Medical Science: THE DOCTOR'S WORLD; When Important Drug Is Scarce

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NITROGLYCERIN is one of the oldest drugs in medicine, and despite the development of many newer heart drugs it still serves a vital need. Put under the tongue, nitroglycerin pills are the fastest way to relieve the crushing chest pains of angina that strike hundreds of thousands of heart patients.

Last week a shortage of nitroglycerin pills developed in some cities around the nation after the drug's only maker, Parke-Davis, a division of Warner-Lambert of Morris Plains, N.J., ran into problems with the machinery used to make the pills.

The shortage is expected to end today as drug stores receive 30 million pills that were shipped over the weekend. Nevertheless, it seems surprising that the United States, with the world's most sophisticated drug industry, could run short of a standard drug for a major health problem.

Yet it was the third time in a year that the United States faced a critical shortage of an important drug, said Dr. David A. Kessler, the Commissioner of Food and Drugs. All three shortages are now solved, he said.

One shortage involved two anti-tuberculosis drugs, streptomycin and PAS (p-Aminosalicylic acid). Tuberculosis is now surging in incidence, and for a time the shortage hampered efforts to control the disease.

The other shortage involved sulfadiazine, a drug to treat toxoplasmosis, a parasitic infection of the brain that is a common among AIDS patients.

Such shortages are unusual. But Dr. Kessler was among several medical leaders who said the shortages should be seen as warnings of an important problem.

Because many drugs are made by only one company, a serious manufacturing or financial problem could leave the United States vulnerable to a sudden disruption in the supply of a standard drug.

The Pharmaceutical Manufacturers Association has not studied the problem but may consider doing so, said a spokesman, Jeffrey L. Trewhitt.

Roger Williams, a Food and Drug Administration official who is involved in

the regulation of generic drugs, said he "would not be surprised if every manufacturer had one or two, or maybe a few more, drugs that fell into" the vulnerable category for which the drug agency would fight to protect the nation's supply if problems arose.

Dr. Kessler said his agency had tightened its vigilance over the integrity of drug manufacturing in the last two years. Although the three shortages did not result from violations of Federal regulations, the drug agency's more aggressive surveillance could lead to detection of such violations, threatening to make disruptions more common.

The drug agency's chief responsibility is to review applications for new drugs. The agency does not manufacture or test drugs, and it cannot order drug companies to make a drug.

When a drug is temporarily in short supply, the manufacturer may notify the drug agency, but the agency has no direct power to fix it. The agency's powers are in jawboning, cajoling manufacturers to solve the problem as quickly as possible, and promising expedited reviews of the proposed solutions.

All three shortages involved drugs whose patents had expired. But the problem also concerns new drugs still under patent because most such drugs are made only by the innovating company.

Broader issues emerge from the nitroglycerin shortage. They include: difficulties in making drugs, even old ones like nitroglycerin; difficulties in deciphering trade secrets used by the company that innovated the drug; lack of standards for judging whether a generic drug is equivalent to a previously patented one; small profit margins from low-volume sales of a drug, and consolidation of the drug industry.

It is widely believed that when a drug goes off patent, the monopoly ends, resulting in increased competition and lowers prices. But that is often not the case. Some drugs are still made exclusively by one manufacturer, although they are no longer protected by patent. Many experts say they do not know why that is. When only a few generic companies make a much needed drug, "we need to find out the reasons," said Dr. Raymond Woosley, chairman of the pharmacology department at Georgetown University.

There is an urgent need for more research to insure the wider availability of generic drugs, but there is little incentive for the drug industry to sponsor such work, Dr. Woosley said.

Drug companies spend billions of dollars each year to develop expensive new drugs but only a few million dollars to develop improved cheaper generic drugs.

Yet there is growing concern about the need to find ways to inform doctors about what is the most effective, least expensive drug to treat patients, not what is the most expensive drug that will give the drug company a profit.

Most generic drug companies are not innovators but copiers. The steps needed to get a generic drug on the market can differ significantly from those needed to market the drug in the first place.

Most brand-name drugs are marketed after the sponsors show the drugs are safe and effective in trials. Most generic drugs are marketed after a company provides evidence that the generic drug is biochemically equivalent to the previously patented drug.

Performing clinical studies to prove the benefit of a generic drug takes money and time, and many generic manufacturers do not have the expertise to conduct such studies.

It can be very hard to prove that a generic drug is equivalent to a patented one, Dr. Woosley said. Among the reasons are that scientists have not developed such methods or done the research to come up with standards to show that the old and new drugs are equivalent.

One test is to determine the amount of drug that enters the blood. If the generic and patented drug produce the same blood levels, they are considered bio-equivalent.

An additional factor is how long it takes a drug to be released in the body to exert its pharmacological effect. Standards for such determinations are inadequate, Dr. Woosley said.

Drugs often contain several ingredients, and sometimes experts do not know which ones are the most important.

Many estrogen drugs, for example, contain a mixture of several female hormones. Scientists are not certain which estrogen should be measured to determine that a patented and generic drug are equivalent, Dr. Woosley said.

Another difficult area is determining the bio-equivalence of the metered amount of asthma drugs delivered by inhalers. The asthma drugs are prescribed to widen the bronchial tubes in the lung. But because most of the drug is delivered to the lungs, and little gets into the blood, "we do not know how to test generic and patented bronchodilators to make sure they are equivalent," Dr. Woosley said.

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