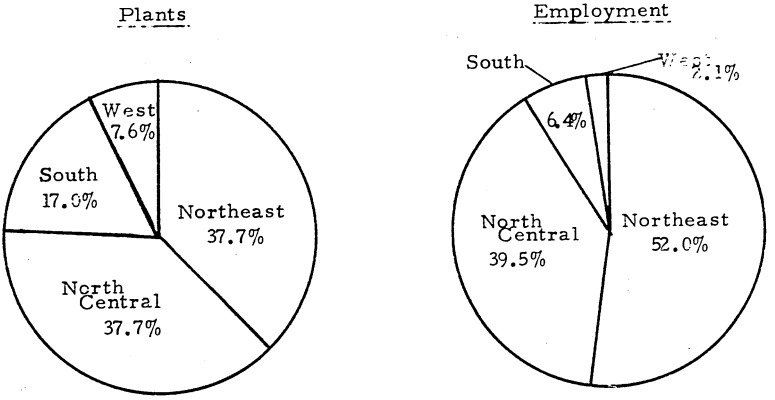
8/ An additional 33,000 people are employed in U. S. companies' ethical drug production plants and administrative offices abroad.

Smaller firms concentrated entire operations in the manufacturing plant. On the average 72 percent of the employees worked at the production facility locations. However, this ratio was inversely related to firm size. While firms with annual global sales exceeding $100 million maintained 69 out of every 100 employees in production plants, firms with annual sales less than $5 million averaged 92 employees.

Several multi-unit companies housed their marketing, research and other administrative staff outside of manufacturing establishments. However, a large number of administrative personnel were located in manufacturing facilities and accounted for 45 percent of total employment at the plant site.

Chart 9

Regional Distribution of
U. S. Plants and Employment, 1965



The responding companies reported 40 production plants in the Northeast region. An equal number of manufacturing facilities was located in the North Central region. Plants in the Northeastern states were relatively larger, and accounted for more than half of the total employment reported (see Chart 9). These establishments also had a higher average ratio (one to one) of administrative personnel to production workers.

On the average, a plant located in one of the Northeastern states employed 865 people. The average for the North Central region was 655. Pharmaceutical plants in the South and the West were relatively smaller -- averages per plant were 275 and 170, respectively. Additionally, these plants concentrated mostly on manufacturing, employing a higher percentage of production workers -- 70 percent.

In a separate survey (see Table 30) New Jersey and New York emerged as the leading industrial drug research centers of the nation. This survey indicated that New Jersey and New York were also the leading production centers of the country in 1965 and jointly accounted for two-fifths of all production and other employees. While Pennsylvania ranked third as a drug research center, it had a smaller number of production workers than each of the states of New Jersey, New York, Indiana, Michigan, and Illinois.

Footnotes for Table 14, page 29:

1/ 57 reporting companies.

2/ Analysis is based on data furnished by respondents on manufacturing plant employment.

3/ States are listed in each Census Region in descending order by number of employees with the exception of "other".

4/ Includes plants in Connecticut (1), Massachusetts (1), and Rhode Island (1).

5/ Includes plants in Kansas (1) and Minnesota (1).

6/ Includes plants in South Carolina (2), Mississippi (1), Tennessee (1), Arkansas (1), Georgia (1), North Carolina (1), Maryland (1), and West Virginia (1).

7/ It is estimated that the industry employs an additional 18,000 - 20,000 people in various other ethical pharmaceutical plants in the United States.

Table 14

U. S. MANUFACTURING PLANTS AND RELATED EMPLOYMENT, 1965 [1]

Region and State	Number of Plants [3]	Employment [2]		
		Production	Other	Total
NORTHEAST				
New Jersey	16	6,795	8,150	14,945
New York	13	6,925	5,710	12,635
Pennsylvania	8	3,330	2,805	6,135
Other [4]	3	750	115	865
Regional Total	40	17,800	16,780	34,580
NORTH CENTRAL				
Indiana	8	5,360	5,335	10,695
Illinois	5	3,340	3,390	6,730
Michigan	8	4,090	1,520	5,610
Ohio	5	1,005	815	1,820
Missouri	4	270	290	560
Wisconsin	3	185	165	350
Nebraska	5	255	70	325
Other [5]	2	105	80	185
Regional Total	40	14,610	11,665	26,275
SOUTH				
Virginia	5	535	510	1,045
Texas	4	350	260	610
Other [6]	9	2,120	495	2,615
Regional Total	18	3,005	1,265	4,270
WEST				
California	7	880	355	1,235
Other	1	85	40	125
Regional Total	8	965	395	1,360
TOTAL	106	36,380	30,105	66,485 [7]

Footnotes for Table 14 on page 28.

SECTION TWO: RESEARCH & DEVELOPMENT

HIGHLIGHTS

EXPENDITURES

MANPOWER

FACILITIES

HIGHLIGHTS OF 1965-1966 RESEARCH AND DEVELOPMENT ACTIVITY[1]

Expenditures: Seventy-seven PMA members, their subsidiaries and affiliates, spent $365 million for research and development during 1965. These firms budgeted an additional $47 million for 1966, 13.4 percent above 1965 expenditures. The firm with the largest company-financed research and development expenditure accounted for nine percent of the total.

Capital Investment: The 1965 value of manufacturers' investment in research and development equipment and facilities was $260 million. In 1965 alone manufacturers spent $60 million for purchases and construction of research and development equipment and facilities.

Basic Research: PMA members allocated 15.8 percent of their total research and development spending to basic research in 1965.

Applied Research and Development: More than half of the applied research and development funds were directed toward the creation of drugs to be effective in three classes; (1) central nervous system and sense organ disorders; (2) parasitic and infective diseases; and (3) neoplasms, endocrine system and metabolic diseases.

R&D Manpower: More than 16,400 research and development personnel were employed in 1965. Approximately one-fourth held a doctoral degree. On the average, firms spent $76,700 to finance the activities of a doctoral-level research worker.

Research and Development Facilities: The major portion of research activity was conducted in company research centers in 20 states and 20 nations. New Jersey, New York and Pennsylvania were the three leading research centers in the United States. And the United Kingdom accounted for more than half of the industry's overseas R&D employment.

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[1] The following PMA analysis is based on data obtained from 77 member firms. Not all 77 firms reported statistics for all parts of the survey questionnaire. Certain sections of the report are based on a smaller sample. This fact should be kept in mind when utilizing these findings in conjunction with figures from Part One: "Operations", which generally relates to total industry operations.

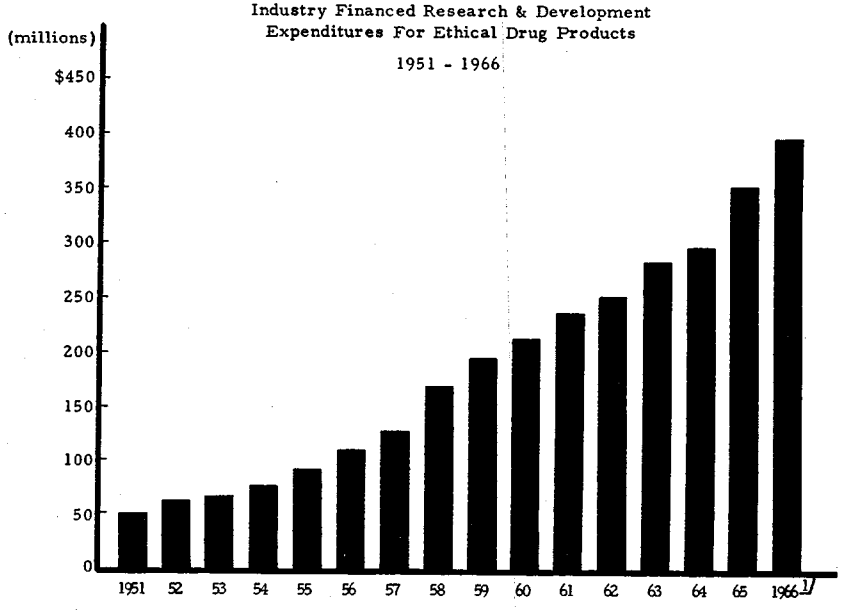
EXPENDITURES

In the 16-year period between 1951 and 1966, the prescription drug industry's funds for research and development amounted to $3 billion. The 1951 expenditures totaled $50 million. By the end of 1966 the annual level had reached $400 million, eight times the 1951 amount (see Chart 10).

Chart 10

Industry Financed Research & Development Expenditures For Ethical Drug Products

1951 - 1966



1/ Estimated.

EXPENDITURES

Company Financed Expenditures: In 1966 manufacturers spent over 92 percent of their funds within the boundaries of the United States. Two-thirds of the eight percent spent abroad was for work conducted within company facilities. Of the company financed 1966 R&D expenditures of nearly $400 million, 87.5 percent was spent for work conducted within company facilities, both in the United States and abroad.(see Table 15).

In 1966, $49 million of company expenditures were for research conducted by outside organizations. Of this $44 million was allotted for research contracted to various groups in the United States. Educational institutions, hospitals and non-profit organizations accounted for $23 million of these funds. Next in importance were private practitioners and consultants. Commercial laboratories and other performers made up the balance.

Research and Development Abroad: While company financed research and development between 1964 and 1965 for the discovery of human-use prescription drugs increased 18 percent domestically, research and development spending abroad rose at a faster rate of 20 percent. Company budgets for foreign research forecast a 24 percent increase in 1966. Manufacturers' allocations for research and development activities in foreign laboratories amounted to $24.5 million in 1965, accounting for 2.6 percent of overseas sales of human-use pharmaceuticals.

Table 15

RESEARCH AND DEVELOPMENT EXPENDITURES, 1965-1966[1]
(millions of dollars)

Company Financed or Conducted R&D	1965 Actual	1966 Budgeted
Company Financed Expenditures for Human Use Drugs:		
(1) Amount spent within firms	$ 285.8	$ 322.3
a. In the United States	266.6	296.6
b. In foreign countries	19.2	25.7
(2) Amount spent outside firms by	$ 42.8	$ 48.8
a. In the United States	37.5	44.0
b. In foreign countries	5.3	4.8
TOTAL, Human Use R&D	$ 328.6	$ 371.1
Company Financed Expenditures for Veterinary Use Drugs:		
(1) Amount spent within firms	$ 21.9	$ 26.7
(2) Amount spent outside firms	$ 0.8	$ 0.9
TOTAL, Veterinary Use R&D	$ 22.7	$ 27.6
Government Grants and Contracts for Company Conducted Drug R&D	$ 13.7	$ 14.1
TOTAL R&D EXPENDITURES	$ 365.0	$ 412.8

[1] The data recorded here represent 77 PMA member firms' R&D costs, accounting for practically all industry-conducted ethical pharmaceutical research. Proprietary drug research is excluded. Such ethical drug research and development work as is conducted by other industrial firms is estimated to be about $12 million.

CAPITAL INVESTMENT[1/]

To facilitate in-house research work, the responding firms spent $60 million for capital investment in 1965, increasing the value of total investment in research facilities and equipment to $260 million (see Table 16). With $36 million, construction of new buildings continued to account for the greatest portion of physical research capital. In 1965, reporting PMA members also purchased $23 million worth of new scientific equipment.

Table 16

CAPITAL INVESTMENT IN RESEARCH AND DEVELOPMENT
(millions of dollars)

Type & Cost of Capital Investment	1965 Additions	Total Investment
Land	$ 0.7	$ 8.6
Building	36.0	225.6
Scientific & technical equipment	22.6	127.6
Other capital investment	7.0	28.9
TOTAL COST	$ 66.3	$390.7
Less: Depreciation	5.9	131.0
Book Value	$ 60.4	$259.7

[1/] This analysis was based on reports received from 49 member firms whose R&D spending accounted for 94 percent of the 1965 total.

DISTRIBUTION OF RESEARCH AND DEVELOPMENT EXPENDITURES

Table 17 displays the breakdown by sales groups of expenditures for each major area of research, as sponsored or conducted by the firms and as allocated between the United States and foreign sectors. In 1965, the leading 13 firms sponsored two-thirds of the total research and development reported. These firms accounted for three-fourths of the research and development conducted in U. S. company laboratories abroad and nearly 90 percent of the total research funds directed toward the discovery of veterinary-use drugs.

Table 17

RESEARCH AND DEVELOPMENT EXPENDITURES BY SALES GROUP SHARE, 1965

Research & Development Expenditures	Sales Group over $100 million	$30-$100 million	$5-$30 million	Less than $5 million	All Firms
Human Use Drugs	64.9%	25.6%	8.4%	1.1%	100.0%
Amount spent within firms	66.2	24.2	8.4	1.2	100.0
In the United States	65.4	24.5	8.8	1.3	100.0
In foreign countries	77.7	19.3	3.0	*	100.0
Amount spent outside firms	55.9	35.0	8.4	0.7	100.0
In the United States	58.8	31.0	9.5	0.7	100.0
In foreign countries	35.8	62.8	1.2	0.2	100.0
Veterinary Use Drugs	89.9	3.7	4.8	1.6	100.0
Amount spent within firms	89.7	3.7	5.0	1.6	100.0
Amount spent outside firms	93.4	3.9	0.9	1.8	100.0
Government Grants & Contracts	76.4	20.8	2.8	*	100.0
Average Distribution	66.9%	24.0%	8.0%	1.1%	100.0%
(Number of Respondents)	(13)	(14)	(25)	(25)	(77)

*Less than .05%

Table 18 represents how a firm in a specific sales group typically allocated its R&D dollar among the organizations performing research; whereas the preceding table indicated the proportion of R&D expenditures accounted for by groups of companies. The table depicts the "typical" allocation of the firm's own R&D dollar for human-use drugs, excluding R&D funds for veterinary-use drugs as well as monies received from the government.

Manufacturers with global sales of $100 million and over perform, intramurally, a larger percent of their research abroad, as compared with other sales groups. Medium-to-small producers direct a larger portion of their funds for projects contracted to outside organizations.

Table 18

RESEARCH AND DEVELOPMENT EXPENDITURES
BY COMPANY SALES, 1965

Company Financed R&D for Human Use Drugs by Performing Organization	Sales Group: over $100 million	$30-$100 million	$5-$30 million	Less than $5 million	Avera All Firm
Amount spent within firms	88.8%	82.2%	84.7%	86.4%	86.7%
In the United States	81.8	77.7	82.2	86.4	80.8
In foreign countries	7.0	4.5	2.5	*	5.9
Amount spent outside firms	11.2	17.8	15.3	13.6	13.3
In the United States	10.3	13.8	15.0	13.2	11.6
Manufacturing & other companies	0.1	0.4	0.3	0.1	0.2
Commercial laboratories	1.2	1.9	2.8	1.2	1.5
Private practitioners, consultants	3.1	4.1	4.5	3.8	3.5
Educational institutions & hospitals:					
Medical schools	2.0	2.5	2.1	6.0	2.2
Other academic institutions	1.0	0.9	0.6	0.7	1.0
Hospitals and clinics	2.1	2.8	3.3	1.0	2.3
Non-profit research institutions	0.6	0.8	1.3	0.4	0.7
Other	0.2	0.4	0.1	*	0.2
In foreign countries, total	0.9	4.0	0.3	0.4	1.7
TOTAL, Human-Use R&D	100.0%	100.0%	100.0%	100.0%	100.0%
(Number of Respondents)	(13)	(14)	(25)	(25)	(77)

*Less than .05%.

SIZE DISTRIBUTION OF R&D BUDGETS

Research and development spending was related to sales group in Table 18. It was observed that medium-to-small producers allocated a comparatively larger share of their R&D funds for projects delegated to outside organizations. In the following, spending patterns are analyzed on the basis of research and development budget size.

In Table 19 companies are classified into seven groups on the basis of their research and development budgets, including monies received from the government: Group A -- $20 million and over; Group B -- $10 to $20 million; Group C -- $5 to $10 million; Group D -- $1 to $5 million; Group E -- $0.5 to $1 million; Group F -- $0.1 to $0.5 million; and Group G -- less than $0.1 million.

Table 19

SIZE DISTRIBUTION OF R&D BUDGETS, 1965

Classification of R&D Budget	Number of Firms	Average Per Company Expenditures[1] (thousands)
A. $20 million and over	6	$24,325
B. $10 to $20 million	7	14,855
C. $5 to $10 million	8	8,000
D. $1 to $5 million	16	2,480
E. $0.5 to $1 million	9	730
F. $0.1 to $0.5 million	18	250
G. Less than $0.1 million	13	40
Average, All Firms		$ 4,745

[1] Total R&D outlays, including monies received from the government.

Table 20

TOTAL RESEARCH AND DEVELOPMENT EXPENDITURES
BY SIZE OF R&D BUDGET, 1965
(thousands of dollars)

Classification of R&D Budget[1]	Number of Firms	Human Use Drugs	Veterinary Use Drugs	Total Company Financed	Government Financed	GRAND TOTAL
A	6	$122,870	$15,530	$138,400	$ 7,565	$145,965
B	7	95,990	5,080	101,070	2,920	103,990
C	8	60,585	670	61,255	2,745	64,000
D	16	38,235	955	39,190	485	39,675
E	9	6,035	515	6,550	--	6,550
F	18	4,630	--	4,630	--	4,630
G	13	510	--	510	--	510
TOTAL	77	$328,855	$22,750	$351,605	$13,715	$365,320

Average Research and Development Expenditures Per Company: Per company spending averaged $4.7 million. However, approximately one-half of the respondents reported R&D budgets of less than $1 million. As Table 21 demonstrates, average expenditures for a Group "A" company exceeded $24.3 million. The company financed most of its R&D work with its own funds. However, on the average, such a firm also received $1.3 million in government funds for R&D contracts.

[1] See page 39, Table 19.

Table 21

AVERAGE RESEARCH AND DEVELOPMENT EXPENDITURES PER COMPANY, 1965
(thousands of dollars)

Classification of R&D Budget[1]	Number of Firms	Human Use Drugs	Veterinary Use Drugs	Total Company Financed	Government Financed	Average, All Firms
A	6	$20,475	$2,590	$23,065	$1,260	$24,325
B	7	13,715	725	14,440	415	14,855
C	8	7,570	85	7,655	345	8,000
D	16	2,390	60	2,450	30	2,480
E	9	670	60	730	--	730
F	18	250	--	250	--	250
G	13	40	--	40	--	40
Average, All Firms	77	$ 4,270	$ 295	$ 4,565	$ 180	$ 4,745

Government Funds for Industry Research: Government financing of industry research accounted for less than four percent of total research activity reported. No government funds were received by firms with budgets of less than one million dollars. More than half was accounted for by firms with budgets exceeding $20 million. About four-fifths was received by PMA members with annual research and development expenditures of $10 million or more.

Research and Development to Sales Ratio: On the average, an R&D performer allocated 10.5 percent of its 1965 sales volume of $40.6 million to research and development. For companies with annual research and development spending exceeding $500,000 the ratio was nearly 11 percent.

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[1] See page 39, Table 19.

Table 22

RELATIONSHIP OF AN "AVERAGE" COMPANY'S OWN RESEARCH AND DEVELOPMENT EXPENDITURES TO SALES BY SIZE OF R&D BUDGET

Classification of R&D Budget [1]	"Average" Company R&D Expenditures [2] (thousands of dollars)	"Average" Company Sales [3] (thousands of dollars)	R&D/Sales Ratio
A	$21,500	$190,110	11.3%
B	13,040	128,990	10.1
C	7,155	57,955	12.3
D	2,390	27,320	8.7
E	685	7,580	9.0
F	250	5,460	4.6
G	40	1,295	3.1
Average, All Firms	$ 4,250	$ 40,620	10.5%

[1] See page 39, Table 19.

[2] Expenditures for company financed R&D work conducted in U. S. laboratories. Excludes monies received from the government. Also excluded are company funds spent abroad.

[3] Domestic sales plus all exports.