

FROM TEST TUBE TO PATIENT:
IMPROVING HEALTH
THROUGH HUMAN DRUGS



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INTRODUCTION

Welcome to the 1999 edition of one of the FDA's most popular and enduring publications: *From Test Tube to Patient*. This book tells the story of new drug development in the United States and highlights the consumer protection role of the Center for Drug Evaluation and Research. The drug regulatory system in the United States has been evolving over most of the 20th century. This latest update captures the most recent changes and reforms, including those stemming from the 1997 FDA Modernization Act.

This publication recognizes the importance of drug development in the total picture of healthcare for the American people. Articles discuss various aspects of this process, from test tube to medicine cabinet; drug testing from laboratory, clinician and patient perspectives; how scientists and physicians in the center balance benefits and risks; and the roles of consumers, healthcare providers, advisory committees and FDA inspectors in making sure drugs are safe and effective. Since the center's and FDA's responsibilities do not end once a drug is approved, this publication examines the increasingly important area of post-market surveillance.

Some of the articles in this edition have been updated from previous editions, some are reprinted from recent issues of *FDA Consumer*, and a few are entirely new.

From Test Tube to Patient: *Improving Health Through Human Drugs*

September 1999

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The Center for Drug Evaluation and Research:

Modern medicines are helping Americans live healthier, longer, and more productive lives. Many diseases that once took an early toll on lives and health are now cured or better managed with the help of medicine. American consumers benefit from having access to the safest and most advanced pharmaceutical system in the world.

The main consumer watchdog in this system is the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA). The center's best-known job is to evaluate new drugs before they can be sold (see "Benefit vs. Risk: How CDER Approves New Drugs," p. 33). The center's evaluation not only prevents quackery, but it also provides doctors and patients the information they need to use medicines wisely. The center makes sure that safe and effective drugs are available to improve the health of consumers. CDER ensures that prescription and over-the-counter (OTC)

drugs, both brand name and generic, work correctly and that their health benefits outweigh their known risks.

The center is part of one of the nation's oldest consumer protection agencies (see "The Evolution of U.S. Drug Law," p. 37). CDER is the largest of FDA's five centers, with nearly 2,000 employees. Approximately half are physicians or scientists. Other centers have responsibility for medical and radiological devices, food, cosmetics, biologics, and veterinary drugs.

What Is a Drug?

Consumers usually think of drugs as the medicines they take to treat illnesses, but most Americans use CDER-regulated drug products every day to maintain health. Drugs include more than just medicines. For example, fluoride toothpastes, antiperspirants, dandruff shampoos, and sunscreens are all considered "drugs." Some medicines can be purchased in a store without a prescrip-

tion, while others require a doctor's prescription.

Most drugs that CDER regulates are manufactured by a chemical process. Other products used to maintain health or to treat illness use a biological process in their manufacture, as do blood products. These products, known as biologics, are regulated by the Center for Biologics Evaluation and Research and must also be approved before they are sold. The most common examples of biologics are vaccines. Vitamins and dietary supplements can be sold without prior approval from FDA and are regulated by the Center for Food Safety.

Prescription Drugs

Prescription medicines must be administered under a doctor's supervision or require a doctor's authorization for purchase. There are several reasons that medicines are required to be sold by prescription. The disease or condition may be serious and



require a doctor's management. The same symptoms can be caused by different diseases that only a doctor can diagnose. The different causes may require different medicines. Some medicines can be dangerous when used to treat the wrong disease.

Over-the-Counter (OTC) Drugs

OTC drug products are available to consumers without a doctor's prescription (see "A Special System for OTC Drugs," p. 36). Consumers can successfully diagnose many common ailments and treat them with readily available OTC products. These range from acne products to cold medica-

bewildering choices. CDER has undertaken a major overhaul of the labels found on OTC medicines (see "New Drug Label Spells It Out Simply," p. 92). Thanks to improved labeling, consumers will soon be better able to make better informed choices about their OTC medicines and know when to seek professional advice.

Generic Drugs

A "generic" drug is a chemical clone of a drug sold under a brand name (see "FDA Ensures Equivalence of Generic Drugs," p. 61). There are generic versions of both prescription

pendent and unbiased review establishes that a drug's health benefits outweigh its known risks, the drug is approved for sale. The center doesn't actually test drugs itself; although, it does conduct limited research in the areas of drug quality, safety, and effectiveness standards.

Before a drug can be tested in people, the drug company or sponsor performs laboratory and animal tests to discover how the drug works and if it's likely to be safe and work well in humans (see "The Beginnings: Laboratory and Animal Studies," p. 14). Next, a series of tests in people is begun to determine if the drug is safe

The Consumer Watchdog for Safe and Effective Drugs

tions. As with prescription drugs, CDER closely regulates OTC drugs to ensure that they are safe, effective, and properly labeled. FDA has been evaluating the ingredients and labeling of OTC products that have been marketed for many years. In some cases, familiar brands or products have been withdrawn from the market because they were ineffective or unsafe.

There is a growing trend for Americans to participate more actively in their healthcare decisions. As this trend continues, many more medications purchased will be OTC drugs. Some drugs are approved for first-time sale as over-the-counter products. However, consumers have more choices today than ever because many drugs are switched from prescription to OTC status (see "Now Available Without a Prescription," p. 68).

With both old, familiar products and new, unfamiliar products sold over the counter, consumers can face

and over-the-counter medicines. For example, ibuprofen is the generic name of the anti-inflammatory drug sold under the brand names Motrin or Advil. The biggest difference between a generic drug and a brand name drug is usually price. A generic drug often costs about 30 percent less than the brand name drug. Widespread use of generics helps control medical costs and insurance premiums.

Drug Development and Review

Drug companies seeking to sell a drug in the United States must first test it. The company then sends CDER the evidence from these tests to prove the drug is safe and effective for its intended use. A team of CDER physicians, statisticians, chemists, pharmacologists and other scientists reviews the company's data and proposed labeling (see "The Review Team," p. 38). If this inde-

when used to treat a disease and if it provides a real health benefit (see "Testing Drugs in People," p. 18).

Reforming the U.S. Drug Review Process

Until this century, prescribing and taking drugs was a risky business for doctor and patient alike. Little was known about drugs, no scientific standards existed, and sometimes medicines caused illnesses rather than curing or preventing them. The U.S. drug review process assures that drugs are safe and effective. It had been lauded for years for the scientific and manufacturing quality it ensures in our drugs. However, for decades, the review process drew criticism for taking too long.

Getting beneficial drugs on the market quickly is just as much a part of CDER's public health mandate as keeping unproven and dangerous drugs off. Early in the 1990s,

CDER started reforming the drug review process to speed the delivery of new drugs to consumers while preserving high standards of quality and safety.

To obtain added resources for reform, the FDA, Congress, and the pharmaceutical industry negotiated the Prescription Drug User Fee Act of 1992. These added resources come from the drug company and are called user fees. As a result, the center has been able to hire more scientists to review marketing applications for drugs. As part of the deal, CDER agreed to phase in ambitious performance goals reviewing priority new drugs in six months or less and standard new drugs in a year or less (see “Review Priorities,” p. 35). The center also standardized policies, improved communications, and streamlined many burdensome rules and regulations. CDER has created a review process that not only honors sound scientific principles, but also sound management principles as well.

The outcomes of the reform far exceeded expectations. Review times were cut in half even as the number of drugs approved in a year doubled. CDER’s management reforms even improved programs that were not helped by user fees. Many of CDER’s reforms were incorporated into the FDA Modernization Act and the reauthorization of the Prescription Drug User Fee Act, passed into law in 1997. As part of that law, CDER agreed to further ambitious goals for improved communications, more standardization, and even quicker reviews. In 1997, the Ford Foundation and the John F. Kennedy School of Government at Harvard University presented the FDA with the prestigious Innovations in American Government Award for its successful reforms.

FDA’s MedWatch program enables healthcare professionals and consumers to report suspected problems with their drugs.

Helping Everyone Benefit from Drugs

While awards and kudos testify to CDER’s successes, the center realizes that the drug development and review process doesn’t serve all Americans as well as it could. In some cases, a lack of incentives was hindering the development of new drugs for people with rare disorders. In other cases, we don’t know enough about how existing drugs work for children, women, and the elderly.

Congress passed the Orphan Drug Act to provide incentives to companies to research and develop medicines for people who have disorders that affect fewer than 200,000 Americans. The most powerful incentive in the law is marketing exclusivity. Once the FDA approves a company’s product for a designated orphan disease, competitors are legally blocked from introducing an identical competing product for seven years. Other provisions provide grants, help from the FDA in designing research protocols that will meet regulatory requirements, and tax credits.

A series of bioethical reforms in the 1960s resulted in federal government rules that protect people who volunteer to take part in medical tests (see “Protecting Human Subjects,” p. 24).

These reforms sharply curtail the unnecessary risks faced by volunteers and prevent the exploitation of vulnerable groups, such as charity patients, prisoners or people in the military. An unintended side effect of these reforms, however, was to stunt the development of scientific knowledge about how drugs worked in children, minorities, women, and the elderly. The center has begun implementing a series of reforms to make sure that these groups are included in clinical trials and that knowledge about the effects of existing drugs in these groups is collected and developed (see “Pediatric Drug Studies: Protecting Pint-Sized Patients,” p. 78, and “Medications and Older Adults,” p. 82).

On the Watch for Drug Problems

Once a drug is approved for sale in the United States, CDER’s consumer protection mission doesn’t stop. It monitors the use of marketed drugs for unexpected health risks. If new, unanticipated risks are detected after approval, CDER takes action to inform the public, change a drug’s label, or even remove a product from the market. In addition to evaluating regular reports from manufacturers, FDA’s MedWatch program enables healthcare professionals and con-

sumers to report suspected problems with their drugs (see “MedWatch: FDA’s ‘Heads Up’ on Medical Product Safety,” p. 54).

CDER makes sure that an adequate supply of drugs will always be available. Sometimes, manufacturers run into production problems that might endanger the health of patients that depend on a drug (see “When a Drug Is in Short Supply,” p. 64).

Protecting Drug Quality

The center also promotes public health by regulating the manufacture of drugs and setting standards for drug quality (see “An Inside Look at FDA On-Site,” p. 47). CDER works closely with FDA’s field inspectors to make sure that manufacturers comply with current good manufacturing practices. Before a drug is approved, investigators determine if the manufacturing data in the application are accurate. Once a drug is approved, another inspection is required to show the firm can consistently make a drug in large quantities. Periodic inspections check a firm’s overall operation.

In addition to setting standards for safety and effectiveness, the center also sets standards for drug quality and manufacturing processes. The center is working closely with manufacturers to see where streamlining can cut red tape without compromising drug quality. As the pharmaceutical industry has become increasingly global, the center is involved in international negotiations with Japan and the European Union to harmonize standards for drug quality and data needed to approve a new drug. This harmonization will go a long way toward reducing the number of redundant tests manufacturers do and help ensure drug quality for consumers at home and abroad.

Drug Information and Advertising

Accurate and complete information is vital to the safe use of drugs. While drug companies have traditionally promoted their products directly to physicians, more and more, they are advertising directly to consumers (see “Direct to You: TV Drug Ads That Make Sense,” p. 74). While advertising of over-the-counter drugs is regulated by the Federal Trade Commission, CDER oversees the advertising of prescription drugs. Advertisements for a drug must contain a truthful summary of information about its effectiveness, side

effects, and circumstances when its use should be avoided.

In addition to its efforts to improve the information that accompanies over-the-counter drugs, CDER monitors a voluntary program that seeks to provide consumer information in the pharmacy for prescription drugs (see “A Dose of Clear Directions for Rx Drug Users,” p. 88). The center watches this program closely to ensure that it meets its goals for quantity and quality of information.

Getting Consumer Input

Protecting consumers means listening to them as well. CDER

routinely consults with the American people in making its decisions about the drugs they use. It holds public meetings about once a week to incorporate expert and consumer input into its decisions (see “Getting Outside Advice for Close Calls,” p. 41). The center also announces many of its decisions in advance so that members of the public, academia, industry, trade associations, consumer groups, and professional societies can comment and make suggestions before decisions become final (See “How to Comment,” p. 96). In addition,

CDER is holding annual public meetings with consumer and patient groups, professional societies and pharmaceutical trade associations to obtain enhanced public input into its planning and priority-setting practices.

The center’s present and future mission remains constant: to ensure that drug products available to the public are safe and effective. The center’s yardstick for success will always be improving the consumer’s health and well-being. CDER has additional resources for the pharmaceutical industry, healthcare professionals, and consumers (see “How to Obtain Information,” p. 98).

CDER makes sure that an adequate supply of drugs will always be available.

Why Should **FDA** Regulate Drugs?



An Interview with **Janet Woodcock, M.D.**
Director of FDA's Center for Drug Evaluation
and Research

What Is CDER's Mission?

CDER's mission is to promote and protect the public health by ensuring that safe and effective drugs are available to Americans. This is a very succinct mission statement, but it encompasses a lot of activities.

What Are the Public's Expectations of Drug Regulation?

The public's expectations—and the drug regulatory system that meets them—have been evolving over the course of the 20th century. Since the early part of this century, the public's basic expectations have been that all marketed drugs should be effective and safe within the context of their use and that unsafe or ineffective drugs should be kept off the market.

Another long-standing expectation of people is that human drugs should be of high quality, because poor quality drugs threatened the lives of many Americans early in this century. Also, there had been cases of false and flagrant claims made for drugs, as well as false and misleading advertising. Americans expect the system to take care of that.

A more recent imperative is that the drug regulatory system must allow generic competition to help maintain reasonable prices for drugs and to help control healthcare costs. Clearly, it is an expectation of various groups that the generic industry should flourish and that it should set a standard for drug pricing in the United States.

Over the past decade, it has become very important to many Americans that seriously ill patients who lack treatment alternatives should have access to investigational drugs. Another expectation that is becoming more and more widespread is that all patient groups should have information for their patients about how to use approved drugs. For example, there should be information available on how to use drugs for children. Use of approved drugs should be studied enough in children so that pediatric information and, perhaps, formulas are available. Also, there are growing expectations that information about drugs—targeted at specific vulnerable populations such as the elderly and

women—will be made available, and that the drug regulatory system will somehow make this happen.

Finally, Americans realize that while it is important to keep unsafe and ineffective drugs off the market, a robust and flourishing drug development research program is also necessary in this country. Americans expect the drug regulatory system

Over the past decade, it has become very important to many Americans that seriously ill patients who lack treatment alternatives should have access to investigational drugs.

will get drugs through the pipeline, make them available to patients rapidly, and ensure all studies on human subjects are ethical and safe.

What Has CDER Done to Improve Service to the Public?

For a long time, people lauded the quality of the CDER drug review process, but criticized it for being too slow. FDA began to address the issue in 1993 with the establishment of user fees. Since the industry is receiving a service from the government through CDER's review of its marketing applications, many felt industry should contribute directly toward the costs of the review process. Congress, industry, and FDA negotiated the user fee program. Industry pays fees to add to FDA's resources for reviewing new drug applications. In exchange, FDA makes a commitment to meet certain goals for review times.

CDER has been meeting all those goals. In fact, it has exceeded almost all of the goals, and it expects to

continue to exceed them. Basically, the number of new approved drugs has doubled, and the review times have been cut in half. The program has been so successful that it has been renewed for five more years, as part of the FDA Modernization Act of 1997. The approval process has been further improved by CDER's accelerated approval procedure.

Under this procedure, drugs for serious and life-threatening diseases can be approved before CDER is positive the drugs will help someone. CDER does this on the condition that there are indicators—called surrogate endpoints—that can allow us to reasonably predict that the drug will provide some benefit. The manufacturer still must continue clinical testing after the drug is made available, but patients with life-threatening diseases benefit by getting the drugs they need faster.

For instance, under this program, CDER approved the protease inhibitors used to treat HIV infection. Many Americans who have started therapy with these drugs have had their health restored to them and have returned to productive lives. All of the protease inhibitors were approved in a matter of months; one was approved in only 42 days. A major decline in AIDS-related deaths in the United States is partly attributed to the availability of these drugs.

What Assurance Does the Public Have That FDA Regulation Will Be Balanced?

I believe quite strongly that a democratic government has to be fair. It's one of the principles of our society. One of the reasons that the citizens are willing to give power to the government is that the government is perceived as being fair and just. This requires balanced regulation, and that is why I have emphasized consistency in regulatory matters and policy, professionalism, and evenhandedness.

I also feel that human beings work together better in a nonadversarial manner. An adversarial relationship, although sometimes necessary, is not the best way to conduct public affairs. It wastes a lot of resources, and it doesn't get the best results. A by-product of working closely with industry, consumer groups, Congress, and the public is that you are much more likely to get balanced regulation.

In the regulatory area, we are talking about the exercise of federal power over other citizens in this country. It requires professionalism, tact, diplomacy, and a whole set of skills that may not be required in other areas.

Why Not Trust Consumers to Decide for Themselves Which Medicines Work for Them?

I don't think it's in the government's best interest to stand between people—especially those who are desperately ill—and their desire to take particular medicines. But this libertarian issue shouldn't be confused with the scientific issue of whether patients can tell what medicines work, because with almost any drug treatment we use today, they can't tell.

Doctors thought for years they could tell what worked. In the 1960s, for example, doctors were

convinced that diethylstilbestrol, or DES, was terrific for preventing early miscarriages, and they gave it to thousands of women in pregnancy. "The women had miscarriages before, and I put them on this DES, and some of them didn't have miscarriages. So obviously, it's very effective," doctors thought.

In fact, when DES was actually subjected to scientific testing, it had no effect on miscarriage whatsoever. Not only was it absolutely ineffective, but unfortunately, it had delayed negative health effects on the fetus.

FDA who said the drug ought to be tested. NIH set up a trial, and what they discovered shocked everyone: Yes, the drugs make the beats go away, but the people who were put on the drugs had sudden death at a substantially higher rate than the people who were just left having the beats. The drugs actually made the problem worse, and maybe more likely to occur.

Even the people who did the trial were later haunted by the fact that they had given some people that drug. They were people whom the researchers knew, and some of them died.

A by-product of working closely with industry, consumer groups, Congress, and the public is that you are much more likely to get balanced regulation.

We had a more recent experience like this with a heart rhythm drug. After people have heart attacks, they can have extra beats. And it's known that a percentage of people with those extra beats will have sudden death. Well, drugs were discovered that made the sudden beats go away, and people thought, "Wonderful! Make the beats go away, and sudden death will go away." The medicine became the standard of practice throughout the United States; everybody was using the drug.

There were some skeptics at the National Institutes of Health and

So the answer is, many, many very smart people have thought they knew what drugs would help them and what drugs would hurt them, and clinical tests again and again have proven them wrong. They didn't know.

What Is There to Lose by Giving People with Life-Threatening Diseases Like AIDS and Terminal Cancer Access to Whatever Drugs They Want?

If we didn't test drugs—if people could take whatever drug they wanted without any testing—there would be no way to tell whether any of the

thousands, millions, of candidate drugs out there worked. So no one would ultimately benefit.

For people with life-threatening illnesses, even the patient groups don't agree on where the right balance is between identifying treatments that will really improve patients' health and allowing people to have immediate access to experiment with drugs that might work for them.

I think AIDS is a good example. We had a lot of discussions with the AIDS activists early on about access

anything with no testing, we'd still be at the same point so much later into the epidemic: Everyone would have total availability to all drugs, but we wouldn't know what worked.

Some of the AIDS activists have actually told us they want more rigorous testing because, as they study their disease and the treatments, they realize they need information to make choices about which drugs they should take, even among the approved drugs. They want CDER to mandate a greater number of big

So, although some other kinds of speech are less restricted, things that are promotional in nature may have certain constraints legitimately put on them.

For example, drug labeling and advertising must be balanced about a drug's risks and benefits and not be misleading. In my opinion, consumers want truthful information, not hype.

Because people would like to receive all the latest information about a drug from the manufacturer, there has been a lot of debate about uses that are considered "off-label"—not approved by CDER. Obviously, medical science doesn't happen in spurts, but continuously. After a drug is put on the market, health professionals continuously experiment with new uses. We think that is appropriate and don't want to restrict that kind of use of drugs. But we don't want manufacturers to promote these uses to consumers until they are proven safe and effective.

The FDA Modernization Act allows manufacturers to provide physicians with articles from scientific journals and textbooks about new uses if they are conducting a study on the drug's new use or they promise to conduct one in the near future. To help the situation, we've put out a guidance document on how much information a manufacturer needs in order to get a new use on the label. We are also being very aggressive in getting new uses approved for people who were traditionally excluded from drug testing—children, women of child-bearing age, and the elderly. New uses have been approved in the latter half of the 1990s at more than double the rate they were approved in the first half. We think that manufacturers are motivated to submit applications for new uses because they know that we have been approving them promptly if they are found to work.

In my opinion, consumers want truthful information, not hype.

to treatments. FDA put together many programs to allow people early access to those drugs even before they were approved.

But at the same time, companies pursued testing to see if these agents worked. Ultimately, some drugs were dropped because they didn't work or because they were so toxic that the risks outweighed the benefits. Ultimately, good drugs were found and then approved by CDER.

Now we're decreasing mortality with HIV. So every person with HIV has a path of drugs to take that he or she knows will work to improve health and has been proven to do so. If we'd gone down the other path, and everyone had been able to try

trials that would include combination therapy. "What if I start this combination early, versus if I take this single drug first? Which would help me to be in better health 10 years from now?" Those are the kinds of questions they want answered, and you can't answer those questions unless you do scientific testing.

Isn't CDER Infringing on Drug Marketers' Freedom of Speech When the Agency Restricts What Is Said in Drug Labeling and Advertising?

There is a category of speech called "commercial speech," used when you're making a sales pitch.

We're getting to the point where we have new, effective antibiotics that may be the only antibiotic that can treat a certain bug.

What Else Can FDA Do to Shorten Drug Development Times?

What we can do is evaluate our standards to make sure that all the information we require is absolutely necessary and that there are no unnecessary requirements. And we must be very clear about what information is required at each stage of drug development. The clearer we are, and the more universal the standards, the easier drug development will be.

Also, the United States, Japan, and the European Union have been negotiating to standardize technical requirements for human drugs under the International Conference on Harmonization (ICH). Companies then won't have to repeat tests unnecessarily.

What harmonization among countries means is that data that a drug company collected to submit to, say, Japanese authorities will be the same or similar data as that required for CDER. It means reducing the amount of testing, but each country would still make its own decision about whether to approve a drug. So far under the ICH, major progress has been made toward standardizing the information that is filed about

side effects so that unexpected side effects may be detected earlier, and standardizing the kinds of safety testing in humans that are required.

But to say CDER alone should decrease development times of drugs would be a big stretch. Because pharmaceutical companies develop the drugs, not CDER, much of the burden for shortening development times and decreasing development costs lies with them.

Is the Center's Rapid Approval of Drugs Compromising Public Safety?

Everybody has to be aware that the clinical testing—the premarket testing of drugs—will not detect all the problems. It just can't. It won't detect some of the problems with the drug or some of the toxicities with some drugs. This fact is something that the public and the medical and pharmacy community really needs to understand better.

Why doesn't testing detect them all? Well, it isn't because the review process breaks down. First of all, it's because some of the events are rare. They may occur in one out of 10,000 people. So, if you test 5,000 people in your clinical development program, you probably won't see it.

Even if you test 10,000, you may not see it; or if you see it, you wouldn't believe it was related. We know this is going to happen sometimes after a drug is approved.

Second, some problems with drugs are caused by the way they're used outside of the parameters for which they're approved. I think the diet drug fenfluramine is a good example. It caused heart-valve problems. It was only approved for three months' use, but people used it for longer periods of time.

Also, sometimes we encounter errors in the use of the drug, for example, medication errors that were hard to foresee prior to approval. Maybe the name, even though we look at the names, was too close to another drug name, and once they get out on the market, they get mixed up.

For all these reasons, a vigorous program is needed after drugs are marketed, to detect these safety problems and to correct them as soon as possible. We have a spontaneous reporting system through which people can report all these problems to the agency. We get a tremendous number of reports—about a quarter a million a year.

We are upgrading this system. Because it has a very large number of reports, it is hard to deal with them all. We're totally computerizing this, and with the industry, we're trying to move toward electronic submission of all of the reports. This will help us analyze them faster and disseminate information better.

What's in the Future for CDER?

First, we are moving toward a completely electronic submission and review environment by 2002. Right now, a typical drug application has so much paper that we need a forklift to transfer it. With electronic submissions, we'll be able to fit it all on a CD-ROM or two. This means less

Traditional Expectations for the Drug Regulatory System:

All marketed drugs are effective and safe within the context of their use.

Human drugs are of high quality.

Generic competition keeps drug prices reasonable.

All advertising and promotion of drugs are informative and are not false or misleading.

Evolving Expectations for the System:

Patients who lack alternatives have access to investigational drugs.

High-quality information about how to use drugs is available, including information on children, elderly patients, and other groups.

Robust drug development programs that thoroughly protect human subjects flourish and are productive.

paperwork for everyone and quicker, more accurate reviews.

Second, I think CDER is really going to have to step up to the plate in the new world of medical care, where managed care is the paradigm of how patients are being taken care of in this country. We need to think about how our information and how our role of drug approval and regulation fit in with the newly emerging healthcare system in the United States.

How does the pharmaceutical firm's role in the managed care industry fit with FDA's traditional method of regulating what pharmaceutical firms can say about their drugs? This, again, is a very controversial issue. The public has a lot of issues about having their medicines switched.

Antibiotic resistance is something you'll be hearing about in upcoming years. We're getting to the point where we have new, effective antibiotics that may be the only antibiotic that can treat a certain bug. Should this antibiotic be allowed to be administered widely throughout the country to the point where it, too, has resistance developed to it? What should be the national approach to this upcoming problem of antibiotic resistance?

More and more drug development is aimed at treating chronic diseases. We can't ask drug developers to study a drug for the entire lifetime of a patient with a chronic disease. They may study it for one or two years total per patient. So what should we do after that drug is approved? How much information should be collected, and what happens if you take the drug for 5 years, or 10 years, or 20 years? What should we do? And what power should we have to compel that kind of information to be collected?

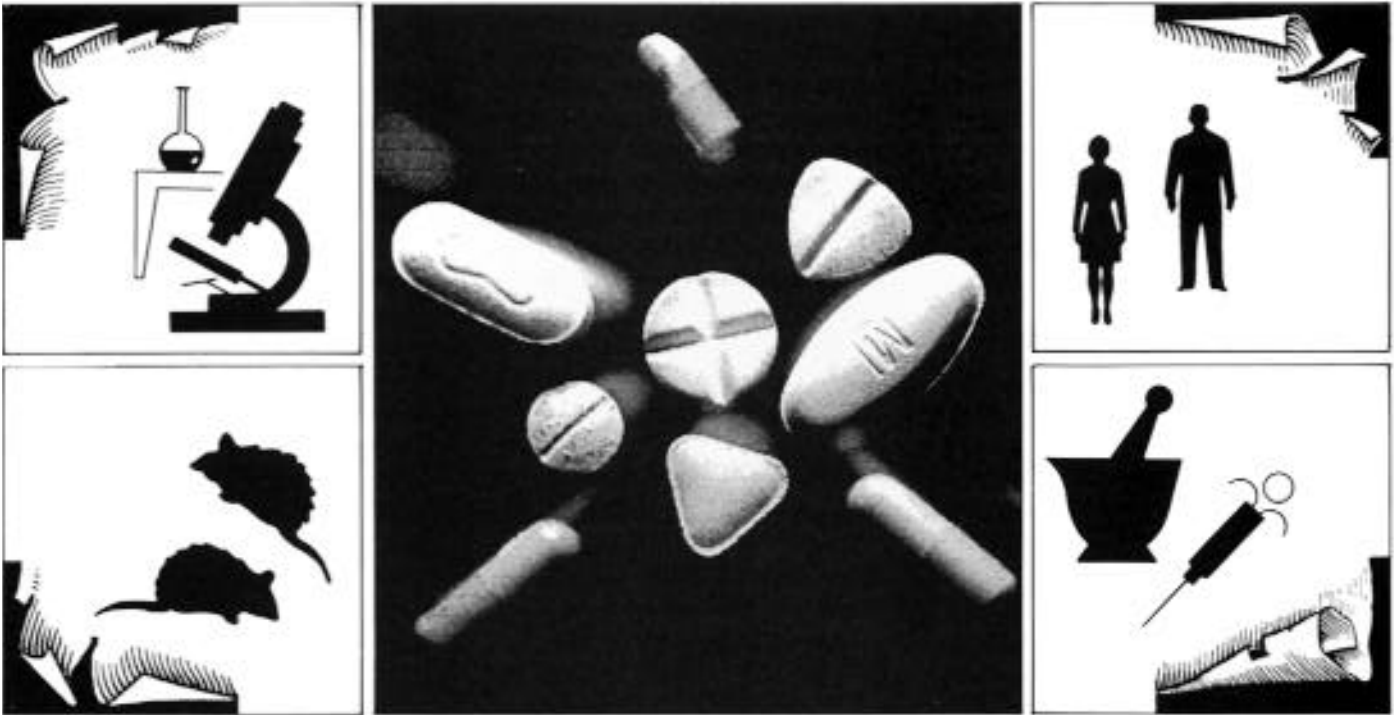
Finally, in my opinion, effective communication is linked to drug

CDER is really going to have to step up to the plate in the new world of medical care, where managed care is the paradigm of how patients are being taken care of in this country.

safety. If we can get the information about potential or actual problems with drugs out to doctors, patients, and those people who need it, then drugs are going to be safer. If people are in the dark, then misuse of drugs will occur more frequently. We are working toward improving prescription drug labeling and improving over-the-counter drug labeling.

Most people cannot have missed the increased prominence of direct-to-consumer advertising recently. In addition, there's a private, ongoing, voluntary process to have consumer information available at the pharmacy for prescription drugs. So when consumers fill their prescriptions, they will receive information sheets. This process is being monitored by the FDA to ensure that it happens adequately. This is a very important issue for drug safety: that consumers get adequate information on how to use their drugs and that the information they get is correct.

The Beginnings: Laboratory and Animal Studies



The scene is a typical one. A patient, perhaps you or I, goes to a doctor and gets a prescription. Then a pharmacist fills the prescription, with instructions to take the drug in the prescribed amount and manner over the following days, weeks or months. This scene is repeated millions of times across this country every day—some 2 billion prescriptions are filled every year in the United States. In fact, the process is so commonplace that the pills, tablets, capsules, and other medications that virtually every one of us relies on to restore or maintain good health at some point in our lives come to be taken for granted.

Yet these drugs—and the improved quality of health they bring to the American people—are truly “miracles of modern science.” In fact, the process for discovering, developing and testing new drugs encompasses some of the most exciting areas of scientific discovery today. The endeavor runs the gamut from basic biomedical investiga-

tion of living cells and molecules to applied research that yields new consumer products to improve healthcare.

The Cutting Edge

“We are on the cutting edge of the biological sciences,” says Rhoda Gruen, Ph.D., special assistant to the president of international research and development at Hoffmann-La Roche, Inc., a pharmaceutical research and manufacturing firm headquartered in Nutley, N.J. “We suck up new information like a sponge. Everything we do is subject to change as new scientific information becomes known.”

The research process is a complicated, time-consuming, and costly one whose end result is never known at the outset. Discovering a new drug has been likened to searching for the proverbial needle in a haystack. Literally hundreds, and sometimes thousands, of chemical compounds must be made and tested to find one that can achieve the desirable result without too-serious side effects.

The complexity of the process can be gauged, in part,



by the diversity of scientific disciplines engaged in finding new drugs. Traditional organic chemists, physiologists and statisticians have been joined in recent years by new kinds of specialists. Biochemists study the chemistry of life processes. Molecular biologists study the molecules that make up living matter. Toxicologists investigate chemicals' potential for harm. Pharmacologists look at how drugs work. And computer scientists apply the power of their sophisticated machines to analyze and assess new chemicals. Each provides a different way of looking for that needle.

Such a complicated process costs vast amounts of time and money. FDA estimates that, on average, it takes eight-and-a-half years to study and test a new drug before the agency can approve it for the general public. That includes early laboratory and animal testing, as well as later clinical trials using human subjects.

Drug companies spend \$359 million, on average, to develop a new drug, according to a 1993 report by the Congressional Office of Technology Assessment. A company such as Hoffmann-La Roche, whose annual sales in the United States alone are about \$3 billion, spends about \$1 billion a year on research worldwide.

Building on Good Science

There is no standard route by which the thousands of drugs now sold in the United States were developed. "Each drug has its own way of being born," says Clement Stone, a former senior vice president for Merck and Co. Inc., research laboratories, in West Point, Pa. "Often, we consciously search for a drug for a specific use, but more often, it is serendipity. What is required, though, is good science building on good science."

In some cases, a pharmaceutical company decides to develop a new

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drug aimed at a specific disease or medical condition. In others, company scientists may be free to pursue an interesting or promising line of research. And, in yet others, new findings from university, government, or other laboratories may point the way for drug companies to follow in their own research.

Indeed, the process typically combines elements of all three avenues. New drug research starts by studying how the body functions, both normally and abnormally, at its most basic levels, Ronald Kuntzman, vice president for research and development at Hoffmann-La Roche, says. The pertinent question is: "If I change it [the body's functioning], will I have a useful drug?" That, in turn, leads to a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. Once the concept has been developed, the researcher has a target to aim for, Kuntzman adds.

Gruen elaborates: "Disease processes are complex and involve a sequence of events. If you want to intervene in the disease process, you try to break it down into its component parts. You then analyze those parts to find out what abnormal events are occurring at the cellular and molecular levels. You would then select a particu-

lar step as a target for drug development with the aim of correcting the cellular or molecular dysfunction."

A Cholesterol Drug

Take cholesterol, a waxlike substance found naturally in the body. Too much cholesterol, either naturally or in the diet, can cause it to build up on the inside walls of blood vessels. This can clog the arteries that deliver blood to the heart muscle, blocking the flow of oxygen and nutrients, causing a heart attack.

There have been few drugs that effectively cut cholesterol levels without either toxic or unpleasant side effects. This has limited their use. Others that were tested acted too late in the process by which the body makes cholesterol to lower its levels. What was needed, says Eve Slater, M.D., executive vice president for worldwide regulatory affairs for Merck, was a drug that would act earlier in the cholesterol-making process.

To find one, scientists at Merck and elsewhere spent decades studying how the body makes and uses cholesterol. Along the way, they identified more than 20 biochemical reactions necessary for the body to make cholesterol, along with the enzymes required at each step to turn one chemical into

the next one in the chain.

The research problem, Slater says, was to find the step where interference by a drug would effectively lower cholesterol production. By the 1970s, scientists had found a possibility. They had isolated a chemical, mevalonic acid, which was an early link in the cholesterol chain, and an enzyme called HMG-CoA reductase, which produced mevalonic acid.

What was needed, then, was a drug that could either inhibit HMG-CoA reductase or prevent cells from correctly using the enzyme.

Sometimes, scientists are lucky and find the right compound quickly. More often, Gruen says, hundreds or even thousands must be tested. In a series of test tube experiments called assays, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which additions show some chemical effect. Some may not work well, but may hint at ways of changing the compound's chemical structure to improve its performance. The latter process alone may require testing dozens or hundreds of compounds.

Computer Clues

A more high-tech approach is to use computers to simulate an enzyme or other drug target and to design chemical structures that might work against it. Enzymes work when they attach to the correct site on a cell's membrane. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there.

Nevertheless, "computers give chemists clues to which compounds to make, but they don't give any final answers," says Kuntzman. "You still have to put any compound you made based on a computer [simulation] into a biological system to see if it works."

Yet a third approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses, and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what they call a fermentation broth, one type of organism per broth. Sometimes 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

In the search for a new cholesterol drug, scientists found a fungus that inhibited the HMG-CoA reductase enzyme in a test tube. Chemists then had to identify which of the fungus's dozens of chemical by-products was actually inhibiting the enzyme. Once that was done, the chemical's structure was analyzed and improved to enhance its effects.

To this point, the search for a new drug has been confined to a laboratory test tube. Next, scientists have to test those compounds that have shown at least some desired effects in living animals. "We have to find what the drug is doing on the down side," Kuntzman explains.

Animal Testing

In animal testing, Kuntzman says, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Two or more species are typically tested because a drug may affect one differently from another. Such tests show whether a potential drug has toxic side effects and what its safety is at different doses. The results "point the way for human testing and, much later, product labeling," Kuntzman says.

So far, research has aimed at discovering what a drug does to the body. Now, it must also find out what the body does to the drug. So, in animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity

of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body. Sometimes, such tests find a metabolite that is more effective than the drug originally picked for development.

Of particular concern is how much of the drug is absorbed into the blood. "If a drug's active ingredients don't get into the blood," Kuntzman says, "it won't work." Scientists may add other chemicals to the drug to help the body absorb it or, on the other side, to prevent it from being broken down and excreted too soon. Such changes in the drug's structure mean even more testing.

Absorption rates can cause a host of problems. For example, for a certain drug to be effective, 75 percent of it may need to reach the bloodstream. But absorption rates can vary among individuals from, say, 10 to 80 percent. So, the drug must be able to produce the desired effects in those who absorb only 10 percent, but not cause intolerable side effects in people who absorb 80 percent.

"If we can improve the absorption rate we can reduce the variation in what real dosages people would be subject to," Kuntzman says. A more standard absorption rate for all individuals, say around 75 to 80 percent, would mean that the dose could be reduced and still have the desired effects.

The Wrong Road

By this time in the testing process, many drugs that had seemed promising have fallen by the wayside. More often than many scientists care to admit, researchers just have to give up when a drug is poorly absorbed, is unsafe, or simply doesn't work. "In research you have to know when to cut your losses if you are going down a wrong road," says Clement Stone. And, he adds, there are many more wrong roads than right ones.

Nevertheless, progress may yet be

made. Occasionally, Stone says, a stubborn scientist keeps looking and finds a usable compound after others had given up. In other cases, compounds may be put aside because they failed to work on one disease, only to be taken off the shelf years later and found to work on another.

Such was the case with Retrovir (zidovudine, also known as AZT), the first drug approved for treatment of AIDS. The drug was first studied in 1964 as an anticancer drug, but it showed little promise. It was not until the 1980s, when desperate searches began for a way to treat victims of the AIDS virus, that scientists at Burroughs Wellcome Co., of Research Triangle Park, N.C., took another look at zidovudine. After it showed very positive results in human testing, it was approved by FDA in March 1987.

Even so, “a minuscule number of drugs we test ever reach testing in man,” says Richard Salvador, Ph.D., a Hoffmann-La Roche vice president and international director of preclinical development. The organization Pharmaceutical Research and Manufacturers of America estimates that only five in 5,000 compounds that enter preclinical testing make it to human testing, and only one of those five may be safe and effective enough to reach pharmacy shelves.

FDA's Role

The role of FDA in the early stages of drug research is small. The Federal Food, Drug, and Cosmetic Act requires FDA to ensure that the new drugs developed by pharmaceutical companies are safe and effective. It does not give the agency responsibility to develop new drugs itself. So, FDA physicians, scientists, and other staff review test results submitted by drug developers. FDA determines whether the drug is safe enough to test in humans and, if so—after all human testing is completed—decides

whether the drug can be sold to the public and what its label should say about directions for use, side effects, warnings, and the like.

FDA first becomes involved when a drug company has completed its testing in animals and is ready to test a drug on humans. (Actually, some animal testing continues after human

In animal testing, Kuntzman says, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care.

tests begin to learn whether long-term use of the drug may cause cancer or birth defects. Also, more animal data may be needed if human tests turn up unexpected effects. And new therapeutic uses may be found by continued animal studies.)

Although FDA usually does not tell drug companies what specific laboratory or animal tests to run, the agency does have regulations and guidelines on the kinds of results FDA expects to see in any request to conduct human testing.

And the drug companies listen to

those signals. Both Hoffmann-La Roche's Kuntzman and Merck's Stone say their companies follow and sometimes exceed FDA's guidelines. “We want to optimize our chances of taking a compound from animal to human testing,” Stone says.

So drug research is a long, difficult, and costly road, certainly. But sometimes the hard work, the scientific sleuthing, and the time and dollars spent pay off. Such was the case in December 1992, when FDA approved Taxol for treatment of advanced cases of ovarian cancer in five months. Taxol is an important second-stage drug for ovarian cancer because, while most patients respond to chemotherapy initially, the disease often recurs.

But to scientists like Kuntzman, drug research goes even beyond preventing or curing diseases or making money. It is also a tool for finding out more about the human body and its basic life processes.

“Research is an evolutionary process,” Kuntzman says. “You change studies and use experiments to lead to other experiments. As you go along you may not even see the connection between studies. In a sense, research has no end. The only end would be when we understand everything there is to know about the human body. I expect that we will never know enough about the body.”

Merck's Slater agrees. “We can make progress,” she says, “but we are unlikely to achieve perfection.” In the end, that is what researching and developing new drugs is all about—understanding and progress.



TESTING DRUGS

in People

Most of us understand that drugs intended to treat people have to be tested in people. These tests, called clinical trials, determine if a drug is safe and effective, at what doses it works best, and what side effects it causes—information that guides health professionals and, for nonprescription drugs, consumers in the proper use of medicines. Clinical testing isn't the only way to discover what effect drugs have on people. Unplanned but alert observation and careful scrutiny of experience can often suggest drug effects and lead to more formal study. But such observations are usually not reliable enough to serve as the basis for important, scientifically valid conclusions. Controlled clinical trials, in which results observed in patients getting the drug are compared to the results in similar patients receiving a different treatment, are the best way science has come up with to determine what a new drug really does. That's why controlled clinical trials are the only legal basis for the FDA to conclude that a new drug has shown "substantial evidence of effectiveness, as well as confirmation of relative safety in terms of the risk-to-benefit ratio for the disease that is to be treated."

Does It Work?

It's important to test drugs in the kind of people they're meant to help. It's also important to design clinical studies that ask, and answer,

the right questions about investigational products.

The process starts with a drug sponsor, usually a pharmaceutical company, seeking to develop a new drug it hopes will find a useful and profitable place in the market. Before clinical testing begins, researchers analyze the drug's main physical and chemical properties in the laboratory and study its pharmacologic and toxic effects in laboratory animals. If the laboratory and animal study results show promise, the sponsor can apply to FDA to begin testing in people.

Once FDA has seen the sponsor's plans and a local institutional review board—a panel of scientists, ethicists, and nonscientists that oversees clinical research at medical centers—approves the protocol for clinical trials, clinical investigators give the drug to a small number of healthy volunteers or patients. These phase 1 studies assess the most common acute adverse effects and examine the size of doses that patients can take safely without a high incidence of side effects. Initial clinical studies also begin to clarify what happens to a drug in the human body—whether it's changed, how much of it gets into the blood and various organs, how long it stays in the body, and how the body gets rid of the drug and its effects.

If phase 1 studies don't reveal major problems, such as unacceptable toxicity, the next step is to con-

duct a clinical study in which the drug is given to patients who have the condition it's intended to treat. Researchers then assess whether the drug has a favorable effect on the condition.

Usually, No Miracles

The process appears straightforward—simply recruit groups of patients to participate in a clinical trial, administer the drug to those who agree to take part, and see if it helps them. Sounds easy enough, and sometimes it is. In what may be medicine's most celebrated clinical trial, Louis Pasteur treated patients exposed to rabies with an experimental antirabies vaccine. All the treated patients survived. Since scientists knew that untreated rabies was 100 percent fatal, it wasn't hard to conclude that Pasteur's treatment was effective.

But that was a highly unusual case. Drugs do not usually miraculously reverse fatal illnesses. More often they reduce the risk of death, but don't entirely eliminate it. They usually accomplish this by relieving the symptoms of the illness, such as nasal stuffiness, pain, or anxiety. Or a drug may alter a clinical measurement—reduce blood pressure or lower cholesterol, for example—in a way that physicians hope will be valuable. Drug effects like these can be more difficult to detect and evaluate than a result as dramatic as Pasteur's rabies cure.

This is mainly because diseases don't follow a predictable path. Many acute illnesses or conditions—viral ailments like the flu, minor injuries, insomnia—can usually be counted on to go away spontaneously without treatment. Some chronic conditions like arthritis, multiple sclerosis, or asthma often follow a varying course—better for a time, then worse, then better again, usually for no apparent reason. And heart attacks and strokes, for example, have widely variable death rates depending on treatment, age, and other risk factors, so that the “expected” mortality for an individual patient can be hard to predict.

A further difficulty in gauging the effectiveness of an investigational drug is that in some cases, measurements of disease are subjective, relying on interpretation by the physician or patient. Such measurements can be influenced by a patient's or physician's expectations or hopes. In those circumstances, it's difficult to tell whether treatment is having a favorable effect, no effect, or even an adverse effect. The way to answer critical questions about an investigational drug is to subject it to a controlled clinical trial.

Understanding Controls

In a controlled trial, patients in one group receive the investigational drug. Those in a comparable group—the controls—get either no treatment at all, a placebo (an inac-



Depicting one of medicine's most celebrated clinical trials, this wood engraving from an 1885 issue of *Harpers Weekly* shows a young patient receiving an anti-rabies vaccine developed by Louis Pasteur. A physician administers the treatment while Pasteur, a chemist, looks on. (Courtesy of the National Library of Medicine.)

tive substance that looks like the investigational drug), a drug known to be effective, or a different dose of the drug under study.

Usually, the test and control groups are studied at the same time. In fact, usually, the same group of patients is divided into two subgroups with each subgroup getting a different treatment.

In some special cases, a study uses a “historical control,” in which patients given the investigational drug are compared with similar patients treated with the control drug at a different time and place.

Sometimes, patients are followed for a time after treatment with an investigational drug, and investigators compare their status before and after treatment. Here, too, the comparison is historical. It is based on an estimate of what would have happened without treatment. The historical control design is particularly useful when the disease being treated has high and predictable death or ill-

ness rates. Then investigators can be reasonably sure what would have happened without treatment.

It's important that treatment and control groups be as similar as possible in characteristics that can affect treatment outcomes. For instance, all patients in specific groups must have the disease the drug is meant to treat or the same stage of the disease. In a clinical trial of a drug to treat angina (chest pain associated with cardiovascular disease), for example, if one group of patients being studied actually had sore ribs rather than angina, their differing response to the drug could not be assumed to be due to its effectiveness or lack thereof.

Treatment and control groups should also be of similar age, weight, and general health status, and be similar in other characteristics that could affect the outcome of the study, such as other treatment being received at the same time.

A principal method used to achieve this is called “randomization.”

Patients are randomly assigned to either the treatment or control group, rather than deliberately selected for one group or the other. When the study population is large enough and the criteria for participation are carefully defined, randomization yields treatment and control groups that are similar in important characteristics. Because assignment to one group or another is not under the control of the investigator, randomization also eliminates the possibility of “selection bias,” the tendency to pick healthier patients to get the new treatment.

When It Helps to Be ‘Blind’

In clinical trials, the hope for a good outcome can influence patient selection so that the treatment group includes a disproportionate number of patients likely to do well whatever their treatment. The same kind of inadvertent bias can lead both patients and investigators to overrate positive results in the treatment group and negative findings among controls, and cause data analysts to make choices that favor treatment. Clinical trials that include such biases are likely to be incapable of assessing drug effect.

In conjunction with randomization, a design feature known as “blinding” helps ensure that bias doesn’t distort the conduct of a study or the interpretation of its results. Single-blinding consists of keeping patients from knowing whether they are receiving

the investigational drug or a placebo. In a double-blind study, neither the patients, the investigators, nor the data analysts know which patients got the investigational drug. Only when the study is unblinded (the closely guarded assignment code is broken to identify treatment and control patients) do the people involved in the study know which is which.

Ethical Questions

Testing experimental drugs in people inevitably presents ethical questions. Is it ethical to give patients a placebo when effective treatment is available? Not all authorities agree on the answer. But the generally accepted practice in the United States—and one increasingly being adopted abroad—is that fully informed patients can consent to take part in a controlled-randomized-blinded clinical trial, even when effective therapy exists, so long as they are not denied therapy that could alter survival or prevent irreversible injury. They can voluntarily agree to accept temporary discomfort and other potential risks in order to help evaluate a new treatment.

In any trial in which a possible effect on survival is being assessed, it’s important to monitor results as they emerge. That way, if a major effect is seen—positive or negative—the trial can be stopped. This happened in the first clinical study of the AIDS drug zidovudine (AZT), when a clear survival advantage for patients receiving zidovudine was seen well before the trial was scheduled to end. The trial was then ended early, and within a week FDA authorized a protocol allowing more than 4,000 patients to receive zidovudine before it was approved for marketing. More recently, the results from the National Institute of Health’s Breast Cancer Prevention Trial were announced, which enrolled more than 13,000 women at high risk for breast cancer. The results showed a

45 percent reduction in new cases of breast cancer in women who took the drug tamoxifen (Nolvadex) versus women who took a placebo. It was this clear evidence of reduction in breast cancer in the tamoxifen group that led those monitoring the trial to recommend that the study be unblinded 14 months earlier than expected. These are examples of the ethical principle that if a lifesaving or life-extending treatment for a disease does exist, patients cannot be denied.

In some cases, a new treatment can be compared with established treatment, as long as the effectiveness of the latter can readily be distinguished from placebo and the study is large enough to detect any important difference.

It is also possible to evaluate new drugs in this situation in “add-on” studies. In this kind of trial, all participants receive standard therapy approved for treating the disease, but those in the treatment group also get the investigational drug. The control group gets either no added treatment or placebo. Any difference in results between the treatment and control groups can be attributed to the investigational drug. It is common to study new antiseizure drugs in this way, as well as new agents intended to reduce mortality after a heart attack.

Testing in Women, Children, and the Elderly

In recent years there has been growing interest at FDA in testing drugs in patient populations that have been relatively neglected in clinical trials, especially women and children. Children are generally not included in trials at all until the drug has been fully evaluated in adults, unless the drug is intended for a pediatric disease, such as acute lymphocytic leukemia. When children are not likely to use drugs frequently (for example, drugs to treat high blood pressure), they often have not

A New Drug Application (NDA) contains the following:

- Pre-clinical studies
- Human clinical studies
- Manufacturing details
- Labeling
- Additional information

been included in clinical trials at all. To promote the inclusion of children, the FDA published a final rule in December 1994 revising the “Pediatric Use” subsection of the professional labeling requirements for prescription drugs to include more complete information about the use of a drug in the pediatric population (See “Pediatric Drug Studies,” p. 78).

Although both sexes now are generally represented in clinical trials in proportions that reflect gender patterns of disease, FDA and women’s health advocates agree that less care has been taken to develop information about significant differences in the ways men and women respond to drugs and other FDA regulated products.

This convinced FDA in 1993 to recommend that women of all ages be included in clinical trials, and results analyzed by gender. The guidance did away with an FDA policy dating from 1977 that excluded women of childbearing potential from participation in early clinical studies because of a risk or potential risk of reproductive or developmental toxicity. The agency believes that institutional review boards, as well as clinical investigators and women themselves can gauge whether women’s participation in clinical trials is appropriate. In all cases, information should be made available informing all participants regarding the potential risk of fetal toxicity. The FDA’s Office of Women’s Health, which functions to include the sponsorship of many research projects, focused on gender-effects of marketed drugs, biologics, and medical devices.

In September 1997 the FDA issued a proposed rule to amend the provisions of its regulation governing investigational new drug applications (INDs). The proposal’s goal is to ensure that in future clinical trials, men and women with reproductive potential and life-threatening diseases are

Testing in Humans

	Number of Patients	Length	Purpose	Percent of Drugs Successfully Tested
Phase 1	20–100	Several months	Mainly safety	70 percent
Phase 2	Up to several hundred	Several months to 2 years	Some short-term safety, but mainly effectiveness	33 percent
Phase 3	Several hundred to several thousand	1–4 years	Safety, effectiveness, dosage	25–30 percent

For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 percent will successfully complete phase 1 and go on to phase 2; about 33 percent of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

not automatically excluded based only on a risk or potential risk of reproductive and developmental toxicity.

As the population of those over 65 years of age continues to grow, the medical community has become aware that FDA-regulated products can produce effects in the elderly patients that are very different from those produced in younger patients. For example, elderly patients are more likely to have impaired mechanisms of drug excretion (e.g., decreased kidney function), to be taking other medications that can interact with a newly prescribed drug, or to have another medical condition that can affect drug therapy. The FDA believes that efforts should be made not to exclude older subjects, especially those over 75 years of age from clinical studies. The agency is encouraging sponsors to increase the number of older subjects,

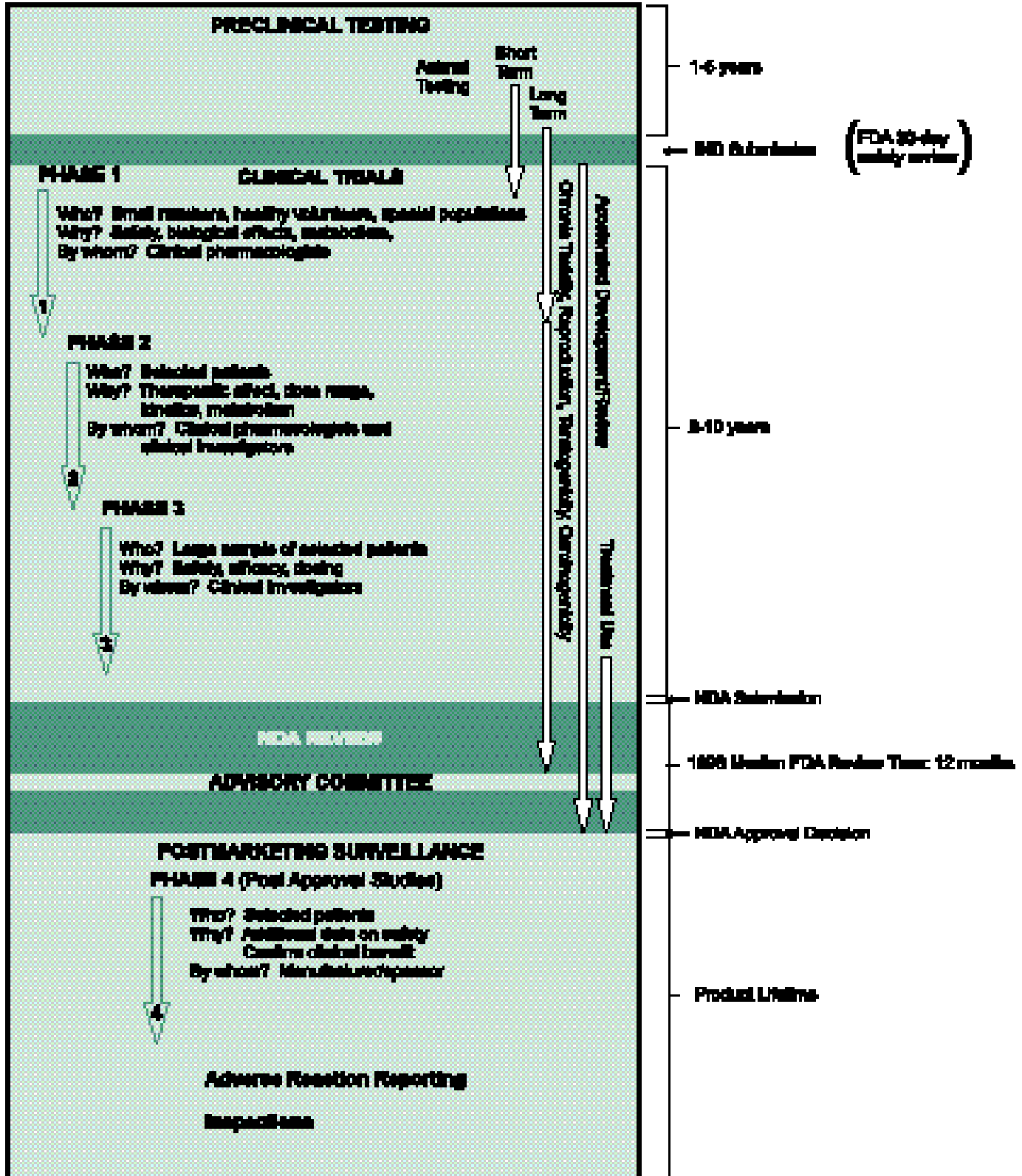
to analyze the data already collected, and to obtain modest additional drug activity information. In August 1997, the FDA published a final rule to promote safe and effective prescription drug use in the elderly by requiring such information to be included in the labeling.

The inclusion of women, children, and the elderly, as well as other populations in clinical trials convinced the agency in 1998 to require sponsors of all new regulated products to analyze safety and effectiveness data for important demographic subgroups, including gender and racial subgroups. Enrollment of subjects into clinical studies for drug and biological products must be tabulated by important demographic subgroups in IND annual reports, (e.g., age group, gender, and race), and must be included in all New Drug Applications (NDAs).

New Drug Application (NDA) Review Process

FDA Time

Industry Time



This final rule allows the agency to refuse to review any NDA that does not analyze safety and efficacy information appropriately by gender.

Studying medical therapies in humans will probably never be an exact science. But steady progress in the methodology and, in a way, the philosophy of clinical trials is making the process more productive, more reliable, and more beneficial for us all.

A Sceptic's Guide to Medical 'Breakthroughs'

Everyone is gratified by news of a major drug breakthrough, especially if it promises help for people who are terminally ill or severely disabled. And if you or a loved one has been praying for such a drug, the news may seem like a miracle.

But can you accept the good news at face value? All too often you can't, because many such reports are either exaggerated or seriously inaccurate interpretations of scientific findings. Really significant advances in drugs and drug therapy don't happen nearly as often as magazines, television, or the Internet might lead you to believe. Sober scepticism is a good attitude to have when evaluating news about drug "breakthroughs." Here are a few guidelines:

- Where did the news report appear? Is it in a newspaper, magazine, or broadcast that regularly covers health and medical affairs and assigns specialized reporters to the subject? Or is it part of a publication or broadcast that emphasizes sensational stories that seem too good to be true? Is the reporter someone whose coverage of health and medicine you believe to be accurate and cautious? If you are doubtful about the news medium in which the report appears, it's probably best to take the story with a grain of salt.

- News stories about drugs producing complete cures and unscrupulous cyberspace marketers peddling "miracle" treatments especially in patients with cancer, AIDS, or other grave illnesses, are likely to be cruelly wrong.
- What is being reported? The results of one study in a small number of patients are seldom, if ever, conclusive. This kind of preliminary information is presented at scientific meetings or published in scientific journals whose editors and readers know how to interpret such findings. News stories may place undue importance on these reports and jump to conclusions that the researchers themselves know are unjustified.
- Ask your healthcare provider what he or she knows about the story. While healthcare practitioners can't know everything, there's a good possibility that they would know about a truly important medical advance.

Most medical science writers and reporters try diligently to provide accurate and authoritative information. They avoid unfounded speculation, and they strive to put exciting discoveries in perspective. Their stories don't often grab front-page headlines or lead off the evening news, but they can be trusted to give you solid information. And that's a great deal better than false hope.

Personal Participation

Anyone interested in participating in a clinical trial should discuss the idea with their physician. Doctors are generally aware of investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. Clinical trials are carried out at medical research centers such as teaching hospitals, at specialized clinics for people with AIDS, and even in doctors' offices.

Although they often involve hospitalized patients, many clinical trials are conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out often runs newspaper ads recruiting potential participants for clinical studies that tell readers where to call or write for further information.

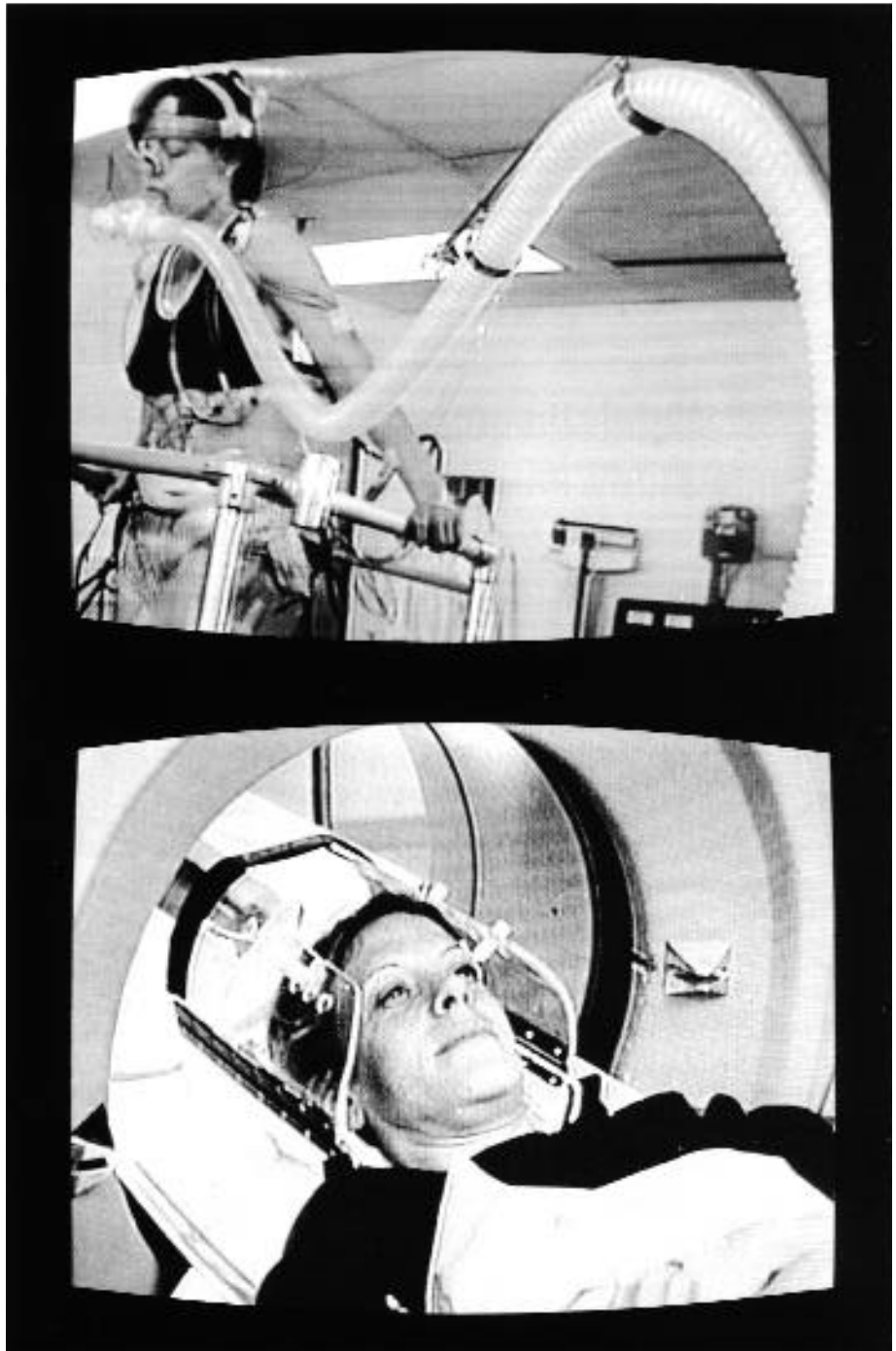
Although investigational drug studies vary widely, some things should be expected by participants in virtually any clinical trial. For example, participants might have to give blood samples more often than during ordinary care. Tests to assess disease status might be more frequent. Participants are often required to keep detailed records of their symptoms and follow strict schedules.

It's also important to understand that volunteering for a clinical trial does not guarantee that an individual patient will receive the drug under investigation. Control patients may get a placebo, a drug already approved for their condition, or perhaps no treatment at all. These and other aspects and implications of taking part in a clinical trial must be fully explained in advance by the people conducting the trial, and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug—or the desire to take part in research that might one day benefit millions—is what makes people volunteer for clinical trials.

Protecting Human STUDY SUBJECTS

In 1963, a New York hospital allowed some elderly, ill, and feeble patients to be injected under the skin with cancer cells to study immune response. Patients were not told what the injections were—just that their “resistance” was being measured. Nothing came from this ill-conceived effort, which was intercepted and stopped soon after it began, with none of the patients getting cancer.

In early 1994, the federal government released documents detailing hundreds of radiation experiments performed on thousands of civilians and military personnel decades ago, apparently in some cases without adequate knowledge or consent. Experiments included giving food mixed with tracer doses of radioac-





*Known as Institutional Review
Boards, or IRBs, these committees
of experts and lay persons also review
the research as it goes along.*

tive substances to subjects and injecting infants with radioactive iodine.

These are worst-case examples of failure to inform and protect human subjects used without their knowledge in drug testing and medical experimentation. They are not remote historical events. The cancer injections were stopped over 36 years ago. The radiation experiments occurred in the 1940s and 1950s.

Such disregard for the rights and welfare of study subjects is far less likely today. Review boards at hospitals and research institutions throughout the country make sure participants are fully informed and willing before studies ever get under way. Known as Institutional Review Boards, or IRBs, these committees of experts and lay persons also review the research as it goes along.

Watching these watchers are FDA and other federal agencies such as the National Institutes of Health (NIH), whose rules are designed to protect those taking part in medical research.

In 1976, FDA issued regulations requiring IRB review of all studies using institutionalized subjects. Regulations amended in 1981 require all studies needing a FDA

research permit to be reviewed and approved by an IRB before tests on humans can begin, whether or not subjects are in an institution.

Edmund Pellegrino, M.D., professor of medicine at Georgetown University in Washington, D.C., and an internationally recognized expert on medical ethics, says that using human subjects to advance scientific knowledge is acceptable "as long as there is informed consent and the rights of the subjects are respected."

In an instructional videotape prepared by FDA, Pellegrino says persons entering a study must be told they are "willing volunteers" who can stop or even leave the study at any time if they become stressed or apprehensive, or suffer too great discomfort, or simply wish to go no further.

The first responsibility of the physician is to "do no harm," and there are few that set out to violate that principle. But at the extreme of those who did were scientists convicted at the 1946 Nuremberg trials of conducting experiments on concentration camp inmates. From these trials came the Nuremberg Code, the first modern-day formal statement on medical ethics, and a precursor to the

Belmont Report, the basic foundation upon which the present U.S. standards for the protection of human subjects of research rest.

Informed consent was added to the requirements of the Federal Food, Drug, and Cosmetic Act by the 1962 Kefauver-Harris Amendments. A signed consent document was not required, only a notation in the chart that verbal consent had been obtained. A 1967 FDA policy statement outlined the consent process and required consent to be obtained in writing for early stages of research.

The U.S. Public Health Service (PHS) in 1966 defined the right of subjects to be told about the benefits, risks, and purpose of the research for which they are volunteering. It made this "informed consent" a condition of PHS funding for research grants, which includes all NIH-funded studies, but not FDA-regulated studies, unless they are also federally funded.

A decade later, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research developed three basic principles governing research involving human subjects that were published in the Belmont Report. The principles are: (1) respect for persons, the requirement to treat individuals as autonomous agents, and the requirement to protect those with diminished autonomy; (2) beneficence, maximizing possible benefits and minimizing possible harms, and; (3) justice, as demonstrated by fairness in distribution of the opportunity to participate in research. The Belmont Report is the basis of the present human subject protection regulations in the United States, which have been now adopted largely unchanged as international standards in the International Conference for Harmonization. The U.S. informed consent regulations contain two exceptions to obtaining the informed consent of an individual

before entering him/her into a study: (1) an unplanned situation, when use of an investigational material is required to save the life of the individual, and (2) a planned study that must be done in the emergency room in order to evaluate use of the test article in that setting. This exception is limited to situations where the intervention must be started in order to save the life of the subject and there is not time to obtain consent. This second excep-

tion requires FDA approval before the study is started, IRB approval, and public disclosure to the community of a summary of the research and that the research is being done without obtaining informed consent. The material provided to the public is available from FDA through the provisions of the Freedom of Information Act.

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Before it will approve a new drug or device for marketing, FDA requires evidence of the product's safety and effectiveness from the manufacturer. The first evidence of safety is obtained from laboratory tests and tests in animals. If favorable test results are obtained, testing in humans may begin. The entire testing process can take a number of years, with only a small percentage of

the drugs, biologics, and devices meeting all of the safety and effectiveness requirements to be approved for marketing. Persons taking part in clinical trials are not necessarily patients in hospitals and institutions. Many are patients of private practitioners involved in clinical research. Many are not patients at all, but are healthy individuals who have been recruited for a study through a newspaper ad, poster, or other source. FDA's IRB

and informed consent regulations ensure that research subjects are informed and willing participants and that their health and safety are not unnecessarily endangered.

An IRB comprises at least five people with varying backgrounds including physicians, scientists, non-scientists, and at least one person not affiliated with the research institution. Maintaining a membership with diverse training helps an IRB stay objective. An IRB should use consultants as needed to assist in the review of studies requiring specialized knowledge not held by the IRB members. The IRB must also be able to determine the acceptability of the research in terms of applicable law, standards, or professional conduct and practice.

The IRB meets to review the protocol, or research plan, for the proposed project and may approve or disapprove it or make changes before granting approval. It also must review and approve, modify, or disapprove the informed consent form to be presented to prospective research subjects. The IRB also conducts continuing review at least annually while research is under way. IRB review ensures that:

- Risks to subjects are minimized. Procedures must be used that are consistent with good research design and do not expose subjects to unnecessary risk. If the subject is a patient, the study must be designed and conducted in a way that does not adversely affect the patient's progress.
- Informed consent is obtained and documented from each subject or the subject's legal representative.
- Selection of subjects is fair and equitable, and there are safeguards to protect subjects, such as the mentally retarded, who may not be able to look out for their own interests.
- Risks to subjects are reasonable in relation to expected benefit to those subjects and the importance of the knowledge that may be gained.
- Provisions exist to protect the privacy of subjects and to maintain data confidentiality.

IRBs also ensure that appropriate additional safeguards are in place to protect the rights and welfare of vulnerable populations, such as women, children, prisoners, those with mental disabilities, and persons who are economically or educationally disadvantaged.

Periodically, FDA inspects IRB records and operations to certify that approvals, human subject safeguards (including informed consent), membership, and conduct of business are what they should be. Sometimes

these inspections yield evidence of problems, such as in 1993 when FDA imposed penalties on a large California university IRB for infractions that included failure to report deaths.

Informed consent, which is one of three elements in protecting the rights and welfare of study subjects, is not simply a matter of having the subject sign a piece of paper. It requires that the researcher:

- give the subject adequate information about the study;
- respond fully to the subject's questions and be certain that the subject understands all the risks and responsibilities that participation entails;
- ensure that the subject (if a patient is receiving treatment, for example) is aware of other options, along with their advantages and disadvantages; and
- obtain the subject's voluntary consent to take part.

Researcher and subject should discuss the study and the subject's role in it until both are satisfied that the subject can make an informed decision about whether to participate.

In July 1993, FDA released new

guidelines for including women and minorities in clinical research. The guidelines promote recruitment of women and minority participants and foster understanding of cultural nuances. In March 1994, the National Institutes of Health published guidelines implementing a new statutory requirement that women and minorities be adequately represented in federally funded research. IRBs, together with investigators and institutional officials, will play important roles in ensuring compliance with these guidelines.

How an IRB fulfills its role can be seen in a Georgetown University study into the effects of strenuous exercise on blood clotting. The study involved healthy young female runners recruited through the campus newspaper. Runners had blood drawn before and after treadmill exercise, with the fibrin (blood-clotting) time recorded. Blood pressure, heart rate, and respiration also were recorded.

Participants knew that findings might help determine whether exercise is desirable for persons recovering from heart attacks. The study also benefited participants by allow-

ing them to better understand their own physiology when running, an aid when deciding whether to stay in competition. Also, participants and their doctors were informed of any health problems that showed up during the study.

Before approving the study, the IRB at Georgetown University asked that participants be told that the study followed earlier successful research on male athletes; that the total blood drawn would be one-quarter that of a routine blood donation; and that, although it was a low-risk study, emergency equipment would be on standby. The IRB found it a big plus that the physician doing the research had gone through the blood and treadmill test herself when the study was designed.

Pellegrino stresses that study subjects must not be coerced or misled by researchers, who often do not realize how little the subjects understand. He says that patients receiving treatment who are asked to join a study "can easily confuse the experiment with their treatment." He also acknowledges that some scientists feel IRB review "somehow interferes with that research."

FDA does not require that subjects be compensated if there is injury or other unfavorable result. But in any study that involves more than minimal risk, the subjects must be told in the informed consent interview before they enter the study whether compensation and medical treatment are available and what the compensation consists of or how to obtain further information about it. The informed consent form must include an accurate summary of this information.

An additional layer of review sometimes used is an independent Data and Safety Monitoring Board (DSMB). At periodic intervals during the study, this board reviews accumulated data. The DSMB may recom-

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In March 1994, the National Institutes of Health published guidelines implementing a new statutory requirement that women and minorities be adequately represented in federally funded research.

mend stopping the study if the data show either (1) the test article is clearly superior, and all subjects should receive it, or (2) the test article is clearly inferior, in which case, none of the subjects should continue to receive it.

Present FDA policy requires that only under certain circumstances may sponsors charge clinical investigators or research subjects for investigational drugs. A firm intending to charge for experimental drugs must first justify the charges to FDA. Companies sponsoring research with investigational medical devices, however, may generally charge the investigator for the cost of the device. The investigator in turn can pass that charge on to the subject, but no profit is to be made from the experimental drug or device. Subjects must be told before they enter a study whether they will be charged for services or products as a result of taking part in the study, and the IRB must be aware of and approve such proposed charges. The informed consent document must outline any additional costs that will be billed to study subjects or their insurance companies as a result of participation in the study.

The informed consent whether oral or written, shall not contain any wording through which the subject waives or appears to waive any legal rights or releases or appears to release anyone involved in the conduct of the research from liability for negligence. The subjects may not be asked to waive ownership rights in blood or tissue samples as a condition for entering a study, particularly, a study that involves treatment for their diseases. The subjects do not waive the right of privacy; however, the consent form should explain that FDA can inspect and copy medical records as part of its approval process for drugs, biological products, and devices. Usually, FDA does not copy the names of the individual subjects—only study results.

FDA regulations permit use of a test article (drug, biological product, or device) without prior IRB review when a life-threatening condition exists; when no standard acceptable treatment is available; and when there is not time for IRB approval. This means an investigator may, in a life-threatening emergency, use a device or administer one course of treatment to a subject without IRB

review. This was done in the 1980s at the University of Arizona Medical Center, when an artificial heart, not yet approved by FDA, was used in a subject for three days as a “bridge” until a human replacement heart could be found.

If a project carries no greater risk than having a routine physical examination, FDA regulations permit an IRB to use an “expedited review.” This means that the research can be reviewed and approved by the chairman or senior members without convening the full IRB. Minor changes in an existing project also can be approved through an expedited review.

Institutions engaged in research involving humans will generally have their own IRBs that review work done on the premises or elsewhere by the staff of the institution. However, the IRB need not be “on-site” at the institution as long as it is available to review that institution’s research. An IRB in a hospital, for example, is not required to review studies done outside the hospital’s jurisdiction, but the IRB may do so if the hospital is willing.

IRB members usually are not paid for their services, but there is nothing in the regulations to prevent it. Any payment should be a fixed amount and not contingent upon a favorable review. Travel and other expenses may be reimbursed.

The FDA relies upon the careful review by the responsible IRB to ensure that the research studies are not unnecessarily risky and are valid endeavors. The IRB also assures that the process for subject selection is fair and that the subjects are adequately informed about the anticipated risks and hoped-for benefits of participation. Together, these principles serve to protect the rights and welfare of research participants.

FDA Finds New Ways to *Speed Treatments* to Patients-

Moviegoers in the '30s and '40s were regularly treated to the high drama of a dying patient whose only hope lay in an experimental drug—usually called a “serum”—that had to be flown through a raging storm, at night, to the patient’s bedside. In the Hollywood scenario, the “serum” always arrived in the nick of time; the patient was saved, the brave young doctor was acclaimed a hero with a brilliant future, and the world got a miraculous new weapon in the battle against death and disease.

MUSIC UP—FADE TO
BLACK—ROLL CREDITS

Such movies are, of course, fantasy. But underlying their dated and, by today’s standards, corny plot lines is the widely held belief that when nothing else can help, desperately ill patients ought to have access to investigational treatments that show some evidence of being useful. Concerned health professionals and consumers alike have long maintained that even though possibly important new drugs or biologicals haven’t yet completed the complex and often lengthy path to FDA

approval, physicians should nonetheless be able to use them in willing patients who can’t benefit from established therapy.

And, in fact, thousands of people receive investigational products, not only in carefully controlled clinical trials, but also in innovative programs aimed at giving them all the medical help possible.

Using investigational agents in a sort of last-ditch effort to help desperately ill and dying patients is not new to medicine. FDA has permitted the emergency use of unapproved, investigational products for many years. Under the general rubric “compassionate use,” the agency has permitted sponsors of investigational agents to provide them to doctors not involved in controlled clinical trials for use in individual patients who might be helped by the treatment.

In 1987, FDA changed its regulations on investigational new drugs (INDs) to specifically authorize treatment use of such agents. The term “Treatment IND” highlights the fact that an investigational agent is being administered not primarily to gain

information about its safety and effectiveness, as in a controlled study, but to treat certain seriously ill patients.

The change in terminology is emblematic of a shift in the way FDA, the Congress, the pharmaceutical industry, health professionals, and health activists view the role of

designed to generate the information FDA needs to make decisions about approvability. In addition, under a new congressional mandate, the agency will be able to collect user fees from product developers and manufacturers to cover the costs of expediting the review of prescription drug applications.

effectiveness began in February 1986. About 300 people with AIDS at several centers around the country were randomly selected to receive either AZT or a placebo.

These studies were abruptly halted in September 1986 when it was discovered that 19 patients receiving placebo had died, while only one death had occurred among those receiving AZT. Within a week of receiving this information, FDA authorized a treatment protocol for AZT. As a result, more than 4,000 AIDS patients were treated with AZT before its approval as the first anti-AIDS drug under the brand name Retrovir in March 1987.

Building on that and other experience with treatment protocols, FDA developed and issued in May 1987 regulations codifying the circumstances under which Treatment INDs could be granted. While the purpose is to make promising investigational drugs available as early as possible to patients with serious or immediately life-threatening diseases, the Treatment IND regulations also ensure that, despite possibly extensive treatment use of an investigational agent, carefully controlled trials will go forward to demonstrate the drug's safety and effectiveness.

The regulations reiterate the requirement that, as with all clinical use of investigational drugs, informed patient consent must be obtained, and the product cannot be promoted or otherwise commercialized. FDA also requires that a product administered under a Treatment IND must be under (or have completed) active clinical investigation, and its sponsor must be pursuing marketing approval with "due diligence."

It's critically important to complete definitive clinical trials, because once an investigational product appears in early studies to offer an important therapeutic advance and becomes

regulation must be to speed the journey

drug development and drug regulation in this country. All agree that a major goal of drug regulation must be to speed the journey from laboratory to bedside of important new drugs for devastating illnesses.

The shift involves more than just wider treatment use of unapproved agents. It also encompasses steps to accelerate FDA's process for reviewing applications to bring new drug and biological products to the market. Without compromising the approval requirements for safety and effectiveness of new drugs and biological products, FDA has taken numerous steps to shorten the time devoted to preapproval drug testing. This streamlining of the process is geared toward eliminating unnecessary, duplicative studies, and expediting the review of innovative agents for the most serious or life-threatening conditions.

Through published guidelines and meetings with sponsors, FDA reviewers help drug developers plan studies

Treatment INDs

The first class of drugs to generate interest in treatment use outside formal clinical trials consisted of beta-blocking agents used in certain forms of heart disease. During the mid-1970s, many thousands of patients were treated with beta blockers for advanced, life-threatening heart and lung conditions for which no effective alternative treatment existed. In one instance, more than 600 cardiologists treated some 20,000 patients with the antiarrhythmic drug amiodarone before it was approved for marketing as Cordarone in late 1985.

By far the most celebrated use of a Treatment IND involved expanding the availability before approval of zidovudine, commonly known as AZT, to people with AIDS. Initial (phase 1) testing of the drug in 33 patients with AIDS, carried out between July and December of 1985, yielded encouraging results. Phase 2 trials to assess the drug's safety and

available for treatment use, “you may never get another crack at it,” says Robert Temple, M.D., director of FDA’s Office of Drug Evaluation I. “If a study looks favorable—seems to show an effect on survival, for instance—physicians are very reluctant to redo the study. They want the active drug for their patients.”

Ethical concerns make it difficult for physicians to withhold a promising investigational drug that might forestall severe disability or death. But if the study that showed promise was not well-designed—if, for example, there was no control group—what looked like favorable results may prove to be an illusion. “So it’s very important to do a good study early—right at the beginning before impressions form that might turn out to be wrong,” Temple says.

He points out that the early clinical trial showing AZT to be effective in AIDS patients was a placebo-controlled study, the results of which were dramatic and unequivocal. On the other hand, in the case of ganciclovir, an antiviral drug used to treat an eye infection in AIDS patients, the path to treatment use and ultimate approval was quite different. Early suggestions of ganciclovir’s effectiveness led to wide use before controlled clinical trials ever started.

Ganciclovir was approved in 1989 on the basis of a historical comparison with other treatments. But, Temple maintains, approval of ganciclovir was almost certainly delayed for years by the lack of appropriate, controlled clinical investigation.

FDA has indicated, for purposes of Treatment INDs, what constitutes serious or immediately life-threatening illness, what scientific information about the drug’s safety and potential usefulness must be in hand, and how physicians can obtain investigational drugs for treatment use.

As of August 1994, 29 agents had been granted Treatment IND status.

The conditions for which they have been used include AIDS and its complications, control of infection in kidney transplant patients, severe obsessive-compulsive disorder, Alzheimer’s disease, severe Parkinson’s disease, various advanced cancers, and respiratory distress syndrome in premature infants. At press time, 24 of these drugs had been approved by FDA and are on the market.

clinical trials can receive investigational drugs shown in preliminary studies to be potentially useful. At press time, one drug (D4T) had been made available under the parallel track mechanism. D4T was approved for marketing in mid-1994.

Streamlining Review

Less dramatic, perhaps, than rushing investigational drugs to the desperately ill, but almost certainly of

One change FDA has adopted in recent years to speed drug review is categorizing new drugs as either standard or priority.

Other Quick Help

An older, more targeted treatment-use initiative is aimed at making investigational cancer drugs available to patients who are not participating in controlled clinical trials. Since the mid-1970s, FDA has reviewed drugs for limited distribution by the National Cancer Institute (one of the National Institutes of Health) to provide promising new anticancer drugs and drug combinations to cancer patients for whom established therapy is ineffective.

Another mechanism to permit wider availability of experimental agents is the “parallel track” policy developed by the U.S. Public Health Service in response to the AIDS epidemic. Under this policy, patients with AIDS whose condition prevents them from participating in controlled

more long-range benefit to society, are measures to streamline FDA’s review and approval process and expand the agency’s resources for this task. Although not the stuff of which gripping movies are made, these efforts can mean earlier arrival of important new drugs in hospital and community pharmacies for the benefit of everyone who needs them.

One change FDA has adopted in recent years to speed drug review is categorizing new drugs as either standard or priority. Standard drugs are those that offer only minor improvement (or none) over drugs already on the market. Priority drugs, on the other hand—which may in fact be a new dosage form of, or new use for, an existing drug—are believed to represent potential major advances in healthcare.

Distinguishing the two categories of drugs permits speedier review even before a new drug application is submitted.

FDA and sponsors of priority drugs may meet at the earliest stages of clinical testing to plan studies that will help develop the information necessary for a final decision on a product's approvability. Then, when a marketing application is submitted, FDA can mobilize available personnel and other resources needed to review the often large amounts of technical information contained in a priority new drug application.

In another effort to speed the review of marketing applications, the review process is becoming increasingly computerized. New drug applications that commonly run to thousands of pages are now arriving from sponsors in a form suitable for computer processing. This makes review and communication with the sponsor more efficient, saving time for both FDA and the firm.

Accelerated Approval

A highly specialized mechanism for speeding the approval of drugs or biologics that promise significant benefit over existing therapy for serious or life-threatening illnesses—so-called accelerated approval—incorporates several novel elements aimed at making sure that rapid review and approval is balanced by safeguards to protect both the public health and the integrity of the regulatory process itself.

Accelerated review, established by 1991 regulations, can be used in two very special circumstances: when approval is based on evidence of the product's effect on a "surrogate endpoint," and when FDA determines that safe use of a product depends on restricting its distribution or use.

A "surrogate endpoint" is a laboratory finding or physical sign that may not, in itself, be a direct measure-

ment of how a patient feels, functions or survives, but nevertheless is considered likely to predict therapeutic benefit. For example, high blood pressure and elevated serum cholesterol are risk factors for heart and blood vessel disease. Drugs that control blood pressure or cholesterol can reasonably be expected to help control or prevent direct signs of disease, such as angina, congestive heart failure after a heart attack, paralysis following a stroke, and sudden death. Once a drug has been shown effective as measured against such a surrogate endpoint, FDA can grant marketing approval.

As a condition of approval, however, FDA can require the sponsor to carry out postmarketing studies to confirm that the drug does in fact produce a clinical benefit, such as increased survival time. And if further research or experience shows that a product that received accelerated approval cannot safely remain on the market, FDA can order its prompt withdrawal.

As a further safeguard, distribution of accelerated-approval drugs can be limited to institutions that have the capability to use them safely and to physicians with specialized training or experience. The agency can also require that specific medical procedures, such as blood tests, be carried out if they are deemed essential for safe and effective use of the product.

In the summer of 1994, some health professionals and consumers active in the fight against AIDS began expressing concern that drugs in accelerated-approval and expanded access programs (including parallel track and Treatment IND protocols) may be made available with insufficient details about side effects and effectiveness.

FDA convened its Antiviral Drugs Advisory Committee on Sept. 12-13, 1994, as part of a continuing dialogue about expanded access to new HIV drugs.

Based in part on public testimony and committee recommendations, FDA's antiviral drug division is expected to issue a guidance document for sponsors of AIDS drugs applying for expanded access or accelerated-approval status.

The agency has reaffirmed its commitment to these ways to make new drugs available for people with serious and life-threatening diseases. Working with its advisory committees and other outside experts, FDA will continue to consider improvements to these processes, and implement them where appropriate.

It is clearly too soon to know whether efforts to make drugs and biologics more rapidly and widely available to the desperately ill are contributing to genuine advances in healthcare. But many thousands of patients who might otherwise be beyond hope are now able to seek help from investigational agents, and all of us stand to gain from a more efficient, more responsive system through which to bring important new agents to market.



BENEFIT vs. RISK:

HOW CDER APPROVES NEW DRUGS

Under current law, all new drugs need proof that they are effective and safe before they can be approved for marketing. No drug is absolutely safe ... there is always some risk of an adverse reaction. However, when a proposed drug's benefits outweigh known risks, the FDA's Center for Drug Evaluation and Research (CDER) considers it safe enough to approve.

The U.S. drug law first embraced the idea of risk vs. benefit nearly 37 years ago. Providing evidence of safety before marketing was first required by the Federal Food, Drug and Cosmetic Act in 1938. However, it was not until the Kefauver-Harris Drug Amendments of 1962 did firms have to show a drug's effectiveness before marketing.

Before any drug gets on the market today, CDER decides—as quickly as a thorough evaluation allows—whether the studies submitted by the drug's sponsor (usually the manufacturer) show it to be safe and effective for its intended use (see chart, “the NDA Review Process,” p. 22).

“Take AZT, for example,” says Robert Temple, M.D., director of the Office of Drug Evaluation I in CDER. (AZT stands for azidothymidine, the former generic name of the drug now known generally as zidovudine and marketed as Retrovir

to treat AIDS.) “It has significant toxicity. If you weren't quite sure it had a benefit, it would be hard to describe it as ‘safe.’ But we know from well-controlled studies, that it has a benefit. In the first large clinical study with the drug, there were 19 deaths in patients taking a placebo (an inactive substance), but only one death among those on AZT.”

Zidovudine was approved in 107 days, without cutting any corners. CDER expended an estimated eight staff years at a cost of \$600,000 on the drug's evaluation. That the review was so rapid was due largely to the fact that CDER was involved with the drug every step along the way from the start of clinical studies in AIDS patients. In addition, over the past few years, CDER has approved new protease inhibitors for treating HIV infection. All of these products were approved in a matter of months; one was approved in only

42 days. A 12 percent decline in U.S. AIDS-related deaths is partly attributed to the rapid review and approval of these components, as well as, early patient access to them.

CDER has taken steps in a number of ways to make urgently needed drugs available sooner. These are drugs used in treating serious or life-threatening diseases that have no good treatment. Under the accelerated approval rule, the Center can rely as a basis for drug approval on a reasonable surrogate endpoint, that is, a positive effect of a drug on a marker of the disease, rather than an actual, positive effect on survival of an illness. (An example of a marker would be CD4 cell counts, used to measure the strength of the immune system.) Usually, such a surrogate can be assessed much sooner. In accelerated approval, CDER approves the drug on the condition that the sponsor study the actual clinical benefit of the drug.

Promising Experimental Drugs

Today's policies allow broader use of some investigational drugs before approval for marketing. These policies include the treatment IND (investigational new drug application) and the parallel track mechanism. (see, "A Drug Review Glossary," p. 38, and "FDA Finds New Ways to Speed Treatments to Patients," p. 29.)

Both allow promising drugs, not yet approved for marketing, to be used in expanded access protocols—relatively restricted studies in which the intent is to learn about the drug, especially its safety, and provide treatment for people with no real alternatives. These expanded access protocols require researchers to formally investigate the drug in well-controlled studies and to supply some evidence that the drug is likely to be helpful. "This expanded access does not represent just giving the drug out," Temple says. "The sponsor has

the obligation to develop the drug properly, so we will know whether it really is useful."

CDER actively participates in the drug development process, seeking to provide clear standards and expectations. Sponsors are encouraged to meet with CDER before conducting large-scale controlled clinical trials. At this conference, CDER gives advice about the design of the sponsor's study plan to ensure that the trials will be acceptable.

As Temple puts it, "We try to find and eliminate flaws in the individual studies and overall development plan that we know will give us trouble later on in the NDA (new drug application) review. We don't want people to carry out a large study that has no chance of being considered adequate and well controlled."

CDER provides guidelines on how to study particular classes of drugs and on how to submit and analyze data in the marketing application.

To ensure that institutional review boards meet FDA's rules for the protection of the rights and welfare of research subjects, the agency routinely inspects the boards every five years. If problems are found, the agency may inspect the facilities more often. Animal laboratories are routinely inspected every two years, or more often if a review division has a question about a specific study.

Reviewing NDAs

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests; how the drug is constituted—its components and composition; results of the animal studies; how the drug behaves in the body; and how it is manufactured, processed and packaged. CDER requires samples of the drug and its labels.

Full reports of a drug's studies must be submitted so that CDER

can evaluate the data. The controlled clinical trials are especially important because they provide the only basis, under law, for demonstrating effectiveness. They answer the question: "Does this drug work for the proposed use?" The whole data bank is used to look for adverse effects. From analyses of the data, CDER reviewers assess the benefit-to-risk relationship (see "The Review Team," p. 38).

Human studies generate information that will be in the drug's professional labeling—the guidance approved by CDER on how to use the drug. This is the package insert that accompanies a drug in all shipments to physicians and pharmacies.

Whenever an NDA is submitted to CDER, the center lists it in a computer database that is monitored by FDA's division of scientific investigations. The division assigns field reviewers to make on-site inspections to verify that the work cited in the NDA is valid. Since more and more foreign studies are being accepted as primary evidence for drug approval, FDA has been doing a larger number of foreign inspections.

If CDER's evaluation of studies reveals major deficiencies, substantially more work by the sponsor may be needed, ranging from further analyses to the conduct of new studies—either case extends the evaluation time and delays approval.

"It's particularly important," Temple says, "that sponsors use the opportunities CDER offers during the IND to discuss the critical studies and overall plans, so that they know what we expect with respect to study design, conduct, and analysis. This can greatly reduce the chance that the application will recycle."

During the past few years, CDER has cut new drug approval times nearly in half, while the number of drugs approved in a year have dou-

During the past few years, CDER has cut new drug approval times nearly in half, while the number of drugs approved in a year have doubled.

bled. The most significant initiative used to speed the review of, and access to, new medicines was the agreement among FDA, Congress, and the pharmaceutical industry to the Prescription Drug User Fee Act (PDUFA) of 1992. The act allowed the agency to hire several hundred additional reviewers and support staff and expedite its move toward accepting computerized NDAs.

Industry and consumer response to gains made by CDER under PDUFA led, in part, to Congress's passage of the FDA Modernization Act, in November 1997. The act contains some of the most sweeping changes to the Food, Drug, and Cosmetic Act in 35 years. Of significant importance to CDER is the reauthorization of PDUFA, which extends the legislation through fiscal year 2002. It also holds CDER to tighter review standards.

"The center's success in meeting and exceeding the review performance goals agreed to in 1992 give confidence that it can rise to new challenges," says Murray Lumpkin, M.D., Deputy Center Director. "Currently, CDER is reviewing more than 90 percent of priority drug applications in six months or less; and standard drug applications in 12 months or less."

Priorities

CDER classifies investigational new drug applications and new drug applications (NDAs) to assign review priority on the basis of the drug's chemical type and potential benefit. All drugs that offer a significant medical advance over existing therapies for any disease are considered priority drugs.

Which CDER review staff gets an NDA depends on the drug. For example, cancer treatments go the division of oncology drug products; contraceptive drugs go to the division of reproductive and urologic drug products. Generic drugs, quite naturally, go to the office of generic drugs. CDER frequently seeks advice from its standing advisory committees on drugs (see "Getting Outside Advice for Close Calls," p. 41). This is especially true when an approved decision is a close call.

To be sure approval decisions reflect the most recent safety data, CDER requires safety updates four months after the NDA is submitted, again after it sends the firm an "approvable letter," and at other times if necessary. Updates must report new adverse reactions and important changes in the frequency or severity of known effects.

After CDER's primary reviewers finish their evaluation, supervisory personnel often do an additional

review. Office directors generally take final action on new molecular entities, switches from prescription to OTC status, and other important actions, such as a major new use of a drug. Other approval decisions are made at the division level.

Final Actions

In the final analysis, CDER's decision whether to approve a new drug for marketing boils down to two questions:

- Do the results of well-controlled studies provide substantial evidence of effectiveness?
- Do the results show the product is safe under the condition of use in the proposed labeling? Safe, in this context, means that the benefits of the drug appear to outweigh its risks.

When the review is complete, CDER writes the applicant to say the drug is approved for marketing; is approvable, provided minor changes are made; or is not approvable because of major problems. In the last case, the applicant can amend or withdraw the NDA or ask for a hearing. Once CDER approves the NDA, a drug is on the market as soon as the firm gets its production and distribution systems going. So, while change is inevitable and often desirable, there are some constants at the Food and Drug Administration: Safety and effectiveness and benefit vs. risk remain the pivotal issues in drug review.

A Special System for OTC Drugs

The Center for Drug Evaluation and Research has always applied the same standards to nonprescription drugs as it does to prescription ones whenever proposed over-the-counter (OTC) products meet the criteria for new drugs.

An OTC drug product does not need specific approval before marketing so long as it meets its category's standards. Sometimes an approved prescription drug is deemed safe enough for self-use and is switched to OTC status.

In 1966, FDA contracted for a review of the effectiveness of all new drugs approved solely on the basis of their safety since passage of the 1938 Federal Food, Drug and Cosmetic Act. Special attention soon focused on OTC drugs: of the 512 OTC drug products evaluated, 75 percent lacked substantial evidence of effectiveness.

That was when FDA decided it was time to tackle a broader review of OTC drugs—no small job, considering that more than 300,000 products were on the market. Those products, however, involved only about 700 active ingredients. It didn't take long for CDER planners to decide on a strategy: classify the drugs by treatment category (antacids, laxatives, and so on) and evaluate the ingredients. So, rather than review thousands of, say, individual antacid products, CDER evaluated the far fewer active ingredients found in them.

That review, under CDER's Office of OTC Drug Evaluation, is a three-phase rulemaking process, which includes advisory panel recommendations, a tentative final monograph and a final monograph for each therapeutic class of drugs under consideration. The first phase was accomplished by advisory panels that considered drugs by class, to determine whether ingredients could be generally recognized as safe and effective for self-use. Their conclusions and recommendations were presented to FDA. The agency published these recommendations in the

Federal Register and requested public comment. Panel reports have been published on all drug classes.

A number of ingredients were taken off the market as a result of the advisory panels' OTC drug review. Among them were:

- camphorated oil, a liniment often accidentally ingested with frequently toxic results;
- hexachlorophene, once common in deodorant soaps, but now available only by prescription for special antimicrobial purposes because it may damage the central nervous system;

FDA's final monograph, the third phase, identifies those active ingredients that are generally recognized as safe and effective for specified uses and that may be marketed in OTC drug products. The monograph identifies labeling claims that may appear on the products. OTC drug products containing any active ingredient or labeling claim that is not so recognized must be removed from the market. Some products can be reformulated or appropriately relabeled. For ingredients or claims not included in the monograph, a manufacturer has the option of applying for

Sometimes an approved prescription drug is deemed safe enough for self-use and is switched to OTC status.

- tribromsalan, removed from drugs and cosmetics because it was found to make skin extra sensitive to light;
- zirconium, still safe in most forms of antiperspirants, but removed from aerosols because of concern it could cause lung nodules.

For lack of proof of effectiveness, FDA banned some 200 ingredients in 1990, including products used to treat problems ranging from acne and dandruff to diarrhea and pain. In 1993, the agency banned several hundred more, including products for such problems as pain, digestive upsets, menstrual symptoms, and skin rashes.

During the second phase, FDA presented its tentative conclusions. The proposed rule allows time for public comment and for submission of new data.

marketing approval through the new drug approval procedures. A manufacturer may petition to amend the final monograph to include additional ingredients or to modify labeling. However, the firm may neither market the drug, nor use the labeling claim until the NDA is approved or the final monograph is amended.

FDA expects to complete the OTC review by publishing final rules within the next few years. The "Milestone List of OTC Rulemakings" and the "OTC Drug Review Ingredients Status Report" are available on the Internet at: www.fda.gov/cder/otc/index.htm.

The Evolution of U.S. Drug Law

FDA acts as a public health protector by ensuring that all drugs on the market are safe and effective. Authority to do this comes from the 1938 Federal Food, Drug and Cosmetic Act, a law that has undergone many changes over the years, just as it changed earlier drug regulation. Some of the major milestones in the evolution of the U.S. drug law are:

- **Food and Drugs Act (1906):** This first drug law required only that drugs meet standards of strength and purity. The burden of proof was on FDA to show that a drug's labeling was false and fraudulent before it could be taken off the market.
- **Federal Food, Drug and Cosmetic Act (1938):** A bill was introduced in the Senate in 1933 to completely revise the 1906 drug law—widely recognized then as being obsolete. But congressional action was stalled. It took a tragedy in which 107 people died from a poisonous ingredient in "Elixir Sulfanilamide" to promote passage of revised legislation that, for the first time, required a manufacturer to prove the safety of a drug before it could be marketed.
- **Durham-Humphrey Amendment (1951):** Until this law, there was no requirement that any drug be labeled for sale by prescription only. The amendment defined prescription drugs as those unsafe for self-medication and which should be used only under a doctor's supervision.
- **Kefauver-Harris Drug Amendments (1962):** News reports about the role of an FDA medical officer in keeping the drug thalidomide off the U.S. market aroused public interest in drug regulation. Thalidomide had been associated with the birth of thousands of malformed babies in Western Europe. In October

1962, Congress passed these amendments to tighten control over drugs. Before marketing a drug, firms now had to prove not only safety, but also effectiveness for the product's intended use. In addition, firms were required to send adverse reaction reports to the FDA, and drug advertising in medical journals was required to provide complete information to doctors—the risks, as well as the benefits. The amendments also required that informed consent be obtained from the study subjects. (Note: In July 1998, thalidomide was approved by the FDA with significant restrictions. Because of thalidomide's potential to cause birth defects, FDA invoked unprecedented regulatory authority to tightly control the marketing of the product in the United States.)

- **Orphan Drug Act (1983):** "Orphans" are drugs and other products for treating rare diseases. They may offer little or no profit to the manufacturer, but may benefit people with these diseases. To foster



The "Elixir Sulfanilamide" tragedy of 1937 ensured enactment the following year of the Federal Food, Drug, and Cosmetic Act. More than 100 died from using the untested, poisonous new drug formulation, but FDA had legal authority to bring only a trivial charge of misbranding against the manufacturer. The product was labeled an "elixir," which implied it was an alcoholic solution; actually, it was a diethylene glycol solution. If the term "solution" had been used instead, no charge of breaking the law could have been made.

development, this law allows drug companies to take tax deductions for about three-quarters of the cost of their clinical studies.

- **Drug Price Competition and**

Patient Term Restoration Act

(1984): This law expands the number of drugs suitable for an abbreviated new drug application (ANDA). ANDAs make it less costly and time-consuming for generic drugs to reach the market. Patient Term Restoration refers to the 17 years of legal protection given a firm for each drug patent. Some of that time allowance is used while the drug goes through the approval process.

- **Generic Drug Enforcement Act**

(1992): This law imposes debarment and other remedies for criminal convictions based on activities relating to the approval of ANDAs.

- **Prescription Drug User Fee Act**

(1992): In this law, manufacturers agreed to pay user fees for certain new drug applications and supplements, an annual establishment fee, and annual product fees. Using these funds, FDA hired more than 700 new staff by the end of FY 1997, which helped quicken the NDA review process.

- **FDA Modernization Act (1997):**

This act contains some of the most sweeping changes to the Food, Drug and Cosmetic Act in 35 years. Of significant importance to CDER is the reauthorization of PDUFA through FY 2002. The act contains changes in how user fees are assessed and collected. For example, fees are waived for the first application for small businesses, orphan products, and pediatric supplements. The act codifies FDA's accelerated approval regulations and requires guidance on fast-track policies and procedures. In addition, the agency must issue guidance for NDA reviewers.

The Review Team

The members of the CDER review team simultaneously apply their special technical expertise to the review of an NDA:

- Chemists focus on how the drug is made and whether the manufacturing, controls, and packaging are adequate to ensure the identity, strength, quality, and purity of the product.
- Pharmacologists evaluate the effects of the drug on laboratory animals in short-term and long-term studies.
- Physicians evaluate the results of the clinical tests—including the drug's adverse as well as therapeutic effects and whether the proposed labeling accurately reflects the effects of the drug.
- Pharmacokineticists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized, and eliminated.
- Statisticians evaluate the designs for each controlled study and the analyses and conclusions of safety and effectiveness based on the study data.
- Microbiologists with others evaluate the data on anti-infectives (antibodies, antivirals, and antifungals). These drugs differ from others in that they affect the workings of microbes instead of patients. Reviewers need to know how the drug acts on these microorganisms, which ones it affects, any resistance to the drug, and clinical laboratory methods needed to evaluate the drug's effectiveness. Microbiologists also are concerned with ensuring injectable drugs are free of organisms.

A Drug Review Glossary

Abbreviated New Drug

Application, or ANDA: A simplified submission permitted for a duplicate of an already approved drug. ANDAs are for products with the same or very closely related active ingredients, dosage form, strength, administration route, use and labeling as a product that has already been shown to be safe and effective. It must contain evidence that the duplicate drug is bioequivalent (see "Bioequivalence") to the previously approved drug.

Accelerated Approval: A highly specialized mechanism intended to speed approval of drugs promising significant benefit over existing therapy for serious or life-threatening illnesses. In accelerated approval, CDER approves the drug on the condition that the sponsor study the actual clinical benefit of the drug.

Action Letter: An official communication from FDA to an NDA sponsor that informs of a decision by the agency. An approval letter allows the commercial marketing of the product. An approvable letter lists minor issues to be resolved before approval can be given. A non-approvable letter describes important deficiencies that preclude approval unless corrected.

Adverse Event: Unwanted effects that occur and are detected in populations. The term is used whether there is or is not any attribution to a drug or other cause.

Advisory Committee: A panel of outside experts convened periodically to advise CDER on safety and efficacy issues about drugs. CDER is not bound to take committee recommendations but usually does.

Amendment to an NDA: A submission to change or add information to an NDA or supplement not yet approved.

Bioavailability: Rate and extent to which a drug is absorbed or is otherwise available to the treatment site in the body.

Bioequivalence: Scientific basis on which generic and name-brand drugs are compared. To be considered bioequivalent, the bioavailability of two products must not differ significantly when the two products are given in studies in the same dosage under similar conditions.

Clinical Trials: Human studies designed to distinguish a drug's effect from other influences—for example, a spontaneous change in disease progression or in the effect of a placebo (an inactive ingredient that looks like the test drug). Such studies conducted in the United States must be under an approved IND (see “Investigational New Drug Application”) and in accord with FDA rules on human studies and informed consent of participants.

Compound: A chemical synthesized or prepared from natural sources that is evaluated for its biological activities in preclinical tests.

Dosage Form: The delivery system for a drug product, such as tablet, capsule, IV solution, or topical cream.

Dose: The amount of drug administered to a patient or test subject at a single time.

Drug Products: The finished dosage form that contains a drug substance—generally, but not necessarily in association with other active or inactive ingredients.

Drug Substance: The active ingredient to diagnose, treat, cure, or prevent disease or affect the structure or function of the body, excluding other inactive substances used in the drug product.

Effectiveness: The desired measure of a drug's influence on a disease condition. Effectiveness must be proven by substantial evidence consisting of adequate and well-controlled investigations, including human studies by qualified experts, that prove the drug will have the effect claimed in its labeling.

Good Laboratory Practices, or GLP: FDA guidelines governing the conduct of nonclinical studies from which data will be used to support applications for research or marketing permits.

Incidence Rate: The rate at which new cases of disease, adverse reactions, or other events occur per unit of time in a given population at risk. The rate is theoretically calculated as the number of individuals who develop the disease over a period of time divided by the total person-years at risk.

Informed Consent: The voluntary consent given by a patient to participate in a study after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule.

Investigational New Drug Application, or IND: An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

New Drug: A drug first investigated or proposed for marketing after 1938—that is, a drug that was not generally recognized as safe and effective before that date.

New Drug Application, or NDA: An application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for CDER review—including chemistry, pharmacology, medical, biopharmaceutics, statistics and, for anti-infectives, microbiology.

New Molecular Entity, or NME: A compound that can be patented, which has not been previously approved.

Parallel Track Mechanism: Policy that makes promising investigational drugs for AIDS and other HIV-related diseases more widely available under “parallel track” protocols, while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are conducted. The system established by the policy is designed to make the drugs more widely available to patients with these illnesses who have no therapeutic alternatives and cannot participate in the controlled clinical trials.

Pharmacology: The science that deals with the effect of drugs on living organisms.

Phase 1: The first trials in humans that test a compound for safety, tolerance and pharmacokinetics. The trials usually employ normal, healthy volunteers.

Phase 2: Pilot studies to define efficacy and safety in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Dose and dosing regimens are assigned for magnitude and duration of effect during this phase.

Phase 3: Expanded clinical trials intended to gather additional evidence of effectiveness for specific indications and to better understand safety and drug-related adverse effects.

Phase 4: Studies performed after a drug is approved for marketing. The studies are performed to determine the incidence of adverse reactions; to determine the long-term effect of a drug; to study a patient population not previously studied; and for marketing comparisons against other products and other uses.

Postmarketing Surveillance: FDA's ongoing safety monitoring of marketed drugs.

Preclinical studies: Studies that test a drug on animals and other nonhuman test systems. Since animals have a much shorter lifespan than humans, valuable information can be gained about a drug's possible toxic effects over an animal's life cycle and on its offspring.

Priority Drugs: A drug that appears to represent an advance over available therapy.

Raw Data: Researcher's records of patients such as patient charts, hospital records, x-rays and attending physician's notes. CDER may request the data's submission or may audit the data at the researcher's office.

Risk: The probability of an event occurring during a specified period of time. In drug approval, it is a measure of the probability of occurrence to harm human health or of the severity of harm that may occur.

Safety: No drug is completely safe or lacking the potential for side effects. Before a drug may be approved for marketing, the law requires the submission of test results adequate to show the drug is safe under the conditions of use in the proposed labeling.

Safety Update Reports: Reports that an NDA sponsor must submit to CDER about the safety information that may affect the use for which the drug will be approved, or draft labeling statements about contraindications, warnings, precautions, and adverse reactions.

Side Effect: Any effect other than the primary intended effect resulting from drug or nondrug treatment or intervention. Side effects may be negative, neutral, or positive for the patient.

Stability: The drug product's resistance to change of its physical and chemical properties.

Supplement: A marketing application submitted for changes in a product that already has an approved NDA. CDER must approve all important NDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are not adversely affected.

Surrogate Endpoint: A laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions, or survives, but nevertheless is considered likely to predict therapeutic benefit.

Treatment IND: A mechanism that allows investigational drugs to be used in expanded access protocols: relatively unrestricted studies in which the intent is to learn more about the drugs and to provide treatment for people with immediately life-threatening or otherwise serious diseases for which there is no real alternative.

User Fees: Charges to drug firms for certain NDAs, drug products, and manufacturing establishments. FDA uses these fees to hire application reviewers and to accelerate reviews using computer technology.

Getting

Outside Advice

for Close Calls

“Viewpoints vary between concerns of individual clinicians and what may affect the doctor-patient relationship, or how a drug affects a patient circumstance A professional woman on the committee, for instance, takes the position of the woman patient, asking whether medicine is doing something too intrusive, exercising too many prerogatives, or presenting an unreasonable risk for the patient.”



— Ezra Davidson Jr., M.D., professor and chair, Department of Obstetrics and Gynecology, Charles R. Drew-University of Medicine and Science, Los Angeles, discussing the Food and Drug Administration’s Fertility and Maternal Health Drugs Advisory Committee, which he chaired for several years.



Ezra Davidson Jr., M.D., serves on one of 18 committees that advise FDA about safety and effectiveness of drugs—particularly on decisions that are “close calls.”

Of the 11 members of his committee, 10 are educators. Seven of the physicians specialize in obstetrics and gynecology—three also in reproductive biology. Two are epidemiologists (specialists in the incidence and prevalence of disease). Other areas represented are nursing and behavioral sciences. Committees meet in the Washington, D.C., area, generally at FDA headquarters in Rockville, Md., and those on Davidson’s committee travel from as far away as Hawaii. The executive secretary, an FDA medical officer, connects the committee with the agency.

It may seem unnecessary for FDA to seek outside advice. After all, the agency employs its own full complement of scientific specialists. But outside experts add a wide spectrum of judgment, outlook, and state-of-the-art experience to drug issues confronting FDA. “We seek scientists with a broad range of expertise and different backgrounds,” says John Treacy, director of the advisors and consultants staff in FDA’s Center for Drug Evaluation and Research.

These expert advisers add to FDA’s understanding, so that final agency decisions will more likely reflect a

balanced evaluation. Committee recommendations are not binding on FDA, but the agency considers them carefully when deciding drug issues.

Members

Most members of FDA’s drug advisory committees are physicians whose specialties involve the drugs under the purview of their committee. Others include registered nurses, statisticians, epidemiologists, and pharmacologists (who study drug effects in the body). Consumer-nominated members serve on all committees. As voting members, they must possess scientific expertise to participate fully in deliberations. They must have worked with consumer groups, so they can assess the impact of decisions on consumers. The committees range in size from 10 to 15 members, but most have 11. Each committee advises a corresponding FDA drug review group.

All government advisory committees are regulated by the Federal Advisory Committee Act of 1972, although FDA began using panels of outside experts in 1964. Each committee must be renewed by FDA every two years, or its charter automatically expires. Renewals must be approved by the Secretary of Health and Human Services and the Administrator of the General Services Administration.

The FDA Modernization Act of 1997 created a new advisory committee and added new provisions for advisory committees. The new committee is the Pharmacy Compounding Committee, which will advise FDA on a variety of pharmacy compounding issues. Among the new provisions is a requirement that the committee meet within 60 days of when a subject is ready for review and that the agency take action within 90 days of a committee recommendation or give the reason that no action has been taken. New committees are required to have both consumer and industry representatives. In addition, at least two members must be specialists or have other expertise in the particular disease for which the drug is indicated. There are also new conflict-of-interest provisions that limit voting and prohibit members from voting on their own scientific work. Finally, training is mandatory for all members prior to their first meeting.

Committee Independence

To encourage the committees’ independence, FDA recruits members from a broad range of qualified candidates. Sources of nominations—with emphasis on identifying women and minority candidates, include professional, scientific and medical societies; medical and other professional schools; academia; government agen-

Even at a closed meeting, there must be an open portion at which the public can give presentations, ask questions, and take part in general discussions.

cies; industry and trade associations; and consumer and patient groups. FDA's Office of Consumer Affairs, in particular, seeks suggestions for consumer-nominated representatives through agency field offices, current and former consumer-nominated representatives, and diverse consumer organizations with national and local interests and a widely varied membership, representing women, older people, African Americans, Hispanics, and Asians. Requests for candidates also appear in the *Federal Register*.

FDA staff members review the nominations (which can exceed 200 candidates) to identify the best mix of expertise for the particular committee. A list of nominees is then sent to the Office of the Commissioner for final selection. Committee chairs are also selected by the commissioner; they are not elected by the committees.

Meetings

Committees typically meet two to four times a year, but may meet as often as FDA needs them. FDA announces upcoming meetings in the *Federal Register*.

Members receive \$150 a day while attending committee meetings, and reimbursement for costs of travel, food, and lodging. This attendance is a public service on the part of many members, who forgo seeing patients or conducting research or teaching

activities to serve FDA. Thanks to the aptly named "Government in the Sunshine Act" of 1977, meetings of drug advisory committees are public, except when a topic's open discussion would be an invasion of privacy or when confidential, commercial, or trade secret information or law enforcement investigations are presented or discussed. Even at a closed meeting, there must be an open portion at which the public—as time allows—can give presentations, ask questions, and take part in general discussion. Most meetings are entirely open.

FDA almost always sets the agenda and prepares the questions for each meeting. Anyone, however, may ask that a specific drug issue be brought before the appropriate committee. When a committee itself asks to review a matter within its purview, this is granted whenever possible.

Types of Advice

FDA may especially want a committee's opinion about a new drug, a major new indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling.

The committees may advise FDA on necessary labeling information and help with guidelines for developing particular kinds of drugs, such as those for anesthesia, heartbeat irregu-

larities, and cancer.

They also may address such questions as whether a proposed study for an experimental drug should be conducted and whether the safety and effectiveness information submitted for a new drug is adequate for marketing approval.

For instance, Cognex (tacrine), the first drug approved to treat Alzheimer's disease, was the subject of several meetings of the Peripheral and Central Nervous System Drugs Advisory Committee during its clinical testing.

When the committee first met to consider Warner-Lambert Co.'s application for Cognex in March 1991, it concluded that available evidence did not support approval. On the basis of additional data submitted in July, the committee still recommended against approval, but advised that studies be conducted with a higher dose, over a longer time. The committee also recommended a Treatment IND (investigational new drug)—an FDA procedure for promising drugs for serious diseases that provides for wider use than is usual during the preapproval stage—provided no satisfactory approved treatment existed and patients wouldn't be exposed to unreasonable risk. FDA granted the Treatment IND in December 1991, after finding the drug appeared to slightly improve mental function in some patients at low doses and might be more effective at larger doses. The Treatment IND, begun in February 1992 and involving more than 7,400 patients, showed that Cognex provided a small but clinically meaningful benefit for some patients with mild-to-moderate Alzheimer's disease. Meeting again in March 1993, the committee recommended approval of the marketing application. FDA approved Cognex in September, after reviewing the additional information from studies.



During a meeting of FDA's Oncologic Drugs Advisory Committee, committee member Paul Bunn, M.D. (left), director of the University of Colorado Cancer Center, gives his opinion about a cancer drug being considered for approval. Daniel Ihde, M.D., Washington University School of Medicine, St. Louis, Mo., listens.

Below, FDA medical officer Grant Willams, M.D., tells the committee, seated at the tables, about the drug. The audience at FDA headquarters in Rockville, Md., includes drug firm representatives and consumers.



To encourage the committee's independence, FDA recruits members from a broad range of qualified candidates.

Adverse Reactions

FDA's advisory committees may also consider reports of adverse reactions to an already marketed drug. If there are severe reactions or deaths and it's not clear what's going on, the agency might call a special meeting.

For information about FDA advisory committee meetings, call (1-800) 741-8138. In the metropolitan Washington, D.C. area, call (301) 443-0572. This information may also be obtained online by accessing the FDA Internet site on the World Wide Web at <http://www.fda.gov/>.

For information about how to nominate a consumer representative, write to the Office of Consumer Affairs, FDA, HFE-88, Room 16-85, 5600 Fishers Lane, Rockville, MD 20857.

Typical questions include:

- Should the dosage schedule be changed?
- Should certain groups of patients receiving the drug not be getting it?
- Should the contraindications (situations when the drug should not be used) be changed?
- Are the reactions to the drug also seen with other drugs in its class?

FDA received some 50 reports of serious reactions, including three deaths, to Omniflox (temafloxacin) in the first three months of market-

ing. A fluoroquinolone—one of a newer class of antinfective drugs—Omniflox had been approved in January 1992.

Side effects included dangerously low blood sugar levels in elderly patients, anemia due to excessive destruction of red blood cells, kidney failure, blood-clotting problems, and abnormal liver function. The manufacturer voluntarily withdrew the drug.

FDA then asked its Anti-infective Drugs Advisory Committee to discuss the problem and consider implications for quinolones in development.

Nonprescription Drugs

Over-the-counter drugs, too, benefit from advisory committee deliberation. From 1972 to 1981, at FDA's request, 16 special panels evaluated the effectiveness and safety of all classes of OTC drugs then on the market.

During hearings before the Advisory Review Panel on OTC Miscellaneous External Drug Products in 1980, New Jersey pharmacist Carmine Varano cited disastrous incidents involving camphorated oil: A 2-year-old died after exposure to camphorated oil on the chest for nearly 80 hours, a 15-month-old became confused and had seizures after crawling through spilled spirits of camphor, and an infant nearly died

after camphor ointment was rubbed on its chest. Varano reported he had data from a Detroit hospital about 26 camphorated oil poisonings between 1975 and early 1979. FDA accepted the panel's advice to put camphorated oil in its place—off the U.S. market. Those OTC panels completed their review tasks and have been disbanded. OTC issues are now brought to the agency's Nonprescription Drugs Advisory Committee, which includes a voting consumer-nominated representative and a nonvoting industry representative. On a given issue, the committee will ordinarily meet jointly with another committee with special expertise in that issue. There have been a few instances in which FDA has *not* followed a committee's recommendations. Treacy cites the Rx-to-OTC switch of the pain reliever naproxen sodium, previously sold only by prescription under the trade name Anaprox and now also over-the-counter as Aleve. In June 1993, the combined arthritis and nonprescription committees voted 7 to 4 against the switch. "They had a lot of reasons," Treacy says. "The dose was too high. The labeling for people over 65 was incorrect because they excrete the drug at a *slower* rate. The members requested labeling for children because the drug makes the skin more photosensitive, and children already sunburn more easily than adults. Also, the members were uncomfortable with FDA's policy of allowing a manufacturer to mention in the label any of a list of several types of pain on the basis of studies of just any two types on the list. Although this policy had been suggested by an advisory panel before being accepted by the agency, members suggested that our scientific knowledge has increased to the point where we can be more specific."

The manufacturer, Syntex Laboratories, listened to all the

objections, Treacy says, and, working with FDA, immediately altered the dose interval and the dose, and changed the labeling for people over 65 and for children.

FDA had a follow-up meeting to brief the committees on the changes and its decision to approve the switch.

“The bottom line is FDA’s,” Treacy says. “The committees are advisory only. In approving the switch, we took into account the objections of the members. However, we treated it just like all the other OTC painkillers in terms of the labeling in order to give it parity with other OTC analgesics.”

Managing Conflicts

The National Academy of Sciences’ Institute of Medicine published findings in December 1992 of a study it did—at FDA’s request—of the agency’s advisory committees. FDA had been having increasing difficulty identifying potential members with needed expertise, but without financial or professional interests that could lead to conflicts of interest or the appearance of conflicts of interest. The institute confirmed that the system was fundamentally sound and did not need major changes. But it recommended a number of administrative and procedural changes regarding committee membership, committee operations, integrity of the committee system, and FDA organization and management of the system.

While the institute’s study was going on, FDA conducted its own analysis of its advisory committee system. The outcome of the two reviews led the agency to concur with nearly all the institute’s recommendations, which are reflected in how members are recruited and how meetings are managed today.

“We did a lot of work to strengthen the integrity of the system by resolving conflicts of interest up front,”

says John Treacy, director of the advisors and consultants staff for FDA’s Center for Drug Evaluation and Research.

Throughout the government, advisory committee members are subject to federal laws and regulations prohibiting participation in any official action in which they have financial interests—which the law says include those of their regular employing organization. If a member is on the faculty of a university that has a grant from the pharmaceutical firm to study the drug to be reviewed by that committee, the member can’t act on that issue, Treacy says. The law does allow waiver of the interest.

on the firm if a given product is approved or disapproved.

For example, a waiver would not be granted, Treacy says, if a member owned more than \$100,000 in stock in a firm whose drug was coming before the committee, and this was more than 5 percent of the person’s net worth.

“On the other hand,” he says, “if the member’s university had a grant of less than \$15,000 to study a drug to be discussed, and the member was not involved with the grant, we’d generally grant the waiver.”

Nevertheless, Treacy emphasizes that FDA carefully considers committee recommendations, “so we’re reevaluating what is appropriate

Recommendations supplement FDA expertise and add to the quality of the agency’s decisions.

“Before every meeting,” Treacy says, “we send members a questionnaire, stating the issues coming up and the companies with financial interests. We ask, ‘Do you own stock or have grants or contracts involving these issues or firms?’ If there is a conflict, we exclude the person, or, if our need outweighs the conflict, a waiver may be granted.”

In a typical meeting with 11 members, there are usually two or three who have waivers, he says. (Sometimes there are none; other times, more than three.)

Criteria for granting a waiver are based on many factors, such as the amount of the financial interest, what percentage of a person’s net worth that interest is, and the impact

labeling for all OTC painkiller products. In fact, at another advisory committee meeting on Sept. 8 and 9, 1994, the members discussed what indications for the products must be studied.” As these many examples show, recommendations from advisory committees supplement FDA expertise and add to the quality and credibility of the agency’s decisions.

Advisory committee members benefit, too. Says Fertility and Maternal Health Drugs Advisory Committee chair Davidson: “It’s a great educational opportunity, whatever the issue. As an ob-gyn, academician, and otherwise inquisitive person, I find this advisory panel to be a mixture of science and policy that attracts my interest.”



An Inside Look at

FDA On-Site

There are over 18,000 establishments in the United States that manufacture, test, pack, and label drug products for humans. The Federal Food, Drug, and Cosmetic Act requires FDA to inspect each of these facilities at least once every two years. In addition, approximately 1,100 foreign facilities are periodically inspected.

Agency investigators, working from field offices in some 172 locations throughout the country, completed 3,661 domestic inspections in 3,230 human drug establishments in the fiscal year that ended Sept. 30, 1998. Another 356 inspections were done at 323 foreign establishments.

During that year, the agency took a number of legal actions to correct deficiencies for failure to meet drug manufacturing and product standards. These included three prosecutions, three injunctions, 19 seizures, and 244 warning letters. FDA also monitored recalls involving 264 drug products in various dosage forms.

An inspection can last from one or two days to several weeks, depending on its purpose and scope. There are three primary types of inspections: preapproval, postapproval, and surveillance good manufacturing practice (GMP) inspections.

Preapproval inspections are often initiated by the Center for Drug

Evaluation and Research at FDA headquarters. While the center is reviewing a new drug application or abbreviated new drug application, it requests that the field office inspect the drug manufacturing facilities.

This inspection represents a significant step in the drug review process. The investigators must determine if the data submitted in the firm's application are authentic and accurate and if the plant is in compliance with current good manufacturing practice regulations. The district office recommends approval or disapproval of the application, based on its findings.

After the center approves an application and the firm is ready to start marketing the drug, FDA conducts a postapproval inspection, to evaluate the firm's validation studies.

"Validation" refers to FDA's requirement that the firm show it can consistently manufacture a drug product within tight parameters from batch to batch, day to day, year to year. The investigators also verify that the firm has not changed its manufacturing, labeling, or quality control testing for that drug without filing a supplement to its application, and that the firm has not exceeded a tenfold "scale-up" in production.

"Scaling up" is the process of

increasing the batch size for commercial manufacture. "For commercial production, FDA allows firms to manufacture their product in batches ten times larger than those produced for clinical or bioequivalency testing," Matthew Spataro, an investigator with the agency's New Jersey district office, says. "For example, if tablets were produced in batches of 100,000 during clinical testing, the commercial production batch cannot exceed 1 million tablets."

The investigators collect samples at both preapproval and postapproval inspections for analyses that will compare the composition of the product against known standards. The drug's chemical "fingerprint" must match the standard pattern for the compound. Samples are also collected to verify that the firm's laboratory methods are proper and consistent with the drug application.

Finally, a GMP, or "routine," inspection evaluates the firm's entire operations. Although pre- and postapproval inspections include examination of the firm's manufacturing practices, they are product-specific. GMP inspections, on the other hand, involve a comprehensive review of the firm's manufacturing operations.



When FDA's Matthew Spataro (right) arrives to inspect Knoll Pharmaceutical Company's manufacturing plant in Whippany, New Jersey, he shows his credentials and issues a written "Notice of Inspection" to Michael Corey, Knoll's Quality Assurance Manager. A full inspection may take weeks, while a visit to look

at one or two specific things may take only an afternoon. An inspection team may comprise several people, including analysts, chemists, microbiologists, and investigators.

Before coming to the plant, Spataro, an FDA investigator with the New Jersey district office, reviews the plant's inspection history.

In the plant's receiving area, the investigator makes sure the firm is following its written procedures for receiving and handling incoming raw materials. He also evaluates the procedures to make sure they are adequate.



Early in the inspection, Spataro looks over the company's product complaint files. These files not only reveal how a firm conducts its complaint investigations, but they may also help investigators determine what areas to focus on in their inspection.

"If there are substantial problems or complaints about a product, we look at what kind of effort a firm puts into resolving the complaints," Spataro says. "If a firm is responsible for the problem, what is the corrective action taken? Did they look at manufacturing batch records? Did they review the laboratory analyses?"

"If there are excessive complaints about a particular product," Spataro adds, "the investigator may collect a sample from the reserve samples and have it analyzed at FDA's laboratory. A product that doesn't meet its predetermined specifications may be removed from the marketplace."



In the compressing area, precise amounts of materials are compressed for formulated products. Here, Spataro observes the operations that are essential for ensuring the quality of the product.



Spataro and Bob Stewart (left), Knoll's Manager of Packaging, review the label inspection system. Product labels are scanned for accuracy of batch number and expiration dates.

"A batch record is one of the most important documents in drug production because it tells the whole history of that batch," says Spataro. "It's a copy of the master record, the approved way to manufacture a particular product in a particular batch size. The record follows the batch

production from one processing area to the next and records every step from beginning to end. Employee signatures document that the steps in manufacture, processing, packing, or holding were completed."

The record contains everything that happened concerning production of that batch—what went into it, where samples were taken, any problems encountered during manufacturing (such as equipment or power failure or a broken hose)—down to the exact batch yield.

If there is a problem with a product after it's on the market, Spataro says, one of the first things investigators do is examine the batch record for any problems—even those seemingly unimportant at the time—that may have occurred during manufacture.

Spataro checks to see if the equipment log accurately reflects the usage and cleaning of that particular vessel. Proper cleaning between uses is important to avoid contamination of products.



In the laboratory, Quality Control Senior Chemist Mila Cruza shows Spataro the results of a high-performance liquid chromatography (HPLC) assay she's performing on a finished product sample. The test is conducted to ensure the product conforms to standards and contains no impurities.

HPLC tests for the active ingredients of a formulation. "Every formulation has its own 'chemical fingerprint' that appears on the chromatogram as a distinct pattern of peaks," Spataro says: "If the pattern does not match the known standard, then a problem is apparent. Further tests can determine what the abnormal peaks represent.

"When we go into the laboratory, we make sure the HPLC and other instruments are working properly, check the quality of chromatograms, review what analytical methods are used and if they are appropriate and calculated correctly."



Spataro inspects some boxes from the warehouse where a firm may store products not yet distributed. Failed products that have not yet been destroyed would be stored in a separate reject area.

“An investigator may want to look at the reject area early on in the inspection for clues about what to key in on,” says Spataro. “For example, if batches of a particular product have failed or been rejected, then that product will warrant a closer look.”



Spataro observes Senior Quality Control Chemist Dale Kiddoo (right) setting up for a finished product USP (United States Pharmacopoeia) dissolution test. The dissolution test results determine how the tablets dissolve and whether or not they are suitable for marketing.



MedWatch: FDA's "Heads Up" on Medical Product Safety





When the Food and Drug Administration approves drugs and other medical products, the agency takes every precaution to make sure these products are safe when they are marketed.

But that's not always the end of the story. The true picture of product safety actually evolves over the months and even years that make up a product's lifetime in the marketplace. Because the clinical trials that help gauge product safety are conducted on small groups of patients—usually ranging from a few hundred to several thousand—problems can remain hidden, only to be revealed after hundreds of thousands or even millions of people use the product.

For example, clinical trials can't assess the effects of every new drug in combination with other approved drugs. So it is possible that a patient could have a serious reaction from a new drug when taken with another drug in a combination that was not tested in trials.

That's why, through the MedWatch program, FDA conducts "postmarketing surveillance" of medical products to identify safety concerns and take necessary action. MedWatch depends on doctors, dentists, nurses, pharmacists, and other health professionals to pass on to FDA details of serious adverse reactions and medical product problems.

MedWatch reports played major

FDA conducts "postmarketing surveillance" of medical products to identify safety concerns and take necessary action.

roles in recent decisions to remove the painkilling drug Duract (bromfenac sodium) from the market following reports of deaths and injuries. FDA also moved to withdraw the blood pressure treatment Posicor (mibefradil dihydrochloride) after learning of serious adverse reactions.

"To withdraw a drug or device from the marketplace is a very significant step, and it's something that is done only when necessary," says Michael Friedman, M.D., FDA deputy commissioner. "But when such an action occurs, it proves that the postmarketing surveillance system is working just as it should." He

“To withdraw a drug or device from the marketplace is a very significant step, and it’s something that is done only when necessary.”

— Michael Friedman, M.D., FDA

adds that most of the agency’s post-marketing actions are less severe than withdrawal from the market. Educational efforts such as labeling changes or letters to health professionals warning of new concerns are more typical responses.

The agency has had a postmarketing surveillance program in place since 1961. It replaced an earlier system sponsored by the American Medical Association. FDA’s system eventually evolved into five separate reporting forms for different products, such as drugs or medical devices. In 1993, then-FDA Commissioner David A. Kessler, M.D., citing confusion with the multiple forms, moved to consolidate them, and MedWatch was born. Since then, MedWatch has logged more than 85,000 voluntary reports, mostly from health professionals. (The agency also has a separate mandatory reporting system required by law for medical product manufacturers and certain healthcare facilities.)

The MedWatch program has four goals:

- To clarify what should and should not be reported to FDA.
- To increase awareness of serious reactions caused by drugs or medical devices.
- To make the reporting process easy.

- To give the health community regular feedback about product safety issues.

While participation in MedWatch is voluntary, FDA encourages anyone aware of a serious adverse reaction, including consumers, to make a MedWatch report.

“Health professionals are helpful to us because they usually have the clinical or medical documentation we need to assess the situation,” says Dianne Kennedy, FDA’s MedWatch director. “Often, consumers don’t have detailed information. However, consumers certainly can make reports, but whenever possible, they should work with a health professional in filling out a report.” She adds that in cases where consumers are embarrassed or have other reasons why they do not want to report a problem through a health professional, FDA still wants the information and encourages consumers to make the report alone.

Products covered under MedWatch include drugs, biologics (such as blood products), and medical devices (such as heart valves or kidney dialysis machines). FDA also wants reports of serious reactions due to dietary supplements, infant formulas, and medical foods (such as low-nitrogen products used by patients with severely reduced kidney function). Adverse reactions to artificial

How to Make a MedWatch Report

FDA offers several ways for health professionals or consumers to submit MedWatch reports:

- Online—Go to the MedWatch Website at www.fda.gov/medwatch/ and follow the instructions for submitting a report electronically.
- By mail—Use the postage-paid MedWatch form, which includes the address. Many health professionals keep the form in stock. To get a copy, call MedWatch at 1-800-332-1088, and one will be sent by mail or fax. You also can download the software for printing out the form through MedWatch’s Website, www.fda.gov/medwatch/.
- By fax—You can submit a completed form to MedWatch’s fax number, 1-800-332-0178.

Reports of serious adverse reactions or problem products also may be made to product manufacturers, where, by law, they must be reported to FDA.

If you have any questions about the reporting process, call 1-800-332-1088; press “0” or wait on the line. Or send questions by e-mail to medwatch@bangate.fda.gov

MEDWATCH

U.S. FDA MEDICAL PRODUCTS REPORTING PROGRAM

For **VOLUNTARY** reporting
by health professionals of adverse
events and product problems

Form Approved 0988-0102-0101 Expires 12/99
See 48 CFR 101-11.6 for details on GSA FPMR

Fill in this field

Trace and
response

Page of

A. Patient Information

1. Patient Identifier In confidence	2. Age at time of event or Date of birth	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight lb or kg
--	--	--	-----------------------------

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defective/included)

2. Outcomes attributed to adverse event (check all that apply)

<input type="checkbox"/> death	<input type="checkbox"/> disability
<input type="checkbox"/> life-threatening	<input type="checkbox"/> congenital anomaly
<input type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
	<input type="checkbox"/> other: _____

3. Date of event (month/year)	4. Date of FDA report (month/year)
-------------------------------	------------------------------------

5. Describe event or problem

6. Relevant investigational data, including codes

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, reproductive dysfunction, etc.)

C. Suspect medication(s)

1. Name (give generic strength & attributes, if known)

#1 _____

#2 _____

2. Dose, frequency & route used	3. Therapy dates (if unknown, give starting/ending or last therapy)
#1 _____	#1 _____
#2 _____	#2 _____

4. Diagnosis for use (indicate)	5. Event started after use stopped or dose reduced
#1 _____	#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure
#2 _____	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 _____	#1 _____	#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure
#2 _____	#2 _____	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure

9. NDC # (for product problems only)

10. Concurrent medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address	4. Operator of device
	<input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient <input type="checkbox"/> other: _____

5. Registration date (month/year)
6. Model # _____
7. If repaired, give date (month/year)
8. If repaired, give date (month/year)
9. If repaired, give date (month/year)
10. Serial # _____
11. Lot # _____
12. Other # _____

8. Device available for evaluation? (Do not send to FDA)

yes no returned to manufacturer on _____

10. Concurrent medical products and therapy dates (exclude treatment of event)

E. Reporter

1. Name & address

phone # _____

2. Health professional?	3. Distributor?	4. Also reported to
<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> manufacturer <input type="checkbox"/> user/injury <input type="checkbox"/> distributor

5. If you do NOT send your identity disclosure to the manufacturer, please an "X" in this box.

PLEASE TYPE OR USE BLACK INK



Mail to: MEDWATCH
800 Fishers Lane
Rockville, MD 20892-0787

FAX to: 1-800-FDA-0178

FDA Form 1088

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Other Kinds of Reporting

Though FDA accepts MedWatch reports for a variety of medical products, there are two product categories that have different ways of reporting. They are:

- Vaccines—Any adverse events or product problems with vaccines should not be sent to MedWatch but to the Vaccine Adverse Event Reporting System (VAERS), operated jointly by FDA and the national Centers for Disease Control and Prevention. For a copy of the VAERS form, call 1-800-822-7967, or download the form (in PDF format) from www.fda.gov/cber/vaers/vaers1.pdf on FDA's Website.
- Veterinary products—Report any adverse events related to use of medical products in animals to FDA's Center for Veterinary Medicine, 1-888-332-8387.



sweeteners, preservatives, and other food additives also should be reported.

Serious Adverse Reaction

The key point to remember when making a MedWatch report is that the adverse reaction should be serious. FDA does not want reports of all adverse reactions, especially ones that are listed in a product's labeling, such as a minor rash following drug therapy. "All drugs have side effects," says Kennedy. "If we were to get reports of all adverse reactions, we'd be overwhelmed, making it difficult for us to focus on the issues with the most public health impact." She says patients can avoid making an unnecessary report by asking their doctors or pharmacists what side effects to expect from products.

Report to MedWatch only if one or more of the following occurs:

- Death—If an adverse reaction to a medical product is a suspected cause of a patient's death.
- Life-threatening hazard—If the patient was at risk of dying at the time of the adverse reaction or if it is suspected that continued use of a product would cause death (examples: pacemaker breakdown or failure of an intravenous (IV) pump that could cause excessive drug dosing).

- Hospitalization—If a patient is admitted or has a prolonged hospital stay because of a serious adverse reaction (example: a serious allergic reaction to a product such as latex).
 - Disability—If the adverse reaction caused a significant or permanent change in a patient's body function, physical activities, or quality of life (examples: strokes or nervous system disorders brought on by drug therapy).
 - Birth defects, miscarriage, stillbirth, or birth with disease—If exposure to a medical product before conception or during pregnancy is suspected of causing an adverse outcome in the child (example: malformation in the child caused by the acne drug Accutane, or isotretinoin).
 - Needs intervention to avoid permanent damage—If use of a medical product required medical or surgical treatment to prevent impairment (examples: burns from radiation equipment or breakage of a screw supporting a bone fracture).
- FDA emphasizes that it is not necessary to prove that a medical product caused an adverse reaction—a suspected association is sufficient reason to make a report.

“If we were to get reports of all adverse reactions, we’d be overwhelmed, making it difficult for us to focus on the issues with the most public health impact.”

— Dianne Kennedy

FDA also wants to know about defective or malfunctioning medical products. Any concerns about quality, performance or safety of any drug or device warrant a MedWatch report. Some product problems may occur during manufacturing, shipping or storage. For example, a pharmacist may notice an off-color tablet in a drug container. A consumer may hear a rattling noise in a bottle, possibly indicating broken glass. Or a

some SureStep blood glucose meters used by diabetics were giving confusing error readings. Because they could have led to serious adverse reactions or possibly death by failing to indicate high blood sugar, defective devices were subsequently recalled.

- Labeling changes—Sometimes the agency may require the manufacturer to add new information to the product's package insert. Such

Once an adverse event or product problem is identified, the agency can initiate various actions.

nurse may notice a wiring defect on a medical device.

The identity of patients and other persons making MedWatch reports is kept confidential. The agency has regulations in place to preserve privacy.

What does FDA do with the information from MedWatch reports? "All reports are entered into a postmarketing surveillance database and are evaluated by a postmarketing safety evaluator," says Kennedy. Once an adverse event or product problem is identified, the agency can initiate various actions, including:

- Medical alerts—"Dear Health Professional" letters or safety alerts provide important product safety information to doctors, pharmacists, and other health professionals, as well as trade and media groups. For example, FDA issued an alert after receiving reports that

was the case when FDA required strengthened labeling on the diabetes drug Rezulin (troglitazone) to indicate possible liver damage hazards.

- Boxed warnings—FDA can require that warnings be placed in a prominent place—often within a box in the labeling—to ensure that patients and doctors don't miss the warnings. For example, FDA required Roche Laboratories to place boxed warnings in the labeling of its stroke prevention drug Ticlid (ticlopidine) after reports of a life-threatening blood disorder that was not observed in clinical trials.
- Product withdrawals—One of the most serious actions FDA can advise a company to take, withdrawals usually involve removing a product permanently from the

marketplace. Such a withdrawal took place last year when the weight-loss drugs Redux (dexfenfluramine) and Pondimin (fenfluramine) were taken off the market after being associated with heart-valve problems.

MedWatch reports also may prompt the agency to require manufacturers to conduct postmarketing studies on a product or to make manufacturing facilities available for inspection.

Getting the Word Out

The MedWatch program relies on a collaborative network of about 140 health professional and trade organizations to spread the word about MedWatch to their constituents and encourage participation. The list of these MedWatch "partners" reads like a Who's Who of the health profession, with collaborators such as the American Medical Association, the College of American Pathologists, and the National Association of Chain Drug Stores. Partners help by inserting the MedWatch form into their journals or newsletters and sharing important new safety information from FDA with their members.

"We're now going directly to the major pharmacy chains, and several have already joined us as partners," says Gale White, MedWatch deputy director. She says it makes sense to have pharmacies as partners so the agency can have another direct route to patients and any adverse reactions that may occur.

Meanwhile, Kennedy says the MedWatch program has proven its value repeatedly by helping patients escape illness or even death. "The bottom line," she says, "is that we have this system in place and it works."



FDA Ensures **Equivalence of Generic Drugs**

Drug products sold in the United States are approved by the FDA whether they are brand name or generic. “Most people believe that if something costs more, it has to be better quality. In the case of generic drugs, this is not true,” says Gary Buehler, Director of FDA’s Office of Generic Drugs. “The standards for quality are the same for brand name and generic products.”



Despite the strict standards imposed by the FDA for approval of generic drugs, and their enforcement of these standards, a number of misconceptions about generic drugs persist (See “Myths and Facts about Generics” to the right).

New drugs, like other new products, are developed under patent protection. The patent protects the investment in the drug’s development by giving the company the sole right to sell the drug while the patent is in effect. When patents or other periods of exclusivity on brand-name drugs are near expiration, manufacturers can apply to the FDA to sell generic versions.

“Much of FDA’s review of generic drugs and brand name drugs is the same,” Buehler explains (See “Same FDA Requirements for Brand-Name and Generic Drugs” below). There

are eight major parts to the FDA’s review of a firm’s application to sell a generic drug:

- There must be an FDA-approved brand-name drug that is the reference for the proposed generic. The generic must have the same active ingredient or ingredients and the same labeled strength as this reference product. It must have the same dosage form—tablets, patches and liquids are examples of dosage forms. It must be administered the same way, for example, swallowed as a pill or given as an injection.
- The manufacturer must show the generic drug is “bioequivalent” to the brand-name drug (See “What Is Bioequivalence?” below).
- The generic drug’s labeling must be essentially the same as that of the approved drug.

- The firm must fully document the generic drug’s chemistry, manufacturing steps, and quality control measures. Each step of the process must be detailed for FDA review.

Myths and Facts about Generic Drugs

MYTH: *Generics take longer to act in the body.*

FACT: The firm seeking to sell a generic drug must show that its drug delivers the same amount of active ingredient in the same timeframe as the original product.

MYTH: *Generics are not as potent as brand-name drugs.*

FACT: FDA requires generics to have the same quality, strength, purity, and stability as brand-name drugs.

MYTH: *Generics are not as safe as brand-name drugs.*

FACT: FDA requires that all drugs be safe and effective and that their benefits outweigh their risks. Since generics use the same active ingredients and are shown to work the same way in the body, they have the same risk-benefit profile as their brand-name counterparts.

MYTH: *Brand-name drugs are made in modern manufacturing facilities, and generics are often made in substandard facilities.*

FACT: FDA won’t permit drugs to be made in substandard facilities. FDA conducts about 3,500 inspections a year in all firms to ensure standards are met. Generic firms have facilities comparable to those of brand-name firms. In fact, brand-name firms account for an estimated 50 percent of generic drug production. They frequently make copies of their own or other brand-name drugs but sell them without the brand name.

MYTH: *Generic drugs are likely to cause more side effects.*

FACT: There is no evidence of this. FDA monitors reports of adverse drug reactions and has found no difference in the rates between generic and brand-name drugs.

Same FDA Requirements for Brand-Name and Generic Drugs

	Brand-Name Drug	Generic Drug
For reformulations of a brand-name drug or generic versions of a drug, FDA reviews data showing the drug is bioequivalent to the one used in the original safety and efficacy testing.	✓	✓
FDA evaluates the manufacturer’s adherence to good manufacturing practices before the drug is marketed.	✓	✓
FDA reviews the active and inactive ingredients used in the formulation before the drug is marketed.	✓	✓
FDA reviews the actual drug product.	✓	✓
FDA reviews the drug’s labeling.	✓	✓
Manufacturer must seek FDA approval before making major manufacturing changes or reformulating the drug.	✓	✓
Manufacturer must report adverse reactions and serious adverse health effects to the FDA.	✓	✓
FDA periodically inspects manufacturing plants.	✓	✓
FDA monitors drug quality after approval.	✓	✓

“Most people believe that if something costs more it has to be better quality. In the case of generic drugs, this is not true.”

— Gary Buehler, Director of
FDA’s Office of Generic Drugs

- The firm must assure the FDA that the raw materials and the finished product meet USP specifications, if these have been set. The USP, or U.S. Pharmacopoeia, is the non-profit, scientific body chartered by Congress to set standards for drug purity in this country.
- The firm must show that its generic drug maintains stability as labeled before it can be sold. Once on the market, the firm must continue to monitor the drug’s stability. The firm must show that the container and its closure system won’t interact with the drug. Firms making sterile drugs must submit sterility assurance data showing microbiologic integrity of these products.
- The firm must provide a full description of the facilities it uses to manufacture, process, test, package, label and control the drug. It must certify that it complies with federal regulations about current good manufacturing practices and undergo FDA inspection of the manufacturing facility to assure compliance.
- Before FDA approves a generic drug, it usually conducts an inspection at the proposed manufacturing site to make sure the firm is

capable of meeting its application commitments and to ensure the firm can manufacture the product consistently.

“Generic competition helps keep the cost of drugs down,” Buehler says. “It also encourages the research based drug companies to keep finding newer and better medicines that have patent protection.”

When retired federal auditor Stuart Addison went to the pharmacy, he had the pharmacist fill his prescriptions with generic drugs. “My motivation is to keep the prices down,” Addison said, noting that his insurance plan helped pay for his prescriptions. “My pocketbook isn’t directly affected; but, in the long run, I’m helping to keep insurance premiums down.” Generic drugs save consumers an estimated \$8 to \$10 billion a year at retail pharmacies (according to the Congressional Budget Office). Even more billions are saved when hospitals use generics.

“FDA-approved generic drugs are bioequivalent and therapeutically equivalent to their brand-name counterparts,” says Buehler. “People can use them with total confidence.”

What Is Bioequivalence?

Generics are not required to replicate the extensive clinical trials that have already been used in the development of the original, brand-name drug. These tests usually involve a few hundred to a few thousand patients. Since the safety and efficacy of the brand-name product has already been well established in clinical testing and frequently many years of patient use, it is scientifically unnecessary, and would be unethical, to require that such extensive testing be repeated in human subjects for each generic drug that a firm wishes to market. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner) to the pioneer drug.

One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream and its concentration in the bloodstream in 24 to 36 healthy, normal volunteers. This gives them the rate and extent of absorption—or bioavailability—of the generic drug, which they then compare to that of the pioneer drug. The generic version must deliver the same amount of active ingredients into a patient’s bloodstream in the same amount of time as the pioneer drug.

Using bioequivalence as the basis for approving generic copies of drug products was established by the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act. Brand-name drugs are subject to the same bioequivalency tests as generics when their manufacturers reformulate them.

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Public Health Service • Food and Drug Administration**

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When a Drug





Is In Short Supply

Infantile spasms, or West's syndrome, is a sometimes crippling and even life-threatening seizure disorder that affects about 3,000 babies a year in the United States. The only drug that helps prevent the spasms is Acthar gel, and the drug's only manufacturer is Rhone-Poulenc Rorer Pharmaceuticals Inc.

For several months in 1996, Rhone-Poulenc stopped making Acthar because of manufacturing difficulties. A crisis resulted, with insufficient supplies to treat patients with West's syndrome and other diseases.

While the company worked with the Food and Drug Administration to fix problems in its plant, the non-profit National Organization for Rare Disorders helped dole out the very limited supplies for emergency cases of infantile spasms and other conditions. "During the shortage, even some people with severe pain from rheumatoid arthritis couldn't get the drug in favor of babies with life-threatening West's syndrome," says NORD president Abbey Meyers.

Severe drug shortages like this one are infrequent, but a minor supply problem creating a potential shortage usually arises about once or twice a month, says Mark Goldberger,

Shortages call for rapid communication among the key people within FDA.

FDA's coordinator for new drug review shortages.

Medical Necessity

Potential drug shortages are a top agency priority, according to Mark Lynch, a branch chief in FDA's division of drug manufacturing and product quality. "Shortages call for rapid communication among the key people within FDA," he says. "Those

When a product is in dangerously short supply, the manufacturer or another party may set up an allocation program.

involved have to drop what they're doing and react rapidly to the crisis."

But a reduction in the drug supply doesn't always warrant this emergency status. To be defined as a high-priority drug shortage, the drug must be found to be "medically necessary." The FDA division responsible for the drug leads the determination of medical necessity. The division considers several factors, including:

- the opinion of health professionals about the drug's usefulness,
- the seriousness of the medical condition, and
- the availability of acceptable brand-name or generic alternatives.

For example, a dangerous drug shortage occurred a few years ago when the supply of the anemia drug Desferal (deferoxamine mesylate) suddenly dropped. Desferal is the standard treatment for a fatal blood disease called Cooley's anemia. In 1995, an FDA inspection uncovered some manufacturing problems at the Swiss facility of the former Ciba-Geigy Corp., the only plant where Desferal was made, leading to a plant shutdown.

"We were fearful about the potential danger to patients based on the fact that there was no alternative

source for Desferal," says Gina Cioffi, national executive director of the Cooley's Anemia Foundation. "Our patients must use this drug every day, or they're taking time off their life as iron builds up in their blood."

In a drug shortage situation like the one involving Desferal, FDA takes steps to find alternative sources of the drug or to control the distribution to make sure the most needy patients have access to it.

"These are acute problems that need to be addressed swiftly, with either a resolution or a short-term fix," Goldberger says. "If you've got a drug like Acthar that you need to prevent mental retardation or a drug like Desferal that you need to prevent iron overload, you can't take years. You either have to make it available quickly or figure out a substitute drug."

Increasing the Supply

The review division and office of compliance in FDA's Center for Drug Evaluation and Research work with manufacturers and third parties to find ways to keep a drug available despite various obstacles. "It's a problem-solving exercise," Lynch says. "Each situation is different;

each drug is different; and the people are different each time."

The Acthar gel shortage was "different" because the drug is made from animal pituitary glands. "Because it is not synthetic, it is a difficult drug to manufacture," Goldberger says. "We worked with Rhone-Poulenc to bring the product to market while not placing an unrealistic burden on the company."

Sometimes FDA must take steps to avoid a drug shortage when the agency takes regulatory action, such as seizure or injunction, against a company. If shutting down a plant while the manufacturer corrects problems could lead to a shortage of a medically necessary drug, the agency may exempt that drug from the ban to keep it available.

To decide whether to make an exception for a certain drug, FDA must balance two risks: the risk from the noncompliance—for example, a manufacturing violation could result in a slightly less potent medication—and the risk of not having the product available at all.

For example, in spite of manufacturing problems, FDA allowed Ciba-Geigy's Desferal (as well as two other medically necessary drugs) into the United States from the firm's Swiss facility. FDA compliance officer Richard Friedman checked the quality of each lot of Desferal entering the country by analyzing extra data submitted by the company. "We worked closely with the firm to assure that products made it to pharmacies without delay and with no sacrifice in quality," Friedman says.

In other cases, a manufacturer may decide to stop making a drug simply because it is not a money-maker. In these cases, FDA or the National Organization for Rare Disorders may speak with other companies about making up the void. "To a big company, a market of \$10 million or \$20 million usually isn't enough," says

NORD president Meyers, “but to a small company, that market might be attractive.” (See sidebar below.)

Other times, because of poor planning or an unforeseeable event such as a plant explosion or fire, a company may not have the usual amount of time required to get agency approval of a manufacturing change, such as a move to a new plant. If an interruption in manufacturing may lead to a dangerous drug shortage, FDA can expedite its inspection of the new plant or its review of required applications.

In cases where a company is experiencing a temporary delay in production, FDA may talk to other companies who have the facilities to make the product for the short term, or the agency may see if the manufacturer has some extra stock in its plant or warehouse that can help bridge the gap.

Managing the Demand

When a product is in dangerously short supply, the manufacturer or another party may set up an allocation program. That way, the drug is shipped directly to those who need it, rather than being shipped in large quantities to sit in a warehouse.

“Without a controlled allocation program,” Goldberger says, “it’s kind of like a gasoline shortage. Everyone rushes out and keeps their tanks full, and by keeping their tanks full, there’s less gasoline to go around for

“Without a controlled allocation program it’s kind of like a gasoline shortage.”

— Mark Goldberger, FDA
Coordinator for New Drug Review Shortages

those who really need it. If people just filled up when they needed to, you might not have a shortage.”

To make sure anemic patients possessed only the amount of Desferal they really needed, Ciba-Geigy set up a distribution schedule to ensure that pharmacies only gave out a two-week supply at a time. “The company responded quickly by coming up with a distribution plan to make sure there was no gap in getting patients their drug,” says Cioffi.

Shared Responsibility

Usually, dire shortages that require rationing can be avoided. Communication with the company and with specialized organizations such as NORD is the key, according to Goldberger.

The earlier FDA becomes aware of a possible shortage of a critical drug, the more effectively the agency can deal with it. “Part of the responsibility lies with the companies,” Friedman says. “They should inform us as soon as possible if they anticipate a shortage of a medically necessary product.”

FDA can sometimes help to avert a crisis or minimize the harm to patients if a shortage does occur. But, Goldberger says, “There are certain steps you have to go through to manufacture a product and get a product out on the market. FDA can speed up the process—find bridges—but we can’t abolish it altogether, or we couldn’t be sure of the drug’s quality.”

No Shortage of Incentives

The Orphan Drug Act, a 1983 addition to the Federal Food, Drug, and Cosmetic Act, offers financial incentives to the developer of a drug for a rare disease, including tax credits for clinical research and a seven-year period of exclusive marketing. FDA’s Office of Orphan Products Development identifies orphan products and aids their development with guidance and grants.

A rare disease is one that affects fewer than 200,000 Americans or a population so small that U.S. sales would not cover the cost of developing the drug. There are 5,000 such diseases, which affect a total of 20 million Americans, according to Abbey Meyers, president of the National Organization for Rare Disorders.

“The act has been very successful in attracting companies,” Meyers says. Since its passage in 1983, FDA has approved more than 140 drugs for rare conditions, compared with only 10 such approvals in the decade before 1983.

NEW
Now in non-
prescription strength

Prevents:
Heartburn,
Acid Indigestion
& Sour Stomach.

AXID[®]
AR

Acid Reducer
Nizatidine Tablets 75 mg **12 TABLETS (12 DOSES)**

AXID[®]
AR

Acid Reducer
Nizatidine Tablets 75 mg **12 TABLETS (12 DOSES)**





Now Available *Without a* **pRx**escription

For those who yearn to break their cigarette addiction but don't fancy a trip to the doctor's office, the ability to get the nicotine patch without a physician's prescription may be just what the doctor ordered.

Until a few years ago, the nicotine patch was available by prescription (Rx) only. In July 1996, the Food and Drug Administration approved the "switch" of the Nicotrol patch to over-the-counter (OTC) status, following on the heels of a February 1996 switch of another smoking cessation aid containing nicotine, Nicorette gum. Then, on Aug. 2, 1996, FDA approved the switch of a second nicotine patch, Nicoderm CQ.

On the right is the prescription-strength Axid and on the left the OTC product. Axid and three other heartburn medications—Pepcid, Tagamet and Zantac—were switched to OTC status. To enable consumers to treat their own heartburn safely, FDA approved the over-the-counter drugs with easy-to-understand labeling and at a lower dosage than the prescription versions.

Over-the-counter switches provide increased access to effective drugs.

The "patch" and Nicorette gum join more than 600 other OTC drugs that, according to the Non-prescription Drug Manufacturers Association, would have required a prescription only 20 years ago. The 600-plus products are now available without a prescription because FDA, in cooperation with panels of outside experts, determined they could be used safely and effectively without a doctor's supervision.

In the last year and a half alone, FDA has given OTC approval to drugs with such household names as Children's Advil and Children's Motrin (ibuprofen), Orudis KT (ketoprofen) and Actron (naproxen sodium), for pain relief and fever

reduction; Femstat 3 (butoconazole nitrate), for vaginal yeast infection; Pepcid AC (famotidine), Tagamet HB (cimetidine), Zantac 75 (ranitidine hydrochloride), and Axid AR (nizatidine), for heartburn; and Rogaine (minoxidil), for hair growth.

Over-the-counter switches provide increased access to effective drugs. Eighty-five percent of Americans feel it is important to have OTC medications available to relieve minor medical problems, according to a 1992 Heller Research Group study, "Self-Medication in the '90s: Practices and Perceptions."

"There is an important trend toward consumer participation in their own healthcare," says Debra

“There is an important trend toward consumer participation in their own healthcare.”

— Debra Bowen, M.D., FDA

Director of Over-the-Counter Drug Products Division

Bowen, M.D., director of FDA's division of over-the-counter drug products. “It's part of our mission to keep up with the consumer's wish to be more involved.”

Switches have a huge impact on the healthcare economy. The greater availability of medicines over the counter saves approximately \$20 billion each year, according to the *1995 Physicians' Desk Reference for Nonprescription Drugs*, a book of drug information published annually by Medical Economics in cooperation with drug manufacturers. The \$20 billion takes into account prescription costs, doctor visits, lost time from work, insurance costs, and travel.

The Switch Process

The original Federal Food, Drug, and Cosmetic Act of 1938 made no clear-cut distinction between Rx and OTC drugs. The 1951 Durham-Humphrey amendments to the act set up specific standards for classification.

The amendment requires that drugs that cannot be used safely without professional supervision be dispensed only by prescription. Such drugs may be deemed unsafe for nonprescription use because they are habit-forming or toxic, have too

great a potential for harmful effects, or are for medical conditions that can't be readily self-diagnosed.

All other drugs can be sold OTC. A drug must be made available without a prescription if, by following the labeling, consumers can use it safely and effectively without professional guidance.

Some drugs are approved initially as OTC drugs. More often, though, medications are first approved Rx and later switched. “While a product is available by prescription, we can learn about the drug's safety profile in a much more controlled environment,” Bowen says.

Drugs are commonly switched one of two ways: under the “OTC drug review,” or by a manufacturer's submission of additional information to the original drug application.

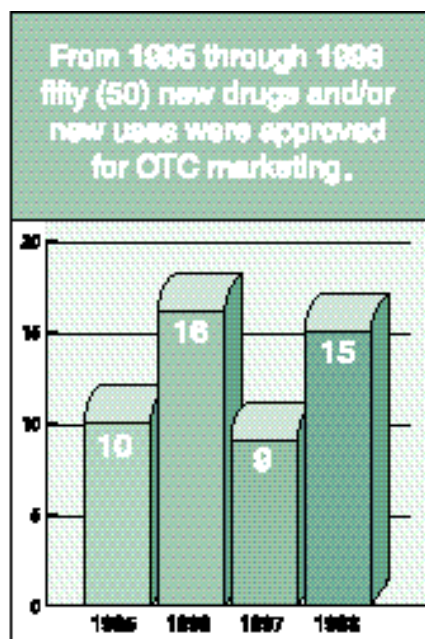
The OTC drug review is an ongoing public process that allows communication through rulemakings and publications in the *Federal Register*, uses public meetings of nongovernment experts, and incorporates the agency's scientific opinion to establish the general recognition of safety and efficacy of OTC drugs that were in the marketplace prior to a certain date in the 1970s. Some of the expert review panels also reviewed

prescription ingredients to recommend whether these ingredients were appropriate for certain OTC uses and for OTC marketing.

The second common path to OTC approval is submission of data to FDA (almost always by a manufacturer) showing the drug is appropriate for self-administration. Often, the submission includes studies showing that the product's labeling can be read, understood, and followed by the consumer without the guidance of a healthcare provider. FDA reviews the new data, along with any information known about the drug from its prescription use.

Some new drug applications for OTC use are presented to a joint advisory committee made up of members of the agency's Nonprescription Drugs Advisory Committee and another advisory committee with expertise in the type of drug being considered. For example, because Rogaine is for conditions of the hair and scalp, representatives of the Dermatologic Drugs Advisory Committee participated in this joint advisory committee meeting.

While not bound by the advisory committee's counsel, FDA frequently follows its recommendation.



Benefit vs. Risk Comparison

When considering an Rx-to-OTC switch, the key question for FDA is whether the drug can benefit consumers without endangering their safety.

No drug is absolutely safe. There are risks associated with every medication, so FDA assesses both the benefit and risk to determine whether it is appropriate for consumers to self-medicate with a drug for a certain use.

On the safety side, the agency looks at the drug's toxicity—its potential for poisonous effects—when the drug is used according to its labeled directions. The agency also determines whether the drug's side effects are acceptable given the benefit that the drug will provide. Finally, the agency evaluates the drug's potential for misuse or abuse.

While misuse by some consumers is inevitable—some people may over-medicate on the mistaken assumption that more is better—the Heller study showed that consumers appreciate the risks of taking any drug. Ninety percent of those surveyed said medications should only be used when absolutely necessary. Seventy percent said they prefer to fight symptoms without any medication.

FDA weighs a drug's safety against its benefit to consumers. The agency considers whether consumers will be able to understand and follow label directions, whether they can recognize their symptoms or condition themselves, and whether a medical examination or practitioner-prescribed laboratory tests are required for specific diagnoses or for the continued safe use of a drug.

No easy risk vs. benefit formula exists. FDA does a case-by-case review of each drug along with its intended use. In the past few years, the agency considered OTC switch applications for two very different drugs—Rogaine, for hair regrowth,

*Some people may overmedicate
on the mistaken assumption
that more is better.*

and the nicotine patch, as an aid to smoking cessation. Each raised unique issues, yet the risk vs. benefit comparison led FDA to the same conclusions in the two assessments—over-the-counter status is appropriate.

Concerns about side effects can sometimes be managed by approving OTC drugs at lower doses than their prescription counterparts. The drugs must still be effective for the short-term symptoms for which they're intended.

The issue of whether a condition can be self-diagnosed was a central one for the Rogaine advisory committee. Most OTC drugs are intended for treatment of symptoms that can be easily recognized, like headache or upset stomach. Others, though, are intended to treat diseases like asthma or vaginal fungal infections, which cannot be self-diagnosed.

Consumer-Friendly Labeling

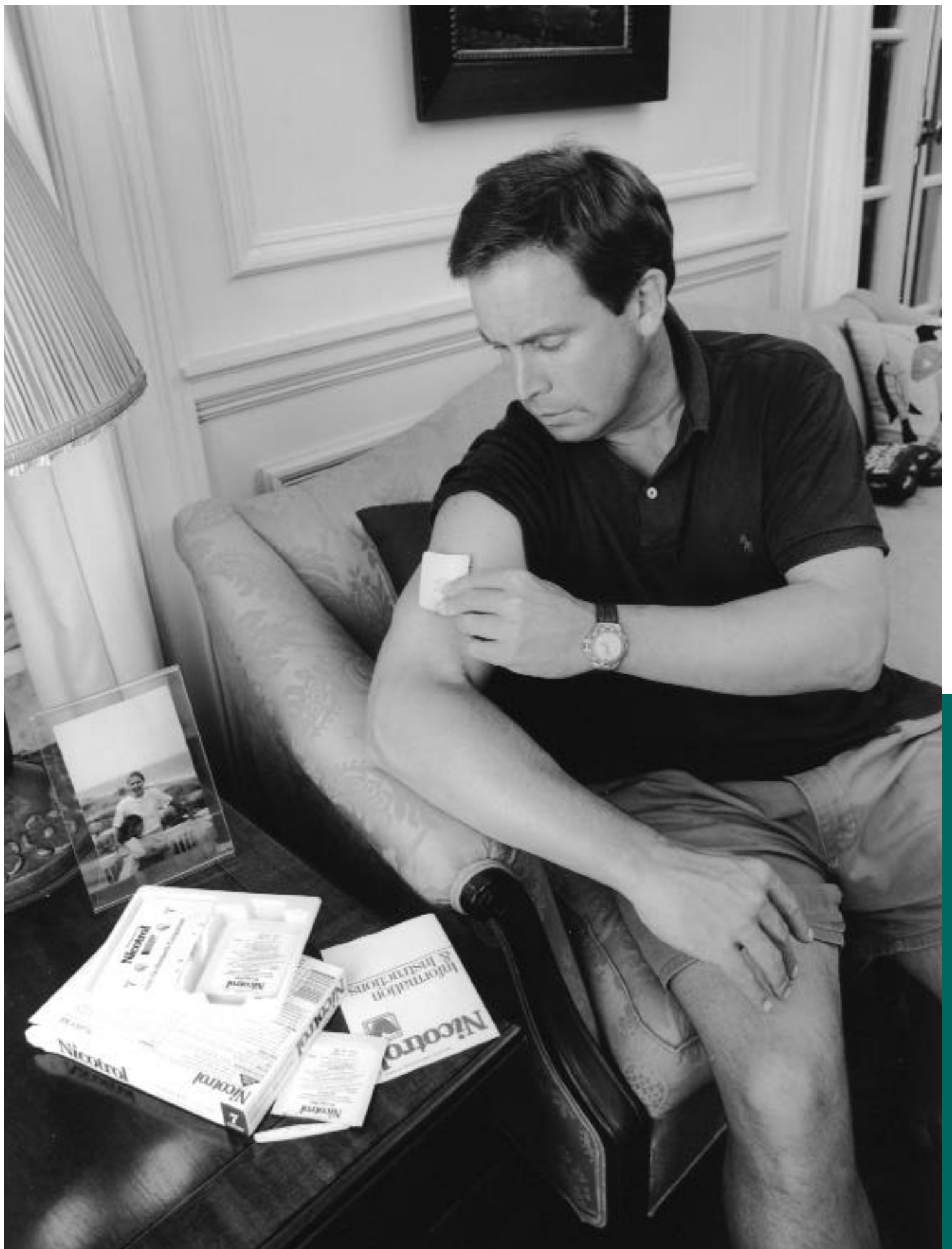
Labeling is an influential element in deciding whether the risk of using the OTC drug is acceptable. The decision about a drug's safety for OTC use cannot be made in a vacuum, by looking only at the drug ingredients. Every drug, used improperly, can cause adverse reactions. Even appropriate use can lead

to side effects (e.g., antihistamine use may cause drowsiness). And some drugs can be dangerously unsafe or ineffective if taken while a person is using certain other drugs.

Labeling can alert consumers to such potential problems. Labeling of all drugs must be clear and truthful. For OTC drugs, the intended uses, directions, and warnings have to be written so consumers, including individuals with low reading comprehension, can understand them.

FDA is working with the pharmaceutical industry to increase the readability of OTC labels by making the language more consumer-friendly and standardizing the format, including where important information is placed.

In some cases, Bowen says, consumers can get more information in the OTC labeling than they would get from their doctors. "For the nicotine patch, we developed a package—a package containing not only a drug that relieves withdrawal symptoms, but also behavioral modification information. The package provides an element of support, which studies showed some people weren't getting from their doctors, by telling them when they'll most likely feel the urge to smoke, what they can do in



place of smoking, and where they can go for support.”

A Popular Alternative

Nicorette gum magazine ads announce, “Nicorette Gum Is Now Available Full Strength Without A Prescription. Hallelujah!”

“Hallelujah” may be the victory cry for those who, with the aid of OTC nicotine gum, were able to beat the cravings. But consumers aren’t the only ones with something to gain from Rx-to-OTC switches.

Some manufacturers are exclaiming “Hallelujah” as well, over profits gained from direct access to millions of consumers. Pepcid AC for heartburn, for example, had sales topping \$200 million in the first year after the product’s April 1995 switch approval, making it the most profitable switch to date.

Today’s emphasis on self-managed care fuels the popularity of nonpre-

scription drugs. But OTC products are intended to supplement the medical options of the consumer, not substitute for a prescriber’s medical knowledge. If a health problem persists or worsens while you are using an OTC drug, consult a healthcare provider.

“People must be in a partnership with their healthcare providers for opti-

mal health,” Bowen says. “Many situations aren’t appropriate for self-treatment, and others may require professional guidance for self-treatment.”

If you do choose OTC treatment, heed Bowen’s warning: “Drugs aren’t candy; they aren’t risk-free. You have to follow the label and take appropriate responsibility for your own self-care.”

In some cases, Bowen says, consumers can get more information in the OTC labeling than they would get from their doctors.

9-0 Vote for OTC Nicotrol

Nicotrol was the first nicotine patch for smoking cessation approved by FDA.

It received an advisory committee’s unanimous recommendation for a prescription-to-OTC switch on April 19, 1996. Worn for 16 hours a day, the patch reduces nicotine cravings by providing a constant, controlled flow of nicotine into the bloodstream.

The committee concluded that the benefits of this smoking cessation aid outweigh its risks, but only after considering manufacturer McNeil Consumer Products’ proposed labeling and marketing plans, and the company’s studies comparing quitting rates for OTC and prescription patches.

The company presented data showing that prescription and OTC patch users achieved similar quitting rates (19 percent of OTC users abstained in weeks 2 through 6, versus 16.6 percent of Rx users) and experienced no serious adverse reactions.

McNeil demonstrated that smokers understood the proposed labeling, including the warning not to smoke while using the patch and directions on how to apply and remove the patch. According to the company, more than 80 percent of consumers used the behavioral modification materials, including handbooks, an audiotape, and toll-free help line.

The committee was told that abuse was not expected to be a problem, especially for adults. The patches are not to be sold to minors and will not be distributed through vending machines. Advertising will be targeted to adults.

FDA agreed that the benefits of the patch—an increased chance for people to quit smoking—outweighed any slight risks, and approved the product for OTC sale July 3, 1996. The OTC patches became available in retail stores July 18, 1996.



Direct to You: TV Drug Ads *That Make Sense*

The secret's out. The prescription drug Claritin is an antihistamine for seasonal allergies, new TV commercials reveal. Before August 1997, the Claritin television ads said little beyond, "At last, a clear day is here," and "It's time to see your doctor."

Not much to go on in those earlier ads, and the commercials for Claritin's main competitor, Allegra, were equally unrevealing. Why the secrecy? Because, by stating the drug's name but not what it was used for, the ads were exempt from a Food and Drug Administration regulation that generally requires prescription drug advertisements to disclose the risks of the medication as well as its benefits. From the drug companies' perspective, it was impractical to include detailed risk information in a 30- or 60-second TV spot.

But the so-called "reminder ads" for Claritin and other drugs left consumers puzzled. "We used to get a

tremendous amount of phone calls saying, 'What is Claritin? What is it for?'" says Alex Giaquinto, senior vice president for worldwide regulatory affairs for Schering-Plough Corp., the drug's manufacturer. "You'd be surprised. We got calls from gynecologists saying patients were asking if they were candidates for Claritin."

In part, because of the consumer confusion and concerns that some TV and radio advertisements might be misleading, FDA reviewed its policies on broadcast ads and, in August 1997, issued a draft guidance for public comment. The new guidance describes how prescription drug companies can advertise a product directly to consumers on TV or radio, including the product's use, without scrolling the type of detailed risk information that accompanies magazine and other print advertisements.

The makers of Claritin and Allegra

soon began airing revised ads. "Only one tablet means 24-hour, nondrowsy seasonal allergy relief," announced the new Schering-Plough commercial.

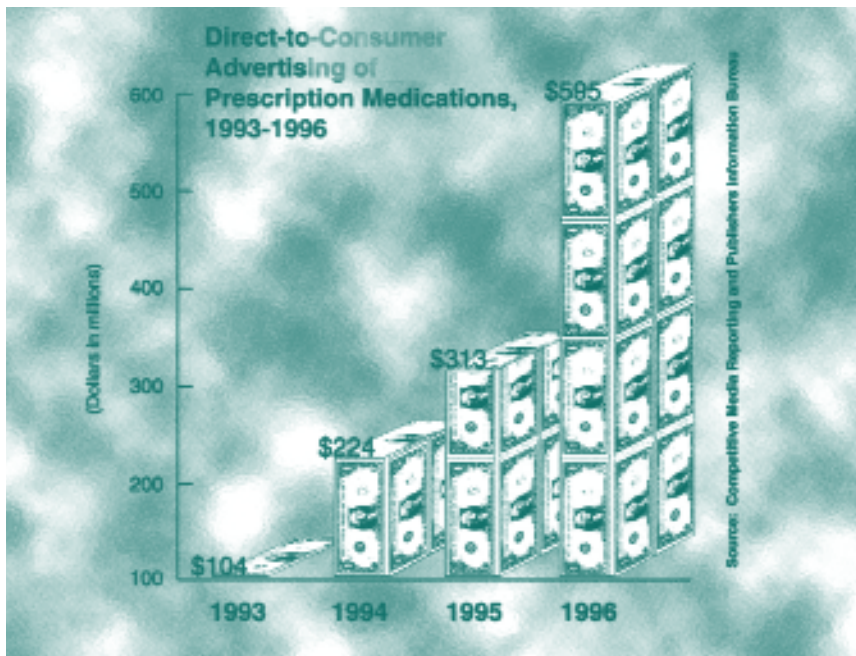
Not everyone agrees that these "direct-to-consumer" ads are beneficial. At a 1995 public hearing on consumer-directed advertising, FDA heard from scientists, drug companies, patient advocates, and medical professionals. Some objected to direct-to-consumer ads, saying that they mislead consumers because they don't provide a complete picture of the drug. Others favored the ads, telling the agency that a consumer-directed ad can be an important educational tool in an era when patients want to be more involved in their own healthcare.

But, says Nancy Ostrove, chief of marketing practices and communications in FDA's division of drug marketing, advertising, and communica-



Before August 1997, many TV commercials for prescription drugs stated little more than the product's brand name and "ask your doctor" (left). Now, drug companies are airing TV commercials that tell viewers not just the name of the drug, but also the medical condition it is used to treat (right). Source: Schering Corp.





tions, “Direct-to-consumer advertising is not inherently bad or good. It can be useful or harmful, depending on how it’s done.”

Truth in Advertising

FDA has regulated the advertising of prescription drug products since 1962, under the Federal Food, Drug, and Cosmetic Act and related regulations. Most other advertising, including the advertising of over-the-counter drugs, is regulated by the Federal Trade Commission, under a different set of rules.

FDA generally interprets the term “advertisement” to cover information other than labeling that promotes a product. The term includes promotions broadcast on television or radio, conducted by telephone, or printed in magazines or newspapers. (See “Drug Promotion in Cyberspace,” p. 77.)

For many years, prescription drug makers promoted their products exclusively to healthcare professionals. But about 15 years ago, some manufacturers began to produce ads targeted to consumers.

Since then, direct-to-consumer advertising has become a popular promotional tool. In 1996 alone, prescription drug manufacturers spent almost \$600 million on this type of advertising, according to Competitive Media Reporting, which

projected 1997 spending to be at least twice that.

And consumer-directed ads seem to be capturing consumers’ attention. In a 1996 study by drug industry consultant Scott-Levin, three-quarters of the doctors surveyed said their patients have talked about drug ads they heard or saw.

FDA regulates consumer-directed ads under the same regulations as professional-directed ones. Like promotions directed to healthcare providers, consumer ads may only make claims that are supported by scientific evidence and that are not inconsistent with the FDA-approved product labeling. And, like professional-directed advertisements, they may not be false or misleading.

FDA oversight helps ensure that consumers understand both the benefits and limitations of an advertised drug. (See “In Trouble with FDA,” p. 76.) The agency monitors ads to make sure they are tailored for the target audience. For example, a consumer-directed ad may be considered misleading unless it explains the drug’s benefits and risks in words that people who aren’t medical professionals can understand.

FDA regulations call for “fair balance” in every ad. FDA reviewers look at the entire advertisement to see if it is balanced. The risks as well as the benefits must be clearly identi-

fied, and the risks must be presented prominently and readably so that the benefits are not unfairly emphasized.

Under the Federal Food, Drug, and Cosmetic Act, most ads must include a “brief summary” describing the effectiveness of the drug and its risks. In print ads, drug companies usually meet the requirement by including entire risk-related sections of the approved labeling. Many people have expressed concern to FDA that, because drug labeling is primarily written for doctors, much of it cannot be understood by consumers.

“The brief summary might be fine for someone who went through medical school,” says Linda Golodner, president of the National Consumers League. Even then, she says, “you have to get out a magnifying glass to try and sort out the information.”

FDA is considering what steps can be taken toward a more consumer-friendly format. In the meantime, says Ostrove, “We encourage manufacturers to write the brief summary information to be more understandable to consumers.”

TV Reality

In a short television or radio ad, manufacturers have found it difficult to meet the brief summary requirement. “Scrolling a long, detailed brief summary on a television screen is not practical on commercial television,” writes drug law expert Wayne Pines in the Thompson Publishing Group’s *Advertising and Promotion Manual*.

So, for television commercials and sometimes print ads, companies have historically opted for two types of ads — “reminder” ads and “help-seeking” ads—that are exempt from the brief summary requirement.

Reminder ads, like the original version of the Claritin commercial, call attention to a drug’s name, but don’t state the condition it is used to treat.

Help-seeking ads tell consumers only that there are treatments available for a particular condition and encourage them to talk to a health-care professional. To be considered a help-seeking advertisement, an ad may not state or imply the name of a particular product, although it can mention the manufacturer's name. One such magazine ad said simply, "Life without ulcers. It is now possible. See your doctor."

The reminder and help-seeking ad "each has only part of the information a consumer wants, which can create a lot of confusion," Ostrove says.

Completing the Puzzle

FDA regulations have always permitted sponsors of television and radio ads to present a brief summary. Or, instead, they could make "adequate provision" for interested people to get the approved labeling.

Before August 1997, FDA had not described "adequate provision" for consumer-directed ads, so drug companies were not taking advantage of the option because they were uncertain about whether their ads would meet FDA's standards.

The draft guidance doesn't change the regulation, but rather describes one way to meet the requirement. Under the approach described in the guidance, "adequate provision" is accomplished if the ad contains the following:

- a toll-free telephone number so consumers can request the approved package labeling by mail, fax, or prerecorded telephone message;
- a reference to print ads about the product in consumer magazines so consumers can read more detailed drug information, or to brochures containing the package labeling that a consumer can find conveniently in public places such as libraries, pharmacies, doctors' offices, and grocery stores;
- a statement that additional product information is available from a doctor or pharmacist; and
- an Internet address where package labeling can be found.

Whether the brief summary or "adequate provision" is used, however, the most important risk information must always be included in the ad itself. This information is often referred to as the "major statement."

Joint Responsibility

Some consumer-directed ads can raise awareness that drugs are available to treat certain conditions, including diseases such as seasonal allergies that might not require a doctor's care, and undertreated conditions such as depression and impotence. "We have a huge patient population for which there are drugs available to help them live longer and better lives," says John Kamp of the American Association of Advertising Agencies. He adds that government agencies and medical professionals "can use their tools until they're blue in the face and not reach the people who will be reached through television."

While a doctor's prescription is necessary to get these medications, some at the 1995 public hearing expressed a concern that this alternative source of drug information would interfere with the doctor-patient relationship. The National Consumers League's Golodner and others, however, feel that consumers will communicate with their physicians more, not less, if they are aware that a drug exists for their condition.

In Trouble with FDA

Generally, FDA does not require preclearance of promotional materials. But the agency often reviews drug companies' draft promotional materials at their request.

If FDA finds that company's advertisement is false or misleading, the agency may take enforcement action against the company. The agency regulates all of a drug company's prescription drug promotions, including the promotional tactics of its salespeople.

For the least serious violations of advertising regulations, FDA will send the drug company an "untitled letter" outlining the agency's findings.

For more serious violations, FDA may

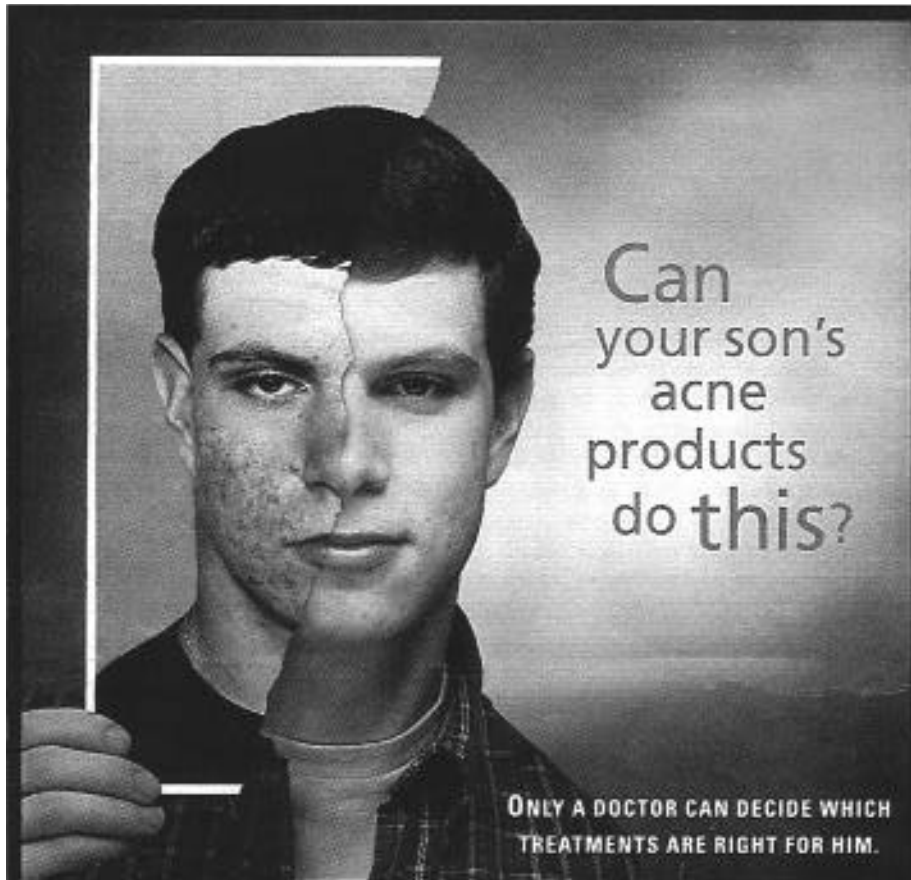
issue a "warning letter" requesting that the company immediately stop the violative advertising and, in many cases, take other corrective steps.

For example, the company may be asked to send a "Dear Doctor" letter to alert those who prescribe the medication to FDA's finding. The company may also be asked to run corrective advertisements setting forth FDA's concerns and bringing the ad's language into compliance. Finally, a warning letter may request that a company send its future promotional materials to FDA for clearance before they are used.

Beyond sending untitled letters and warning letters, FDA may stop violative

promotions by seizing affected products or enjoining the use of promotions that make the same or similar claims. These actions and the most serious remedy, criminal prosecution of the company or the individuals involved, are used rarely—generally when intentional and serious misstatements are involved.

The threat of agency action isn't the only thing that keeps companies honest, says John Kamp of the American Association of Advertising Agencies. "A drug company won't play fast and loose with the rules because its most important asset is its reputation with the American people."



“In healthcare,” Golodner says, “there is a general trend toward having consumers more responsible for their own health. Now, consumers can go to their physicians with a little more information.”

A related issue raised at the 1995 public hearing is whether such ads would lead to patients pressuring doctors to prescribe unneeded medications. Many speakers emphasized the doctors’ duty to advise their patients responsibly. Mary Jane Sheffet, from Michigan State University’s marketing department, told FDA, “The doctor needs to be there as a gatekeeper.”

With the health concerns of both supporters and opponents in mind, the agency continues to review its policies on direct-to-consumer promotion. As more ads have been reviewed by FDA, Ostrove says, the

agency “has become more and more confident that the appropriate information, including risk information, can reach consumers and be helpful to them.”

But the foremost goal of advertisers will always remain the same: to get people to use their products. So Ostrove urges consumers to regard prescription drug ads with careful consideration.

“These are prescription drugs with real potential downsides,” she says. “We don’t want people going to their doctors and saying, ‘I want this drug.’ The message should be, ‘I saw this ad. Is it right for me?’”

Drug Promotion in Cyberspace

Like many other companies, prescription drug marketers are beginning to take advantage of the extensive reach of the Internet to promote their products. FDA monitors the Internet to check the quality of the information provided, and encourages consumers to remain vigilant to separate the good information from the bad. (See “Health Information On-Line” in the June 1996 *FDA Consumer*.)

“Generally, FDA is treating Internet promotion like it does other forms of promotion,” says Melissa Moncavage, a public health advisor with FDA’s division of drug marketing, advertising, and communications. “Although the Internet is brand new, the promotion content issues are largely the same as print, broadcast, and other traditional media.”

To address those issues that are unique to the Internet, FDA held a public meeting in October 1996 to hear from consumers, patient groups, health professionals, manufacturers of FDA-regulated products, and others.

The questions discussed at the meeting included:

- Where should promotional product information be located on a company’s Web site?
- How can promotional information on the Internet be clearly distinguished from other information?
- How can Internet users be assured access to a balanced presentation of risks and benefits?
- Should Web sites distinguish between Internet promotions directed to health professionals and consumers? How?
- How should the promotional materials of multinational companies be addressed to ensure compliance with U.S. drug laws and regulations?

Also, in a Sept. 16, 1996, *Federal Register* notice, FDA requested written comments on some of these same Internet-related drug promotion issues. The agency is considering the written comments, suggestions of meeting participants, and information received since the meeting, and plans to publish a guidance to clarify its policies.



PEDIATRIC DRUG STUDIES:

Protecting Pint-Sized Patients

Despite seven days, “about 26 hours a day,” spent preparing to testify about the labeling of drugs for children’s use, Wendy Goldberg told Food and Drug Administration experts at a 1997 hearing, “I have become neither a scientist nor a doctor. Not even close.” But, she said, “I do know one thing—I use a lot of medicines on Abby that are not approved by the FDA for use on children her age.”

Of the nine-item laundry list of medicines Goldberg’s 6-year-old daughter Abby was taking for her severe asthma, not a single one was tested or approved in the United States for children under 12. “I feel as though I am testing drugs on my own child, every day, and it isn’t helping anyone,” Goldberg said.

While some drugs do come with pediatric use information (notably, vaccines and antibiotics), asthma medications by no means stand alone in their lack of labeling for kids' treatment. Other types of drugs that often lack pediatric labeling include those for depression, epilepsy, severe pain, gastrointestinal problems, allergic reactions, and high blood pressure.

Overall, more than half of the drugs approved every year that are likely to be used in children are not adequately tested or labeled for treating youngsters, according to FDA estimates. Safety and effectiveness information is especially sparse for the over 7 million children under age 2.

A recent survey by the agency identified the 10 drugs that were prescribed most often to children in 1994 that lacked pediatric labeling. Together, they were prescribed for kids more than 5 million times. (See "Top 10 Drugs Prescribed to Kids Without Pediatric Labeling.")

"At times, children have been harmed and maybe even killed because of a lack of knowledge of how drugs would affect them," says Robert M. Ward, M.D., chair of the American Academy of Pediatrics' Committee on Drugs. Among Ward's historical examples: the deaths of a number of newborn babies in the 1960s when their immature livers were unable to break down the antibiotic chloramphenicol. "Those types of therapeutic misadventures are certainly part of pediatric medicine, and we'd rather they didn't repeat," he says.

To help prevent future chloramphenicol-type disasters, FDA finalized a rule in December 1998 requiring manufacturers of many drugs to provide information about how their drugs can safely and effectively be used in children (from newborns to adolescents), including information on the proper doses for kids.

A Healthy Dose of Regulation

The pediatric studies rule, published in the Dec. 2, 1998, *Federal Register*, requires that new drugs (generally prescription drugs, including biologics, or drugs derived from living organisms) that are important in the medical treatment of children or will be commonly used in children include labeling information on safe pediatric use.

The information would usually be required when a drug is approved. For drugs already on the market, FDA can require children's studies in certain compelling circumstances—when pediatric labeling could avoid significant risks to kids, for example.

The rule expands on a 1994 regulation that simplified the information needed for a manufacturer to label its drugs for children's use. That rule required drug makers to look at existing data and determine if they could support safe and effective use in children.

"That was the voluntary effort, and we weren't making much headway," says Rosemary Roberts, M.D., chair of the pediatric subcommittee in FDA's Center for Drug Evaluation and Research. "Most manufacturers just went back to saying that safety and effectiveness had not been established for children."

Without pediatric data about a drug, Roberts says, doctors are sometimes reluctant to treat a child with it. "Some physicians won't even try a drug in a child if they don't have enough information," she says. It is legal, however, to prescribe a drug for use in children despite its approval only for adults (termed



"off-label" use).

If doctors decide against using adult drugs in their young patients because the appropriate dose is unknown, children may be deprived of useful treatments, especially some AIDS drugs and other breakthrough therapies that carry considerable risks.

Doctors can be faced with quite a dilemma, says Timothy Westmoreland of the Elizabeth Glaser Pediatric AIDS Foundation. "Do you choose to withhold a potentially effective drug that is useful in adults or expose a child to a drug you don't know is safe?"

Because of their immature organs and different metabolic and immune systems, children react unlike adults to many drugs. Treating children with adult drugs, then, can carry the risk of unforeseen adverse reactions.

Besides the chloramphenicol tragedy, other serious adverse reactions in children have included:

- jaundice in newborns from sulfa drugs
- seizures and cardiac arrest from the local anesthetic bupivacaine
- withdrawal symptoms from pro-

Top 10 Drugs Prescribed to Kids Without Pediatric Labeling

These 10 drugs were prescribed more than 5 million times in a single year to children in age groups for which the drugs were not adequately labeled.

Drug	Condition	Prescribed
1. Albuterol inhalation solution for nebulization	Asthma	1,626,000 times to children under 12
2. Phenergan	Allergic reactions	663,000 times to children under 2
3. Ampicillin injections	Infection	639,000 times to children under 12
4. Auralgan otic solution	Ear pain	600,000 times to children under 16
5. Lotrisone cream	Topical infections	325,000 times to children under 12
6. Prozac	Depression, obsessive-compulsive disorder	349,000 times to children under 16, including 3,000 times to infants under 1
7. Intal	Asthma	109,000 times to children under 2; aerosol prescribed 399,000 times to children under 5
8. Zoloft	Depression	248,000 times to children under 16
9. Ritalin	Attention deficit disorder, narcolepsy	226,000 times to children under 6
10. Alupent syrup	Asthma	184,000 times to children under 6

(Based on 1994 data from research firm IMS America, Ltd.)

longed use of the painkiller fentanyl

- staining of teeth from the antibiotic tetracycline.

“It can be a real guessing game as to whether we’re treating a child effectively,” Roberts says.

“Sometimes a child’s body will handle the drug very much like an adult’s, she explains, “while other times a child’s body will react quite differently. There may be no way of knowing in advance.”

While dosing information sometimes becomes available to physicians through references such as journal articles and pediatric handbooks, it

may take years for this information to appear. Even then, the information may not be based on adequate testing and may contain gaps, about its use in certain age groups, for example.

Even if the correct dose is known, the medicine will do no good, of course, if a child can’t ingest it. So the 1998 rule in some cases requires manufacturers to make a special formulation of a drug product—liquid or chewable tablet instead of a tablet that must be swallowed whole, for example—to enable kids to take the drug.

Wendy Goldberg knows firsthand the frustrations of treating her child

with drugs made in tablet form for adults. “I need to cut two of them in half,” she told the panelists at the hearing preceding the rule. One, she said, is “like a little stone. I got a gadget from my pharmacist that is supposed to cut it in half, but it doesn’t work exactly right. Do I give her the big “half” or the small “half”? I usually give her the big piece in the morning, on the theory that if something bad happens, at least she’ll be awake.”

Controlled Risk

To those who point out that bad things can happen during drug studies, too, the American Academy of Pediatrics has responded that treating



Rx Safety and effectiveness in pediatric patients have not been established.

Rx The effectiveness in pediatric patients with depression or panic disorder has not been systematically evaluated.

Rx This product should not be used in children under 2 years because safety for such use has not been established.

Rx Tablets are not recommended for use in children under 6 years at this time.

Rx Should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

The pediatric study requirement may be waived entirely if a drug is not medically important for children and will not be commonly used in children or if:

- there is strong evidence that the drug product would be ineffective or unsafe in all pediatric patients;
- children's studies are impossible or highly impractical because, for example, the number of patients is too small or geographically spread out;
- attempts to develop a pediatric formulation have failed.

The Pediatric AIDS Foundation's Westmoreland is confident that "virtually all" drugs with significance to children will be studied because of the new FDA rule, as well as the complementary financial incentives under the FDA Modernization Act of 1997, which gives an extra six months of exclusive marketing or patent protection for studying certain drugs in children.

children with untested drugs may place more kids at risk than including them in controlled studies of the drugs in the first place.

Children enrolled in drug studies "are sick children that stand to benefit from getting new drugs sooner," says AAP's Ward. "Yes, they will be at risk, just like adults are at risk, if the drug is later found to have problems. But because we're treating children with illnesses, that risk is justified."

Under the rule, the timing of stud-

ies in children will depend on the seriousness of the disease, the availability of other treatments, the amount of safety and effectiveness information already available, and the types of studies that are needed.

FDA will not delay the approval of a drug for adults to await completion of children's studies. Instead, the agency could approve the drug for adults on the condition that the company completes pediatric studies in a timely way.

"We see the rule as a real victory," says Janis Stire, executive director of the foundation. "For too long, children have been seen as an afterthought, with so many drugs not available to them. A child is not just half an adult to be given half the adult dose."





Medications and Older Adults

Mary Parker of Oak Ridge, Tenn., is quick to joke about her health problems. Her vibrant smile and upbeat attitude belie her age.

But when she was 77 years old she had a health problem she didn't find amusing. The medication she took for her swollen sinuses left her so weak and dizzy she couldn't get out of bed.

"I felt like I wanted to die," she remembers. "It was awful."

She learned an important lesson from the episode. She thinks twice before taking any medication, questions her doctors and pharmacists, and reviews all of her medications regularly with her primary physician.

Parker's attitude is a good one for older adults to have, experts say. As people age, they often develop a number of problems taking medications. Being aware that problems may occur is the first way to minimize them.

"You are a partner in your healthcare," urges Madeline Feinberg, Pharm.D., a pharmacist and director of the Elder Health program of the University of Maryland School of Pharmacy. "This is a partnership between you, your doctor, and your pharmacist. You need to be assertive and knowledgeable about the medications you take."

FDA is also working to make drugs safer for older adults, who consume a large share of the nation's medications. Adults over age 65 buy 30 percent of all prescription drugs and 40 percent of all over-the-counter drugs.

“Almost every drug that comes through FDA [for approval] has been examined for effects in the elderly,” says Robert Temple, M.D., associate director for medical policy in FDA’s Center for Drug Evaluation and Research. “If the manufacturer

hasn’t done a study in the elderly, we ask for it.”

More than 15 years ago, the agency established guidelines for drug manufacturers to include more elderly patients in their studies of new drugs. Upper age limits for drugs were elimi-

nated, and even patients who had other health problems were given the green light to participate if they were able. Also, drugs known to pass primarily through the liver and kidneys must be studied in patients with malfunctions of those organs. This has a

Protecting Older Patients

To help ensure the safe and effective use of prescription drugs in older people (specifically, aged 65 and older), a rule finalized by FDA in August 1997 requires drug companies to include a separate “Geriatric Use” section in their drugs’ labeling. Drug companies do not have to perform additional studies like the pediatric rule requires, but must include available information in a specific format and location.

“If the information is dispersed throughout the whole label, it doesn’t make for a user-friendly information source,” says Robert Michocki, a clinical pharmacist and professor at the University of Maryland’s school of pharmacy. “People are busy. Physicians don’t sit down and read the whole drug label. They try to read the important sections that answer questions like ‘what’s the dose?’ or ‘what are the side effects?’

While drugs for everything from heart problems and high blood pressure to pneumonia and the flu can be lifesavers for older people, the dangers of medicine can be magnified in this population, too.

One reason for the increased risk is people’s changing physiology as they get older, says Charles Ganley, M.D., FDA’s medical team leader for cardiorenal drug products. For example, he says, certain drugs that are eliminated from the body by the kidneys could cause problems in the elderly because kidney function can decline with age.

Also, the elderly take more medicines than any other age group—around 30 percent of the prescription drugs sold in the United States, according to FDA, although they make up only about 12 percent of the country’s population. The use

of multiple drugs can increase the risk of dangerous drug interactions.

Michocki says, “start low and go slow” is an adage that applies to giving older people medicines. “For the most part, with older people you’re using medications to try and manage their chronic diseases like diabetes or arthritis. There’s no reason to go in there and try to fix something overnight.”

The rule will prove beneficial, Michocki thinks, because “after reading the special

section on geriatrics, a physician who is not familiar with the drug may start out giving half the dose he was going to give in the first place.”

New labels are appearing gradually, first on those drugs that FDA has determined are most likely to create problems for geriatric patients. These include psychotropic drugs such as antidepressants and antipsychotics, as well as some heart medications and nonsteroidal anti-inflammatory drugs (NSAIDs).

mined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers
Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil (paroxetine hydrochloride) is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established.

Geriatric Use
In worldwide premarketing Paxil clinical trials, 17% of Paxil-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS Associated with Discontinuation of Treatment
Twenty percent (1,189/6,145) of Paxil patients in worldwide clinical trials in depression and 11.8% (94/842) and 8.4% (44/485) of Paxil patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events (>1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for Paxil compared to placebo) included the following:

term 30-week placebo-controlled trial patients were dosed in a range of 20 day. Reported adverse events were using a standard COSTART-based terminology. The prescriber should be aware that rates cannot be used to predict the incidence of side effects in the course of usual practice where patient characteristics and factors differ from those which prevailed in clinical trials. Similarly, the cited frequencies should be compared with figures obtained from clinical investigations involving different patients, uses and investigators. The data however, do provide the prescribing with some basis for estimating the relative frequency of drug and non-drug factors effect incidence rate in the population.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Depression

Body System	Preferred Term	Paxil (n=42)
Body as a Whole	Headache	19†
	Asthenia	15†
Cardiovascular	Palpitation	3†
	Vasodilation	3†
Dermatologic	Sweating	11†
	Rash	2†
Gastrointestinal	Nausea	20†
	Dry Mouth	10†
	Constipation	14†
	Diarrhea	12†
Musculoskeletal	Decreased Appetite	6†
	Fatigue	4†
	Dyspareunia/Disorder*	2†
	Dyspepsia	2†
Nervous System	Myopathy	2†
	Myalgia	2†
	Muscle Pain	1†
Nervous System	Somnolence	25†
	Dizziness	13†
	Insomnia	13†
	Tremor	8†

9 10

“Almost every drug that comes through FDA [for approval] has been examined for effects in the elderly.”

— Robert Temple, M.D.
Associate Director for Medical Policy

direct benefit for older adults, who are more likely to have these conditions.

In several surveys, FDA discovered that drug manufacturers had been using older adults in their drug studies; however, they weren't examining that age group for different reactions to the drugs. Now, they do. Today, every new prescription drug has a section in the labeling about its use in the elderly.

Says Temple, “The FDA has done quite a bit and worked fully with academia and industry to change drug testing so that it does analyze the data from elderly patients. We're quite serious about wanting these analyses.”

When More Isn't Necessarily Better

Of all the problems older adults face in taking medications, drug interactions are probably the most dangerous. When two or more drugs are mixed in the body, they may interact with each other and produce uncomfortable or even dangerous side effects. This is especially a problem for older adults because they are much more likely to take more than one drug. Two-thirds of adults over age 65 use one or more drugs each day, and one-quarter of them take three drugs each day.

Not all drug combinations are bad. High blood pressure is often treated with several different drugs in low

doses. Unless supervised by a doctor, however, taking a mixture of drugs can be dangerous.

For example, a person who takes a blood-thinning medication should not combine that with aspirin, which will thin the blood even more. And antacids can interfere with certain drugs for Parkinson's disease, high blood pressure, and heart disease. Before prescribing any new drug to an older patient, a doctor should be aware of all the other drugs the patient may be taking.

“Too often, older people get more drugs without a reassessment of their previous medications,” says Feinberg. “That can be disastrous.”

There is also evidence that older adults tend to be more sensitive to drugs than younger adults are, because of their generally slower metabolisms and organ functions. As people age, they lose muscle tissue and gain fat tissue, and their digestive systems, liver, and kidney functions slow down. All this affects how a drug will be absorbed into the bloodstream, react in the organs, and how quickly it will be eliminated. The old adage “start low and go slow” applies especially to the elderly.

Older adults who experience dizziness, constipation, upset stomach, sleep changes, diarrhea, incontinence, blurred vision, mood changes, or a rash after taking a drug should call their doctors. The following sugges-

tions may also help:

- Don't take a drug unless absolutely necessary. Try a change in diet or exercise instead. Ask your doctor if there's anything else you can do besides drug therapy for the condition.
- Tell your doctor about all the drugs you take. If you have several doctors, make sure they all know what the others are prescribing, and ask one doctor (such as an internist or family physician) to coordinate your drugs.
- Some internists and family physicians take extra training and a written examination to receive a Certificate of Added Qualification in Geriatric Medicine.
- Ask for drugs that treat more than one condition. Blood pressure medicine might also be good for heart disease, for example.
- Keep track of side effects. New symptoms may not be from old age but from the drug you're taking. Try another medication, if possible, until you find one that works for you.
- Learn about your drugs. Find out as much as you can by asking questions and reading the package inserts. Both your doctor and pharmacist should alert you to possible interactions between drugs, how to take any drug properly, and whether there's a less expensive generic drug available.
- Have your doctor review your drugs. Take all of your drugs, including dietary supplements, over-the-counter preparations, and vitamins with you on a doctor's visit.
- Ask the doctor, “When can I stop taking this drug?” and “How do we know if this drug is still working?”
- Watch your diet. Some drugs are better absorbed with certain foods, and some drugs shouldn't be taken with certain foods. Ask a pharmacist what foods to take with each drug.
- Follow directions. Read the label

every time you take the medication to prevent mistakes, and be sure you understand the timing and dosage prescribed.

- Don't forget. Use a memory aid to help you—a calendar, pill box, or your own system. Whatever works for you is best. Note: Some drugs, such as nitroglycerin, will lose their strength unless kept in the special containers supplied by your pharmacist.

Medicine and Special Needs

Arthritis, poor eyesight, and memory lapses can make it difficult for some older adults to take their medications correctly. Studies have shown that between 40 and 75 percent of older adults don't take their medications at the right time or in the right amount. About one-quarter of all nursing home admissions are due at least in part to the inability to take medication correctly.

A number of strategies can make taking medication easier. Patients with arthritis can ask the pharmacist for an oversized, easy-to-open bottle. For easier reading, ask for large-print

Among healthy older adults, medications may have the same physical effects as they do in younger adults.

labels. If those are not available, use a magnifying glass and read the label under bright light.

Invent a system to remember medication. Even younger adults have trouble remembering several medications two or three times a day, with and without food. Devise a plan that fits your daily schedule. Some people use meals or bedtime as cues for remembering drugs. Others use charts, calendars, and special weekly pill boxes.

Mary Sloane, 78, keeps track of five medications a day by sorting her pills each evening into separate dishes. One is for morning pills, the other for the next evening. Then she turns each medicine bottle upside down after

taking a pill so she can tell at a glance if she has taken it that day.

"You have to have a system," Sloane says. "Because just as soon as I get started taking my pills, the phone rings, and when I come back to it, I think, 'Now have I taken that?'"

Drug-taking routines should take into account whether the pill works best on an empty or full stomach and whether the doses are spaced properly. To simplify drug taking, always ask for the easiest dosing schedule possible—just once or twice a day, for example.

Serious memory impairments require assistance from family members or professionals. Adult day care, supervised living facilities, and home health nurses can provide assistance with drugs.

Cutting Costs

The cost of medications is a serious concern for older adults, most of whom must pay for drugs out of pocket. Even those who have insurance to supplement Medicare must often pay a percentage of the cost of their medicines.

For a new prescription, don't buy a whole bottle. Request starter samples from your physician, or buy just a small amount at first. If you do have to switch, you won't be stuck with a costly bottle of medicine that you can't take.

For ongoing conditions, medications are often less expensive in quantities of 100. Only buy large quantities of drugs if you know your body tolerates them well. But be sure you can use all of the medication before it passes its expiration date.

Call around for the lowest price. Pharmacy prices can vary greatly. If you find a drug cheaper elsewhere, ask your regular pharmacist if he or she can match the price.

Other ways to make your prescription dollars go further include:

- Ask for a senior citizen's discount.
- Ask your physician whether there is a less expensive medication that can work as well.
- Ask your physician or your pharmacist about the availability of a generic rated as "therapeutically equivalent" by FDA.
- Get drug samples free. Pharmaceutical companies often give samples of drugs to physicians. Tell your doctor you'd be happy to have them. This is especially convenient for trying out a new prescription.
- Buy store-brand or discount-brand over-the-counter products. Ask the pharmacist for recommendations.
- Call your local chapter of the American Association of Retired Persons (AARP) and your local disease-related organizations (for diabetes, arthritis, etc.). They may have drugs available at discount prices.
- Try mail order. Mail-order pharmacies can provide bulk medications at discount prices. Use this service only for long-term drug therapy because it takes a few weeks to be delivered. Compare prices before ordering anything.



What to Ask the Doctor

Before you leave your doctor's office with a new prescription, make sure you fully understand how to take the drug correctly. Your pharmacist can also provide valuable information about how to take your medicines and how to cope with side effects. Ask the following questions:

- What is the name of this drug, and what is it designed to do? Is this a generic or a name-brand product?
- What is the dosing schedule and how do I take it?
- What should I do if I forget a dose?
- What side effects should I expect?
- How long will I be using this drug?
- How should I store this drug?
- Should I take this on an empty stomach or with food? Is it safe to drink alcohol with this drug?

Active Lives

Not all older adults are in danger of drug interactions and adverse effects. In fact, as more people live active lives well into their 80s and beyond, many take few prescribed medications or none at all. Among healthy older adults, medications may have the

same physical effects as they do in younger adults. It is primarily when disease interferes that the problems with drug interactions and adverse effects begin.

To guard against potential problems with drugs, however, older adults must be knowledgeable about what they take and how it

makes them feel. And they should not hesitate to talk to their doctors or pharmacists about questions and problems they have with a medication.

Says the University of Maryland's Feinberg, "We need to have educated patients to tell us how the drugs are working."



A Dose of Clear Directions for Rx Drug Users

More than four centuries ago, doctors were considered omnipotent, and the ethical statutes of England's Royal College of Physicians instructed: "Let no physician teach the people about medicines, or even tell them the names of the medicines, particularly the more potent ones ... for the people may be harmed by their improper use."

While doctors today are more forthcoming, many patients still have a hard time getting important information about the drugs their doctors prescribe. In a time when Corn Flakes, over-the-counter Tylenol, and even Alpo dog food come with easy-to-understand information about proper use, many prescription drugs still come with only a "Use as Directed" sticker for patients. The rest of the labeling is for the medical professional, in language that may be difficult for lay people to understand.

This lack of information for patients may be one reason for the finding, published in 1992 in the *Journal of Clinical Pharmacy and Therapeutics*, that about half of prescription drugs don't work as intended because they are improperly used.

Noncompliance can have tragic

consequences. Missed doses of heart medications, for example, may lead to cardiac arrest. And missed doses of antiglaucoma medicines can lead to eye nerve damage and blindness.

To help avoid medication problems, a new "Action Plan for the Provision of Useful Medicine Information" was unveiled in January 1997 to provide more and better information to patients.

Simple, Relevant Information

Under the action plan, health professionals will voluntarily provide prescription drug information to patients in the form of leaflets written in simple language.

Useful prescription drug information must reach at least 75 percent of patients by the year 2000, in keeping with the Department of Health and

Human Services goal under its Healthy People 2000 program. By 2006, the information must reach at least 95 percent of patients. If these goals aren't met, FDA may require the information by regulation.

The plan was developed with the input of health professionals and consumer, government, and industry representatives.

"Working together and using today's computer technology," said Secretary of Health and Human Services Donna Shalala when she approved the plan, "we can make prescription information more widely available, more understandable, and more relevant for each individual patient."

The action plan calls for the written information to include the condition(s) for which the drug is used,

Prescription Drug Information

Cefaclor



Why is Cefaclor prescribed?

Cefaclor is used to treat infections caused by certain bacteria. These infections include middle ear, bladder, and skin infections, as well as strep throat and sinusitis. Cefaclor works by killing certain bacteria or preventing them from growing. It works only for certain bacteria and not for others. Cefaclor is in a class of drugs known as cephalosporin antibiotics. Medicines are sometimes prescribed for uses other than those listed in this leaflet. If you have any questions please call your doctor or other prescriber.

Before Taking Your Medicine

Check with your doctor or other prescriber. This medication may not be right for you, if you:

- have abdominal problems
- are pregnant
- are nursing
- are a diabetic and checking your urine for sugar: Cefaclor can interfere with the urine test you may be using to test for sugar.
- are taking other medications: Do not take this drug if you are allergic to penicillin or any other cephalosporin-antibiotics because it is likely that you may also be allergic to Cefaclor.

While You Are Taking Your Medicine

Continue taking Cefaclor even if you feel better. Be sure to take all of the medication for the length of time prescribed for you. If you stop taking your medication too soon, the bacteria can grow back and you may get sick again with the same infection.

- If you miss taking a dose of Cefaclor, take it as soon as you remember.
- If it is almost time for your next dose, skip the missed dose and take your medicine as scheduled.
- Do not take double your prescribed dose.

Prescription Drug Information



The most common side effects are mild upset stomach, diarrhea, and rash. Call your doctor if these side effects persist or are bothersome.

Call your doctor or other prescriber if the following side effects occur:

- Swelling of the throat or difficulty breathing
- Hives, itching, and rash
- Severe or bloody diarrhea
- Abdominal pain
- Tiredness or lightheadedness (that lasts after taking this medication for 24 hours)
- Fever (that lasts after taking this medication for 24 hours)
- Joint aches or stiffness (that lasts after taking this medication for 24 hours)

Shake your bottle well every time before taking this medicine.

Keep Cefaclor in the refrigerator. Throw away any unused portions after the expiration date.

- Each teaspoon (5ml) of Cefaclor for Oral Suspension contains either 125, 250, or 375 mg of cefaclor monohydrate and is pink in color.
- If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition.
- Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Cefaclor and does not contain all possible information about this drug. If you have any questions or concerns, or want more information about Cefaclor, contact your doctor, other health care professional or pharmacist. Your pharmacist also has a larger leaflet about Cefaclor that is written for health professionals that you can ask to read.

(Name of product and date of most recent publication or revision)

directions for taking the drug correctly, and possible side effects. Doctors or pharmacists can add information about an “off-label” use—a use that is not approved by FDA—if it is written based on an individual patient’s needs.

Health professionals are responsible for getting the information to patients. FDA is available for technical assistance and will work to educate the public about the plan, according to Thomas McGinnis, a pharmacist and FDA’s deputy associate commissioner of health affairs.

FDA will survey consumers nationwide in the year 2000 and again in 2006 to determine if the goals have been met. The agency will evaluate samples of the patient labeling to make sure it provides the required information in simple lan-

guage. (See “Is the Labeling Useful?” p. 91).

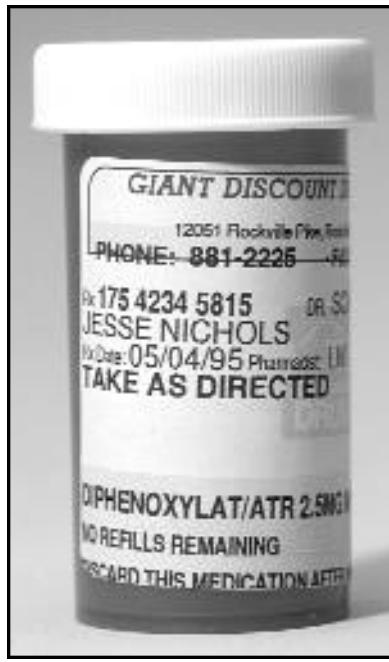
FDA has tried before to provide prescription medicine information to consumers. A rule the agency proposed in 1979 would have required manufacturers to include leaflets known as patient package inserts, or PPIs, with 10 prescription drugs or drug classes. The rule was withdrawn in 1982 to allow private organizations time to provide the information voluntarily.

In the next decade, FDA research showed minimal progress in getting good-quality medication information to patients. So, in 1995, FDA proposed a rule, commonly called MedGuide, that set forth goals for the distribution of useful prescription drug information to consumers and would have required manufacturers

Under the action plan, patients will get leaflets similar to the one above with each prescription drug. The leaflets will explain in simple language how to use the medication correctly.

to include drug information for the patient when a product posed a serious health risk.

In August 1996, Congress passed legislation that put the MedGuide proposal on hold to provide another opportunity for private achievement of the MedGuide goals. The action plan is the private sector’s framework for achieving those goals.



Allergy Tablets

Drug Facts	
Active ingredient (in each tablet)	Purpose
Chlorpheniramine maleate 4 mg	Antihistamine
Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: <input type="checkbox"/> sneezing <input type="checkbox"/> runny nose <input type="checkbox"/> itchy, watery eyes <input type="checkbox"/> itchy throat	
Warnings	
Ask a doctor before use if you have: <input type="checkbox"/> glaucoma <input type="checkbox"/> a breathing problem such as emphysema or chronic bronchitis <input type="checkbox"/> trouble urinating due to an enlarged prostate gland	
Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives	
When using this product	
<input type="checkbox"/> you may get drowsy <input type="checkbox"/> avoid alcoholic drinks <input type="checkbox"/> alcohol, sedatives, and tranquilizers may increase drowsiness <input type="checkbox"/> be careful when driving a motor vehicle or operating machinery <input type="checkbox"/> excitability may occur, especially in children	
If pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.	
Directions	
adults and children 12 years and over	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children 6 years to under 12 years	take 1/2 tablet every 4 to 6 hours; not more than 3 tablets in 24 hours
children under 6 years	ask a doctor

Drug Facts (continued)	
Other information <input type="checkbox"/> store at 20-25°C (68-77°F) <input type="checkbox"/> protect from excessive moisture	
Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch	

Lack of Labeling

Currently, manufacturers provide patient information for about 40 prescription drugs or drug classes. FDA requires patient information for some drugs, including oral contraceptives and isoproterenol inhalation products used by asthmatics. Manufacturers voluntarily provide FDA-reviewed patient labeling with some other products, such as Accutane (isotretinoin) for acne and Halcion (triazolam) for insomnia.

A 1997 FDA survey found that 67 percent of consumers were getting some written information with their prescription drugs, up from 54 percent in 1994.

But the surveys don't take into consideration the quality of the information. "The materials being given to consumers are very variable," McGinnis says. "Some are very poor, some are very good, and some are in-between. Most of the information out there now is going to have to be beefed up to meet the action plan criteria."

By increasing patients' knowledge about their drug therapies, the action plan aims to help patients take their

Prescription drugs with a label saying only "Take As Directed" may soon be a thing of the past, thanks to the new "Action Plan for the Provision of Useful Medicine Information." The plan will give consumers the kind of easy-to-understand information that they already get when they buy over-the-counter drugs or food.

drugs correctly. Improper use of prescription drugs leads to unnecessary illnesses, emergency room visits, hospital admissions, and deaths. FDA estimates extra healthcare costs from preventable drug-related illnesses to be at least \$20 billion a year. (See "Medication Mishaps.")

In addition to instructions for proper use, the information sheets will address a drug's risks and side effects, according to McGinnis. By telling patients what to look for and what to do if they see warning signs, the information may help patients recognize side effects earlier, before serious damage is done.

"These drugs are risky—they wouldn't be prescription drugs if they weren't—and patients have a right to know what the risks are," McGinnis says.

Some groups representing the pharmaceutical industry and health

professionals have expressed concern to FDA that informing patients of risks and side effects may hurt compliance by scaring consumers out of taking the drug as prescribed. To this, McGinnis replies, "We've heard that argument, but we've never seen it supported scientifically."

Empowering the Patient

Written information sheets cannot replace the advice of a health professional. But there are some barriers to communication between patients and health professionals, according to David Schulke, director of policy and regulatory affairs at the American Pharmaceutical Association. "There are financial pressures that cause doctors and pharmacists to talk to more patients in less time, giving less time to each patient."

Because of the competing demands on health professionals' time, written

information is especially important. “The piece of paper becomes a back-up, a safety net that patients can keep with them and refer to for information,” says consumer advocate Arthur Levin, director of the Center for Medical Consumers.

Patients sometimes need to take on a very active role in their own health-care, according to McGinnis. “FDA is hoping the additional information will help the patient feel less inhibited about asking questions,” he says. “We hope it will encourage patients to become more involved, along with their physician, pharmacist, or nurse.”

Medication Mishaps

Accupril and Accutane. The drug names sound pretty similar, but they are prescribed for very different conditions. Accupril (quinapril hydrochloride) is used to treat high blood pressure and heart failure. Accutane (isotretinoin) is for certain types of severe acne.

You wouldn’t want to take Accutane for a heart condition by mistake. But a patient could be given the wrong drug by accident. Confusion can arise from similar drug names or packaging, a prescriber’s poor handwriting, misinterpretation of an abbreviated drug name, or an incorrect data entry into a computer.

To prevent avoidable accidents, FDA’s Center for Drug Evaluation and Research compares drug names to see if a change is needed to avoid confusion.

“FDA’s goal is to try to catch the potential for error before the product is marketed,” says Sharon Smith Holston, FDA’s deputy commissioner for external affairs. “Later, if we get reports of errors, we will work with the manufacturer to correct the problem by making a change in the packaging, labeling, or name.”

Patients themselves can prevent certain types of drug errors. The National Council on Patient

Information and Education recommends asking your health professional at least these six questions about a prescription medication:

- What is the name of the medicine and what is it supposed to do?
- How and when do I take it, and for how long?
- What foods, drinks, other medicines, or activities should I avoid while taking this medicine?
- Are there any side effects, and what should I do if they occur?
- Will this new prescription work safely with the other prescription and nonprescription medicines I am taking?
- Is there any written information available about the medicine?

Patients who get drug information in writing as well as orally, says FDA pharmacist Thomas McGinnis, are much more likely to notice if the drug they got isn’t for the condition they went to the doctor about or if it may be dangerous if taken with certain foods or another medication.

If a medication error occurs or is suspected, a health professional may report it, in confidence, to FDA’s MedWatch program at (1-800) FDA-0178 or the U.S. Pharmacopeia’s Medication Errors Reporting Program at (1-800) 23-ERROR.

Is the Labeling Useful?

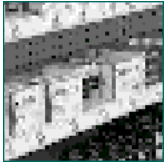
To be acceptable under the action plan, the information given to patients must be scientifically accurate, unbiased, specific, complete, understandable, up-to-date, and useful.

“The criteria aren’t set in stone,” says FDA pharmacist Thomas McGinnis. For example, the format may have to be adjusted for some populations. For the elderly, whose eyesight may be declining, the type may have to be larger.

How will FDA determine if labeling is “useful”? The agency will look for specific information, including:

- Medicine name;
- Critical warnings (prominently displayed);
- Conditions for which the product is used;
- Circumstances under which the product shouldn’t be used and directions about what to do if one of these circumstances applies (for example, “Talk to your healthcare professional before taking this medication if any of these apply to you.”);
- Drugs, foods and activities that should be avoided while taking the medication, and other precautions necessary to take the medicine properly;
- Symptoms of adverse reactions possibly related to the drug;
- Risk, if any, of developing a drug tolerance or dependence;
- Instructions for proper use, including the usual doses, instructions if a scheduled dose is missed, special instructions (for example, whether to take with food or water), and what to do in case of an overdose;
- Storage instructions;
- General information, including a statement encouraging discussion with a healthcare professional and a statement that the drug should not be given to others; and
- A statement that the patient labeling does not contain all possible information about the medicine and that the healthcare professional has more information.

To obtain a copy of the action plan, access the Keystone Center’s Website at <http://www.nyam.org/keystone/> or call (202) 783-0248. To obtain more information about the action plan, contact FDA Office of Consumer Affairs HFE-88, 5600 Fishers Lane, Rockville, MD 20857; tel. 1-888 INFO-FDA (10 a.m. to 4 p.m. Eastern time, Monday through Friday).



New Drug Label Spells It Out Simply

INDICATIONS: Provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.

DIRECTIONS: Adults and children 12 years and over—1 tablet every 4 to 6 hours, not to exceed 6 tablets in 24 hours or as directed by a physician. Children 6 to 11 years—one half the adult dose (break tablet in half) every 4 to 6 hours, not to exceed 3 whole tablets in 24 hours. For children under 6 years, consult a physician.

EACH TABLET CONTAINS: Chlorpheniramine Maleate 4 mg. May also contain (may differ from brand): D&C Yellow No. 10, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch.

WARNINGS: May cause excitability especially in children. Do not take this product unless directed by a physician, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. May cause drowsiness; alcohol, sedatives and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages, and do not take this product if you are taking sedatives or tranquilizers without first consulting your physician. Use caution when driving a motor vehicle or operating machinery. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately.

Store at controlled room temperature 2°-30°C (36°-86°F).

Use by expiration date printed on package.

Protect from excessive moisture.

For better identification keep tablets in carton until used.



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Made in U.S.A.

There's a simpler substitute for the word "assistance": help. For "discard": throw away. And for "aggravate": make worse.

Soon, consumers could see the plain-speaking terms in place of longer, harder-to-understand ones on everything from aspirin for aches and pains to zinc chloride for canker sores. A new Food and Drug Administration regulation allows these pairs of words and some others

to be used interchangeably on the labels of nonprescription, or "over-the-counter," drugs.

In addition to permitting some word swaps, the new rule requires that all OTC drug labels contain certain information—such as ingredients, doses and warnings—in a standardized format.

The rule, published in the March 17, 1999, *Federal Register*, covers some 100,000 nonprescription products, including those like sunscreens that have both drug and cosmetic uses. The goal of the uniform label is to help consumers understand a nonprescription drug's benefits and risks and take the medicine correctly.

The new rule, said Vice President Al Gore when he announced it March 11, will "ensure that the

labels on medicine we buy over the counter are no longer written in language that is over our heads. Starting here and now, when children wake up sick in the middle of the night, parents won't have to read a dictionary to read the directions. And people won't need a magnifying glass to find out what's in their medicine."

FDA hopes the new "Drug Facts" labels will improve the way consumers choose and use over-the-counter medicines just as the simplified "Nutrition Facts" labels have helped consumers eat less fat and otherwise improve their eating habits.

"People have told us, and studies have confirmed, that the food labels are working," says Peter Rheinstein,

Drug Facts

Active ingredient (in each tablet) **Purpose**
 Chlorzoxazone tablets 2 mg **Anti-itching**

Uses Temporarily relieve these symptoms due to hay fever or other upper respiratory ailments: sneezing, runny nose, itchy, watery eyes, itchy throat.

Warnings
 Ask a doctor before use if you have a glaucoma, see breathing problem such as emphysema or asthma, heart disease, or trouble urinating due to an enlarged prostate gland.
 Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives.
 When using this product:
 If you may get drowsy, do not drink alcohol.
 If alcohol, sedatives, oral contraceptives may increase drowsiness.
 Do not drink or drive a motor vehicle or operate machinery if drowsiness may occur, especially in children.
 If pregnant or breast-feeding, ask a health professional before use.
 Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Dosage:

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Drug Facts (continued)

Other information is store at 20-30°C (68-77°F) in original container with desiccant.

Inactive ingredients D&W yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch.

M.D., director of the medicine staff in FDA's Office of Health Affairs. "What's lacking in many OTC labels is readability, consistency—all the things the new food label has. It's not that the information isn't there already. Sometimes it's just hard to find."

Debra Bowen, M.D., who led the FDA team that wrote the regulation, sees the similarity with the standardization of the food label, and adds that using a drug correctly requires even more elaborate information about risks and benefits. So it's all the more important, Bowen says, "to provide not only complete information about the drugs, but complete information in a readable, clear and simple format."

Just the Facts

Americans buy about 5 billion over-the-counter drugs each year, according to government estimates, to treat their headaches, heartburn, coughs and

"If you buy a drug without having all the information, you may not get all the benefit it can provide."

— Peter Rheinstein M.D.

colds, and other routine health problems. According to the Consumer Healthcare Products Association, a trade group that represents nonprescription drug makers, more than 600 OTC drugs contain ingredients and dosages that 20 years ago were available only by prescription.

Over-the-counter drugs are very safe as a rule, but not risk-free, Rheinstein says. "Just because something is sold

over the counter," he says, "doesn't mean it's absolutely safe. Any medicine that's strong enough to help you also has the power to hurt you if you don't take it right."

Taking a medicine right can help avoid dangerous adverse reactions, it's true, but Rheinstein adds that a person who uses a medicine incorrectly can be harmed in another important, although perhaps less dangerous, way: "If you buy a drug without having all the information, you may not get all the benefit it can provide," he says. "The new rule will help people get all the benefit they're paying for."

The new label's simple language and easy-to-read format should help people compare drug products to choose the best one to treat their illness, get the drug's full benefit, and avoid unnecessary adverse reactions.

Under the rule, OTC drug labels must comply with these requirements:

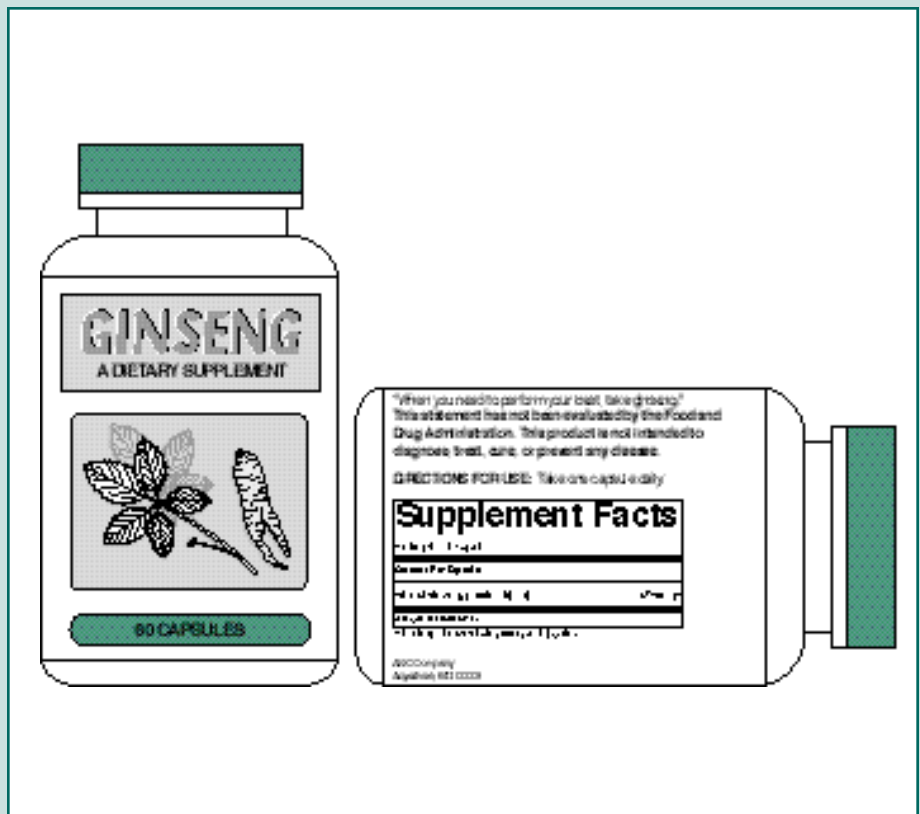
- Information must be presented in a

Supplement Facts

Like processed foods and now over-the-counter drugs, dietary supplements, too, must begin carrying standardized labels with information about their ingredients. The "Supplement Facts" panel will tell consumers the amounts of specific nutrients—vitamins A and C, calcium, iron, and sodium, for example—in vitamin and mineral products. For herbal products, the label will state the part of the plant used in the product (such as the root, stem or leaf).

The new rule went into effect March 23, but supplement makers can sell their remaining stock of products labeled before that date. FDA plans to check marketed dietary supplements to make sure they are complying with the rule.

(For more on dietary supplements, see "An FDA Guide to Dietary Supplements" at www.fda.gov/fdac/features/1998/598_guid.html.)





standardized, easy-to-follow format, usually on the package's outside container or wrapper. Under the title "Drug Facts," the product's active ingredients will be listed first, along with the purpose for each, followed by uses, warnings, directions, and inactive ingredients. Listing inactive ingredients is a new requirement that should help consumers avoid products that may cause an allergic reaction. Also, FDA recommends, but doesn't require, that manufacturers include a phone number on the label for consumers to call for more information.

- Simple language must be used to communicate critical information, such as a drug's ingredients, dose and warnings. For example, the term "uses" replaces "indications," and some other technical words like "precautions" and "contraindications" won't be used anymore, either. Studies have shown that consumers often have difficulty using the information as currently presented on OTC drugs. One study, for example, reported that 70 percent of caregivers could not measure the correct dose of medicine for their child, a problem that puts that child at risk of being overmedicated or undermedicated.

- The label must be printed in type large enough to be easily read and use other graphical methods to improve readability, such as bullets, a certain amount of spacing between lines, and thin lines separating label sections. Studies have shown that many older Americans in particular can't read the small type on some current labels. This increases their risk of taking the wrong dose of a medicine or taking a medicine that could be harmful if combined with another drug they are using.

OTC medicines must begin carrying the new labels within two to six years, depending on the drug, but FDA expects many products to have the new labels sooner.

Lightening the Load

FDA estimates that changing the labeling will cost drug companies about \$58 million. Will drugs cost you more because of this rule? FDA doesn't regulate drug prices, but the agency doesn't expect prices to increase as a result of the regulation because most OTC drug labels are routinely reprinted every few years.

"We're doing what we can to make the rule nonburdensome," Rheinstein says. "Drug companies shouldn't have to throw out any labels, but in most cases can use up the old supplies first." For packages that are too small for the standardized labeling, the rule allows a modified format containing the most critical information.

Drug companies support the idea of making their labels more consumer-friendly, according to Joseph Doss of the Consumer Healthcare Products Association. "We have often said that, next to the medicine itself, the most important thing is the label," Doss says. The label is what separates OTC medicines apart from other drugs. There, the consumer has all the information needed to take the products safely and effectively.



Simplified Label Earns "No Gobbledy-Gook" Award for FDA

"The New Label—It's Clearly Better"

goes the slogan for FDA's over-the-counter drug label change. For leading the effort to develop the new, "clearly better" label, the agency's Debra Bowen got a Plain Language award from Vice President Al Gore.

Gore's "No Gobbledygook" awards recognize those in the federal government who write with their readers in mind.

"People should be able to understand what we write the first time they read it" is the simple reminder to government employees from Gore's National Partnership for Reinventing Government.

How to Comment on Proposals and Submit Petitions

You can influence FDA actions. As a regulatory agency, FDA publishes rules that establish or modify the way it regulates foods, drugs, biological products, cosmetics, radiation-emitting electronic products, and medical devices. FDA rules have considerable impact on individual well-being and the nation's health, industries, and economy. These rules are formed with the help of the medical community, industry, and consumers.

By law, anyone can participate in the rule-making process by commenting in writing on rules FDA proposes. FDA allows plenty of time for public input and carefully considers these comments when it draws up a final rule.

FDA gathers public comments mainly through two channels: proposed rules and petitions.

Proposed Rules

When FDA plans to issue a new regulation or revise an existing one, it places an announcement in the *Federal Register* on the day the public comment period begins. Published every weekday, the *Federal Register* is available at many public libraries and colleges, as well as on the Internet. Issues open to public comment often are reported by the news media and may frequently be found on FDA's Internet home page (see "Using the Internet," below).

In the *Federal Register*, the "notice of proposed rulemaking" describes the planned regulation and provides background on the issue. It also gives the address for submitting written comments, a contact for more information, and the deadline for public comment.

Usually, the comment period lasts at least 60 days, though some comment periods have been as short as 10 days or as long as nine months. Weekends and holidays are included in the comment period.

There is no special form to fill out for comments, nor do submitters have to follow a certain style. But FDA can process comments more effectively if they are presented—either written legibly or typed—on 8 by 11-inch paper.

Here are some other suggestions for making effective comments:

- Clearly indicate if you are for or against the proposed rule or some part of it and why. FDA regulatory decisions are based largely on law and science, and agency reviewers look for reasoning, logic, and good science in public comments.
- Refer to the docket number listed in the *Federal Register* notice.
- Include a copy of relevant articles or other references that support your comments.
- If an article or reference is in a foreign language, you must submit

both a copy of the original document and an English translation verified by a qualified translator to be accurate.

- To protect privacy when submitting medical information, delete names or other information that would identify patients.
- Comments must be postmarked or delivered in person by the last day of the comment period to: Dockets Management Branch, FDA, Room 1061, 5630 Fishers Lane, Rockville, MD 20852.

The number of comments received for proposals have varied greatly. A rule that established reporting procedures for problems with medical devices attracted 300 comments, while a recent proposal to regulate tobacco generated over 500,000 comments. For more information on submitting comments, consult Title 21 of the *Code of Federal Regulations*, Section 10.20.

When FDA receives a comment, it is logged in, numbered, and placed in a file for that docket. It then becomes a public record and is available for anyone to examine in FDA's reading room (Room 1061, 5630 Fishers Lane, Rockville, MD). Under

Using the Internet

Though the *Federal Register* is readily available from libraries in printed form, it also can be accessed through the Internet's World Wide Web at two addresses:

http://www.access.gpo.gov/su_docs/
<http://thorplus.lib.purdue.edu/gpo/>

You also can learn about new FDA issues that are open for public comment through the agency's News Page on its Web site at <http://www.fda.gov/opacom/hpnews.html>.

the Freedom of Information Act (FOIA), visitors to the reading room can receive free copies of comments up to 50 pages if their requests are for noncommercial use. After that, each page costs 10 cents. People also can send FDA an FOIA request and have copies of comments mailed to them (see “How to File a Freedom of Information Request,” to the right). Some documents are already on the Internet and can be found at www.fda.gov/ohrms/dockets/default.htm.

Petitions

Another way to influence FDA is to petition the agency to issue, change, or cancel a regulation, or to take other action. The agency receives about 200 petitions yearly.

Petitions require careful preparation by the submitter. Individuals sometimes submit petitions, but most come from regulated industry or consumer groups. For example, a drug company might request a change in labeling for one of its products; a food company might ask that its product be exempted from some provision of a regulation; or a consumer group might petition FDA to tighten regulation of a certain product.

Petitions submitted to FDA must contain:

- **Action requested**—What rule, order, or other administrative action does the petitioner want FDA to issue, amend or revoke?
- **Statement of grounds**—The factual and legal grounds for the petition, including all supporting material, and information known to the petitioner that may be unfavorable to the petitioner’s position.
- **Certification**—A statement that to the best of the petitioner’s knowledge, the petition includes all information relevant to the petition, favorable or not. The petition must be signed and include the

petitioner’s address and phone number.

In addition, some petitions may require statements on:

- **Environmental impact**—Generally required if the petition requests approval of food or color additives, drugs, biological products, animal drugs, or certain medical devices, or for a food to be categorized as GRAS (generally recognized as safe). Procedures for preparing environmental impact statements can be found in Title 21 of the *Code of Federal Regulations*, Sections 25.24 and 25.31. If an environmental impact statement is not required, petitions should include a statement to that effect.

By law, anyone can

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by commenting in

writing on rules

FDA proposes.

- **Economic impact**—Required only if FDA requests it after review of the petition.

Petitions should be mailed or delivered to: Dockets Management Branch, FDA, Room 1061, 5630 Fishers Lane, Rockville, MD 20852.

Ultimately, FDA management decides whether to grant a petition. But first, agency staffers evaluate it, a process that may take several weeks to more than a year, depending on

How to File a Freedom of Information Act Request

You can get copies of comments on any given issue by filing a Freedom of Information Act (FOIA) request to FDA. The request is best made by letter, specifying exactly what material is sought. Requesters usually should be specific about what comments they want, instead of asking for “all comments” received on a certain proposal, which in some cases can run thousands of pages. (Indexes of comments are available by FOIA request as well.)

FOIA requests should include an address and phone number and be sent to FDA, Freedom of Information Staff (HFI-35), 5600 Fishers Lane, Rockville, MD 20857, or faxed to (301) 443-1726. For more information, call (301) 827-6500.

You can get more information, by visiting FDA’s Electronic Freedom of Information Reading Room located at www.fda.gov/foi/foia2.htm.

the issue’s complexity. After FDA grants or denies the petition, the agency notifies the petitioner directly. If not satisfied, the petitioner can take the matter to court.

For more information on submitting petitions, consult Title 21 of the *Code of Federal Regulations*, Sections 10.30, 10.33, and 10.35.

Besides accepting public comments and petitions, FDA also schedules public meetings and hearings to discuss and explain its proposals. These usually are held with industry representatives or consumer groups, but anyone interested may attend and, with advance notice, may comment on a proposal. Meetings often are held in the Washington, D.C., area, but sometimes are set in other areas across the country. Meetings for the public to present views are announced in the *Federal Register*.

If you have questions about the comment, petition, or hearing process, contact the FDA Dockets Management Branch, (301) 827-6860. Hours are 9 a.m. to 4 p.m., Eastern time, Monday through Friday.

When You Need to Know: How to Obtain Information About Prescription and Over-the-Counter Drugs

The U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) is a knowledge warehouse.

Do you want to know the consequences of drug interactions or the different side effects of drugs? Do you have questions about the effectiveness of the latest baldness cure? If you are not even sure what questions to ask your healthcare provider or if you just wonder what fluoride really does for the teeth; CDER's Drug Information Branch can provide you with the answers to these and hundreds of other questions that you might have about drugs.

Regulating Drugs

Thousands of people call or write FDA each year for information about drugs regulated by CDER. From aspirin to cancer treatments, CDER ensures that the benefits of drug products outweigh the known risks. The center has oversight responsibilities for human prescription, over-the-counter, and generic drugs. This responsibility includes products that many consumers usually do not associate with drugs, such as fluoride toothpaste, sunscreens, and dandruff shampoos.

May I Help You?

Located in FDA's agency headquarters, CDER's Drug Information Branch is the focal point for inquiries

by pharmacists, doctors, nurses, pharmaceutical and insurance companies, Federal agencies, consumers, and other constituents.

Over the years, the Drug Information Branch has handled an average of 4,000 telephone calls per month. Staffed with pharmacists and other healthcare professionals experienced with drug-related issues, the branch's consumer safety officers (CSOs) consult with all areas of FDA to get the most current information necessary to answer often detailed and complicated questions.

The staff services include:

- telephone responses to questions from healthcare professionals and consumers,
- briefings to foreign government and industry representatives,
- regulatory guidance to the pharmaceutical industry, and
- drug information packets.

Written Material

In addition, the team is the storehouse for all CDER publications, *Federal Register* notices, drug product inserts, consumer articles, recall notices, and other drug-related information.

As a follow-up to speaking with a healthcare professional, a CSO can usually give callers additional information. In addition, CSOs often send articles, brochures, press releases, Federal regulations, fact sheets, and other publications.

Strict Confidence

By law, FDA employees cannot release confidential information about unapproved drugs or clinical trials. Consumers should obtain this information from physicians, private/nonprofit organizations, or pharmaceutical companies.

How to Obtain Information

To obtain information or ask specific questions about your condition and prescription, over-the-counter drugs, and related topics, you should consult a healthcare professional.

If you need more information, you can contact the Food and Drug Administration's Center for Drug Evaluation and Research (CDER).

CDER's Drug Information Branch can answer general questions about drugs. The branch can be reached at (301) 827-4573. Or you may call 1-888-INFO-FDA.

In addition, CDER maintains a "Fax-on-Demand" system that contains hundreds of documents about drugs. The telephone number is 1-800-342-2722.

Another source of information is CDER's World Wide Web site at <http://www.fda.gov/cder>.

Soon, all over-the-counter medicines will have one thing in common.



Simplicity.

Soon, all over-the-counter medicines will feature new, easier-to-read labels. And that should help clear up any confusion. For more information, visit our web site at www.fda.gov/cder or call 1-888-INFO-FDA.



U.S. Department of Health and Human Services
Food and Drug Administration

The New Label
— It's Clearly Better —

