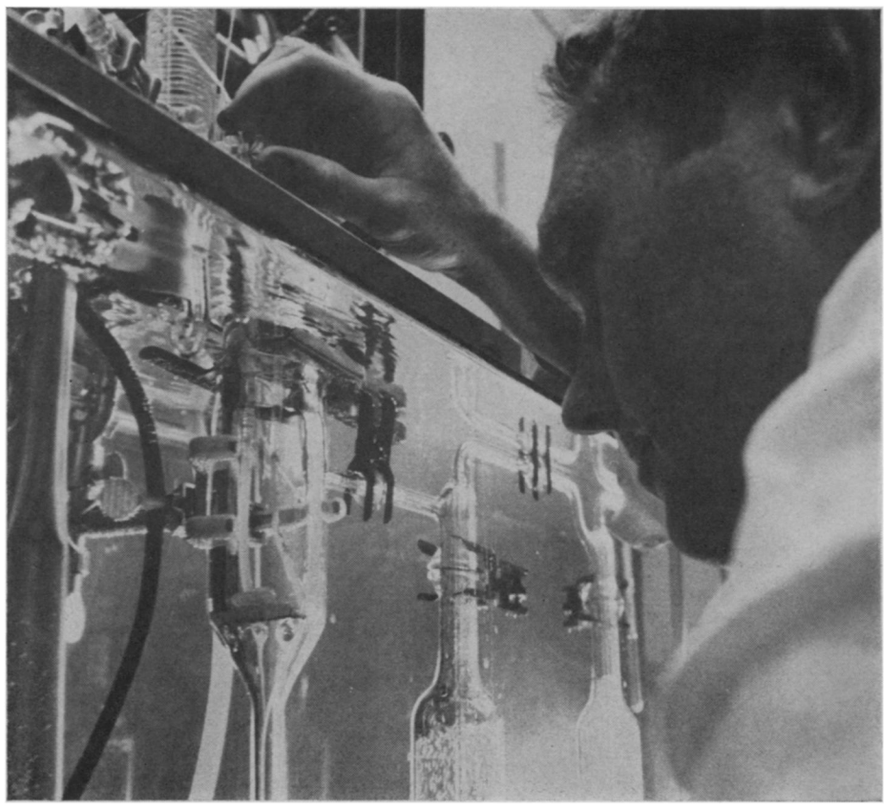
Drug Makers Make A Difference

Supposedly identical drugs differ in subtle ways, and even hand-picked drug makers fail half the time.



Smith Kline and French

Drug behavior is studied in a living segment of rat's small intestine.

by Barbara J. Culliton

All drugs, the law says, must be safe and effective.

The Food and Drug Administration knows whether drugs are safe. It does not always know whether they are effective.

But mounting pressure on Capitol Hill for low-cost generic rather than brand name prescribing may make it imperative that FDA know.

Behind the consumer's desire to buy low-cost generics instead of more expensive brand name drugs is the assumption that the drugs are equal. This assumption is false.

A pill is more than just an amount of an active drug. All kinds of ingredients are mixed with usually small quantities of a chemical to make a tablet or capsule, and these ingredients can be as important to the way it works as the drug itself. There are 32 factors that can significantly alter drug behavior in the body, according to Dr. Max S. Sadove, noted University of Illinois anesthesiologist. Among them are solubility, purity, particle size and even tablet size. Careful control of these variables is the domain of the manufacturer whose skill as a drugmaker is directly related to the uniformity of his product.

It is a tricky business. In one case, the manufacturer of an anticoagulant called Dicumarol found that a number of doctors were prescribing half-doses of the drug. To make things easier for the patient, the company increased the size of tablet so it could be broken in two, but did not increase the active ingredient. Patients who switched from smaller to larger pills suddenly had to take larger doses in order to get the same therapeutic effect. Studies showed the drug dissolved more slowly from the larger tablets.

FDA's Dr. Frances Kelsey suggests a patient on long-term drug therapy learn the manufacturer, size and form of his medicine and get the same thing each time his prescription is filled. It's not necessarily a question of brands being better or worse than generics, she says. It's a question of getting the same thing every time to maintain a consistent level of effectiveness.

Many doctors, having successful experience with a trademarked drug and no facilities to determine equivalency themselves, will continue to prescribe by brand name even though a similar or chemically identical compound may be available at less cost under its generic name. Promotional campaigns by the drug houses also play an undoubted part in brand name prescribing.

Two major bills now before the Senate call for generic naming—and thus lower pricing—of drugs paid for by the Federal Government under its health programs.

Senator Joseph M. Montoya (D-N. Mex.) has introduced legislation to include drugs in Medicare benefits. Senator Russell Long (D-La.) is sponsoring a bill to assure economical drug-buying in all Social Security programs. Both bills would set up an independent Formulary Committee to evaluate brand name and generic drugs to guarantee high quality in those dispensed in Government programs.

FDA Commissioner James L. Goddard, who will become chairman of the Formulary Committee if either bill passes, points out that very few generics would be on the approved list at first. "For one thing," he says, "of the 200 most frequently prescribed drugs, only about 34 have generic counterparts." But the list would surely grow as clinical tests of efficacy are made.

Added fuel for the controversy is expected next month with the publication of "The Handbook of Prescription Drugs" by Richard Burack, M.D., which will list trademarked drugs and their generic counterparts, with manufacturers and prices. The publisher, Pantheon, offers it as a "buying guide designed to help people get prescription drugs cheaper."

Quite apart from the generic vs. trademark struggle, and from the subtle differences that creep in between apparently identical products, the quality of drugs across the board leaves quite a bit to be desired.

Consider the Department of Defense, with its $125 million drug bill each year. It finds itself turning down more than half of the drugs offered it; they

are not good enough for the troops.

Yet these same drugs are freely sold to civilians.

First, DOD inspects the plant of potential bidders. Forty-four percent are rejected for poor quality control or slovenly housekeeping. But these companies sell drugs to the public. Second, DOD tests samples submitted from companies whose houses are clean. Fifty-four percent are turned down for being impure or subpotent. Insects have been found in the drugs offered for sale. Yet drugs from these same manufacturers can be sold to the consumer.

"Military standards are higher than FDA's," Dr. Goddard admits. "We would like to be able to assure doctors that any available drug is good," he said. But FDA can't make this guarantee. And some FDA officials think not all of the nation's 1,200 drug-makers should be in business; as FDA steps up its vigilance, fringe companies will have to either clean up or close down.

At the moment FDA has neither money nor manpower enough to keep tabs on all 1,200. Dr. Goddard says the agency will have to double its staff in 10 years to keep abreast of things, and its eight field offices will have to be automated. Plans are underway to build FDA's St. Louis station into a test center capable of evaluating 150,000 drug samples a year. Today, FDA analyzes only 40,000 samples throughout the country—while the drug industry pours out some $3 billion worth of medicines annually.

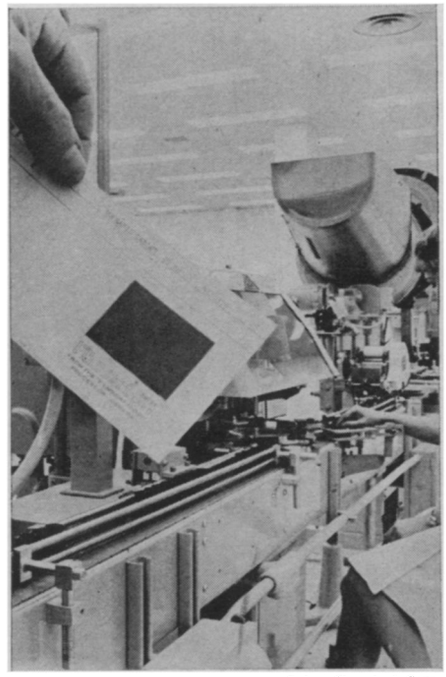
Despite the fact that it leaves them open to charges of bias, and Dr. Goddard himself has expressed his distrust of even the major drug houses, some Federal officials seem to feel that the facts of economic life make the bigger companies the more reliable.

Quality control within drug houses is one step in assuring a consistently high quality product, but efficient quality control requires a working combination of well trained workers and sophisticated equipment. The 12 major houses with annual sales topping $100 million spend as much as $6 million or $7 million a year on physical quality control alone. In 1965, 64 members of the Pharmaceutical Manufacturers Association (whose 140 firms make 90 percent of the drugs sold in the U.S.) reported an outlay of $75 million for quality control. As a result, PMA members are seldom seen on FDA's weekly list of drug recalls of defective products and, according to PMA officials, are seldom, if ever, turned down as unfit by the military. (The military, which keeps its contract lists to itself, refused to comment on this point.)

But quality control and chemical analysis are not enough to test a drug's effectiveness, and are of no help in answering questions about therapeutic equivalency. One brand of vitamins, for example, met all chemical tests, but was wrapped in a coating that failed to dissolve in the stomach. The pills were simply ingested and excreted unchanged. In the case of a heart drug, the size of particles of the active chemical was found to affect the speed with which the drug worked.

Here, clinical tests—actually giving drugs to patients—are imperative, and FDA is moving slowly in this direction. Its first contract for such work was issued a year ago to Georgetown University in Washington, D.C. If the contract's usefulness is proved, Dr. Goddard says, similar efforts may be launched in other hospitals and medical schools.

The only cases in which clinical evidence of efficacy is routinely required now are new drug applications submitted for FDA approval since 1962. Once a new drug is established by usage, other manufacturers of similar products do not have to submit clinical data with their applications, even though subtle manufacturing differences may change the product's action.



Geigy Chemical Corp.

Quality control by computer.

What it all amounts to is that the manufacturer, not the name, of the drug is what counts. Dr. Goddard would like to see FDA begin strict enforcement of Good Manufacturing Practices which were written into the regulations at the time of the Kefauver-Harris Drug Amendments in 1962, but which have never been pushed very hard. When FDA can say every drugmaker in the country follows these quality control practices, the story of drugs in the U.S. will be different.