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## What You Need to Know Before Becoming A Human Subject in a Clinical Trial

Every day, in hospitals, clinics and physicians' offices across the U.S., hundreds if not thousands of patients are recruited to participate in clinical trials. These trials test new experimental drugs, medical devices and other interventions for a wide range of diseases and disorders, including cancer, heart disease, depression, asthma, infections, diabetes and hypertension, to name just a few.

Before they may enroll someone in a clinical trial, the researchers conducting the trial are required by federal regulations to first obtain the individual's informed consent. The process for obtaining informed consent involves communicating to the prospective subjects, among other things, the procedures involved in the clinical trial, its risks and benefits, and the alternatives to participating in the study that may be advantageous to the subjects.

To assist readers in making well-informed decisions about whether to participate in clinical trials if invited, this article explains the fundamental difference between clinical care and research and offers guidance on important issues to consider before becoming a human subject in a clinical trial.

### Clinical care versus clinical research

When doctors invite their own patients to participate in clinical trials, patients may assume that participation in a trial is simply part of clinical care and is in their best interests. However, participation in research and treatment for a medical condition are not

the same. It is important to understand the fundamental differences between clinical care and clinical trial research, between being a patient and being a human subject, and between being a physician and being a researcher.

In the clinical care setting, the physician's sole responsibility is to act in the best interests of the individual patient. Clinical treatment recommendations and decisions are individually tailored and based solely on the unique characteristics, health needs and desires of each patient. The only goal of clinical care is to provide benefit to the patient.

In contrast, the interventions that a human subject receives in the context of a clinical trial are dictated by a research protocol. This protocol generally determines the medical interventions that the subject will receive — such as the type, dose and frequency of drugs and the type and frequency of medical tests and procedures — without respect to the individual needs of the patient or the customized recommendations of the patient's physician.

Furthermore, the primary goal of clinical research is not to provide benefit to the individual subject, but rather to answer a scientific question or test a medical hypothesis and ultimately obtain new medical knowledge that may benefit future patients. Thus, in the clinical trial setting, the interests of the individual subject are secondary to the goals of the research.

Some bioethicists have concluded that the only way to effectively minimize the potential for patients to confuse medical research with clinical care is

to prohibit physicians from recruiting their own patients into clinical trials for which those physicians are also the researchers. Because such a prohibition has not been adopted, it is very important that patients understand the difference between clinical care and research so that they can make well-informed decisions about whether to enroll in clinical trials.

### Important questions

Before agreeing to be a subject in a clinical trial, a patient should be sure to obtain and understand answers to the following key questions:

*What is the purpose and phase of the clinical trial?*

The purpose of a research study tells you why the clinical trial is being conducted. In general, the purpose is defined by the phase of development the experimental intervention being tested has reached. Clinical studies of new experimental drugs, for instance, are typically divided into three phases, referred to as phase 1, 2 or 3.

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# PUBLIC CITIZEN Health Letter

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## HUMAN SUBJECTS, from page 1

Phase 1 clinical trials are studies testing a new drug in humans for the first time. These studies involve exposing a small number of human subjects to a single dose of a new drug and collecting data on short-term toxicity as well as drug metabolism and excretion (how the drug is absorbed, broken down and removed from the body). Phase 1 trials generally enroll healthy adult individuals, but those testing certain types of drugs enroll patients with specific diseases. (For example, phase 1 clinical trials of new chemotherapy drugs for cancer usually involve patients with advanced stages of cancer.)

In phase 1 trials, there are no data from human testing indicating that the drug is safe or effective in those patients for whom it is being developed. The primary purpose of a phase 1 study is to find the highest dose of the drug that does not result in unacceptable toxicity. Data from such trials are used to guide dosing in subsequent phase 2 and phase 3 trials.

Phase 2 clinical trials of drugs are designed to gather preliminary data on the effectiveness of a new drug in patients with a particular disease or condition, as well as additional information on toxicity and metabolism. These trials usually enroll relatively small numbers of subjects (approximately 40 to 200) and involve exposure to multiple doses of the drug being studied. In some phase 2 trials, all subjects receive the new experimental drug being studied, and there is no control group. In other phase 2 studies, one group of subjects receiving the experimental drug is compared to a control group of similar individuals who are given a different intervention, such as an inactive substance (placebo) or another drug that has been shown to be effective for treating the disease of interest.

When phase 2 trials commence, the researchers generally have little or no information on whether the new experimental drug is useful for treating the intended patient group,

and minimal information regarding the drug's short-term toxicity.

For most new drugs, phase 3 clinical trials represent the final level of testing before the drug is considered for approval by the Food and Drug Administration (FDA). These studies, which routinely involve several hundred to several thousand subjects, gather more information about safety and effectiveness by studying the drug in different populations, at different dosages, and sometimes in combination with other drugs. For these trials, there is usually some limited evidence from earlier phase 2 or 3 trials suggesting that the drug may offer some benefit for the intended patient population, but such benefit has not yet been proven.

After a drug is approved by the FDA and is no longer considered experimental for its FDA-approved indication, phase 4 clinical trials will sometimes be conducted. Such studies, performed after a drug's approval, may be required by the FDA as a condition of approval of the drug, or they may be conducted voluntarily by the drug company. They may be similar in design to phase 3 studies or involve only one study group in which all subjects in the trial receive the specific drug being evaluated. The goal of these studies is to collect more information about a drug's safety, effectiveness or optimal use in the real-world setting.

Studies of nondrug interventions, such as medical devices or social and behavioral interventions, don't fall neatly into the same four phases of clinical trials used for developing new drugs. Nevertheless, studies of these other interventions commonly follow a development pathway from early-phase trials, where little is known about the safety and effectiveness of the intervention, to late-phase trials, where more is known. Therefore, before enrolling in any clinical trial, it is important to know where the trial falls in the development timeline.

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*What will the clinical trial involve and how will it differ from usual care?*

Patients considering enrollment in a clinical trial must be provided a detailed description of all procedures and interventions that they will be asked to undergo, and they must be informed about the expected duration of study participation. The study description must identify any procedures that are considered experimental. Ultimately, to make a fully informed decision about whether to enroll in a trial, patients need to clearly appreciate how the interventions and procedures in the clinical trial compare with the treatment and procedures they would otherwise undergo as part of routine clinical care.

Most clinical trials involve three stages. The first stage involves undergoing screening to confirm that an individual meets the criteria for enrollment in the trial. This screening may include undergoing a medical history assessment, physical exam, blood test or tests, biopsy, or imaging study, such as X-ray, ultrasound, or CT or MRI scanning. In some cases, the subject would undergo these same procedures and tests as part of routine clinical care, and in other cases, the testing is solely part of the research.

The second stage of a trial involves receiving the primary study interventions being tested. In studies involving comparisons of different interventions — for example, a new experimental drug for hypertension (high blood pressure) being compared to a standard, FDA-approved hypertension drug or to a placebo — subjects are often randomly assigned to receive one of the two interventions. To minimize the possibility of study bias, many clinical trials use double-blinding, in which neither the subject nor the researcher, who is frequently the subject's physician, know which intervention the subject is receiving. During this stage of a trial, subjects may be required to undergo additional exams, blood tests, biopsies or imaging studies that may or may not be routinely done if they were

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not participating in the research.

The third stage of a trial is a follow-up stage after the interventions being studied have been discontinued and the subjects are followed for a period of time, from a number of hours to many years. During this stage, information about the subjects' clinical status is collected periodically to see how each patient's disease or disorder responded to the primary study interventions being tested. The subjects again may be required to undergo additional tests and procedures that may or may not be routinely done if they were not enrolled in the research.

### *What are the risks of the research?*

Essentially all clinical trials involve risks of harm or discomfort to the subjects. Too often, the risks of a clinical trial are minimized by the researchers.

There are many potential sources of risk from research, including adverse effects resulting from:

- the experimental drug, medical device or other intervention being studied (for example, the experimental drug may cause strokes, heart attacks, liver injury or kidney disease);
- other procedures that the subjects undergo because of the research, such as additional imaging studies, blood tests or biopsies; and
- substandard treatment, or no treatment, of a potentially serious disease if the subjects are assigned to the control group and receive a placebo or nonstandard treatment regimen.

Women of childbearing age need to know about any risks posed by the research to an embryo or fetus. These may include a risk of birth defects, premature delivery and fetal death.

Some trials also involve washout periods, during which all subjects are taken off some or all medications used to treat the disease of interest for a period of days or weeks prior to being randomized to receive one of the specified study interventions being tested. These washout periods are particularly common in trials of diseases such as hypertension and mental health disorders. Washout periods can expose subjects to adverse events related to inadequate treatment of their underlying disease or disorder. For example, a subject with severe hypertension taken off all blood-pressure medication during a washout period could suffer a stroke or other cardiovascular event due to inadequately controlled blood pressure. Likewise, a subject with schizophrenia taken off antipsychotic medication could experience a severe psychotic episode.

Assessing the risks posed by a clinical trial requires considering the various interventions and procedures that are solely a function of research participation, as well as estimating both the probability and severity of the adverse events that may result from those interventions. The probability of a particular adverse event may range from extremely rare to very likely. Likewise, the severity of a particular adverse event may range from mild (for example, slight dry mouth) to extremely severe, life-threatening or even fatal.

Frequently, because of limited prior testing of a particular new experimental drug or medical device, the exact probability of a particular adverse event occurring is unknown. Moreover, potential subjects need to recognize that a particular treatment or research intervention may involve unforeseeable

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risks. The likelihood that a clinical trial involves such unforeseeable risks is highest in early-phase studies (that is, phase 1 and early phase 2 trials) due to limited knowledge of safety at these points. For example, last year, a phase 2 clinical trial testing an experimental drug for hepatitis C infection unexpectedly resulted in severe heart failure and death in some subjects. Because of these unforeseen adverse events, the manufacturer terminated the development program for the drug.

### *What are the alternatives to being in the clinical trial?*

Patients considering enrollment in a clinical trial must be informed of appropriate alternative procedures or courses of treatment, if any, that may benefit them. For many diseases and disorders, there are standard, state-of-the-art treatments available. Patients should be informed of these treatments.

In some clinical trials, different FDA-approved drugs or combinations of FDA-approved drugs are being compared for the treatment of a particular disease. This is particularly common in clinical trials testing new treatment regimens for cancer. Many patients choose to enroll in such clinical trials hoping that they will be randomly assigned to the study group receiving the “newest” regimen or drug being evaluated. For such trials, patients should ask the researchers or their own physicians whether they can receive one of the drugs or drug combinations being tested without enrolling in the clinical trial.

Finally, for some patients considering enrollment in clinical trials of interventions for advanced, terminal illnesses, one alternative that may be advantageous to patients is supportive, palliative care.

### *What are the benefits, if any, to participating in the research?*

The potential benefit to subjects that may result from participation in clinical trials is highly variable across trials. Too

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often, researchers overstate the potential benefits of research, and subjects have unreasonable expectations about them.

For some trials, particularly phase 1 trials in healthy volunteers (who are usually paid for their participation), there is no medical benefit. For patients with a particular disease or disorder being studied, the potential for benefit is lowest in early-phase studies. In fact, as a general rule, subjects in early-phase studies probably are more likely to experience harm than clinically significant benefits.

The prospect of benefit for individual subjects in phase 3 trials is higher than earlier-phase studies, but the degree of benefit is unknown and may be minimal compared with the benefits of routine medical care unrelated to the trial. Indeed, the goal of such trials is to determine what benefit, if any, the experimental interventions provide for treating the disease or disorder of interest.

Ideally, if the trial is well designed and conducted, the researchers will gain important new knowledge that will benefit future patients.

### *What are your rights as a research subject?*

Prospective research subjects must be informed that participation in research is completely voluntary and that refusal to participate will not result in any penalty or loss of benefits to which they are otherwise entitled. For example, patients invited to enroll in a clinical trial can't be threatened with loss of health care benefits if they opt not to participate in the research.

Similarly, patients who enroll in clinical trials are free to discontinue participation at any time without penalty or loss of benefits. Furthermore, while the researchers may recommend that subjects wishing to discontinue participation undergo certain tests and procedures to ensure a safe and orderly withdrawal from a trial, subjects are under no obligation to adhere to those recommendations.

Subjects also have a right to be informed about any new information or findings about the drug or device that develop during the course of a trial that may relate to the subjects' willingness to continue participation. For example, if during the course of a clinical trial, researchers discover that an experimental new drug has a risk of causing severe liver failure, subjects in the trial should be promptly informed of this new risk information so that they can reassess whether they want to continue participation.

### **Advice for readers**

Before enrolling in a clinical trial, you should discuss each of the above questions, in detail, with the researchers. You should ask for a copy of the consent form for the trial and ideally, if time permits, go home and take time to discuss the proposed trial with family, friends or your primary care doctor. Thoughtfully consider whether enrollment in the research is the right choice for you. You also may want to do some independent online research to learn more about the proposed research interventions as well as the currently available treatment options for your disease or condition. Once you are comfortable that you understand the research and have considered all your options, only then should you decide whether participating in a clinical trial is right for you. ♦

# The Ethical Implications of the Global Outsourcing of Clinical Research

The trend toward increased corporate globalization, in which U.S. companies relocate production to lower-cost, “developing” countries, is readily seen in the pharmaceutical sector. Drug companies have outsourced to the developing world not only the production of medicines, but increasingly, the clinical trials necessary to market those drugs. With the increasing privatization of clinical drug research, the developing world has emerged as the ideal environment for a business model that relies on quicker, less-expensive trials and minimal regulatory oversight.

Over the past 20 years, the number of clinical drug trials conducted outside of the U.S. has skyrocketed. The U.S. government estimated in 2010 that between 40 and 65 percent of clinical trials investigating products regulated by the Food and Drug Administration (FDA) are conducted, at least in part, outside of the U.S. Approximately one-third of trials sponsored by the 20 largest drug companies are conducted exclusively in foreign sites. Eighty percent of the marketing applications for drugs and biologics approved in fiscal year 2008 contained at least some data from foreign clinical trials.

Though most foreign-trial subjects and sites are still located in Western Europe, the developing world is the fastest-growing setting for the multi-million-dollar clinical trials upon which the drug industry relies. This growth has far outpaced the ability of U.S. and domestic regulatory agencies to ensure that the trials are conducted ethically, with far-reaching consequences for millions of potential human subjects in the developing world.

## Ethical standards debated

The ethics of conducting clinical trials in mostly impoverished, developing countries has long been debated, as the patients recruited for such trials invariably represent a more vulnerable

population for whom special considerations must be applied.

One question is whether subjects should be exposed to the risks inherent in all pharmaceutical trials if they will not benefit in the form of access to the medicines after the trial’s completion. The Declaration of Helsinki, an internationally recognized code of universal principles concerning the protection of human subjects, states that subjects exposed to the risks of clinical research should stand to benefit from its results. Despite a global movement advocating for increased access to essential medicines (such as antiretrovirals for AIDS patients) that has had some success in opening up markets for generic drugs, the reality remains that many—if not most—drugs tested at foreign sites and subsequently approved for marketing are currently priced out of reach of the vast majority of those in the developing world.

Another issue involves the obligation of trial investigators to administer adequate treatment to study subjects. This is most relevant when considering one of the more common designs employed in pre-approval pharmaceutical studies, the placebo-controlled trial, in which patients with a disease are randomly divided into two groups, with one group receiving an investigative medical intervention and the other receiving a placebo, or inactive therapy.

The ethics of conducting a placebo-controlled trial when there are effective treatments available, particularly if the disease is serious or life-threatening, has been fiercely debated over the years. The Declaration of Helsinki expressly states that “the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention,” with exceptions for cases in which no effective treatment is available, or in which the potential harm to subjects receiving no therapy is not “serious and

irreversible.” For this reason, investigators typically (but don’t always) shy away from such placebo-controlled studies for serious or life-threatening diseases in the developed world.

Some have defended the use of placebo-controlled trials in the developing world, arguing that experiments should only meet the standard of care offered in those countries and that subjects getting placebos would be no better off had they not participated in the trial. But subjects offer a crucial financial benefit to drug companies through their participation, and there are moral implications of actively withholding effective medical therapy from those under one’s care. This line of thinking led to the approval of two controversial clinical trials that highlighted the double standard often applied to subjects in rich countries versus poor ones.

## A lower standard for the developing world

In 1997, Public Citizen documented 18 controlled clinical trials of interventions to prevent perinatal HIV transmission from HIV-positive mothers to infants. The trials were all initiated after a 1994 study showing that giving antiretroviral drugs to pregnant women reduced the HIV transmission rate by two-thirds. The studies recruited pregnant women in Africa, Asia and the Caribbean. Half the women in these trials received AZT, a therapy proven to help prevent HIV transmission to the fetus, while the other half received placebos.

In the two studies performed in the U.S., the patients in all the study groups had unrestricted access to zidovudine or other antiretroviral drugs. In 15 of the 16 trials in developing countries in Africa, Asia and the Caribbean, however, some or all of the patients in the control groups were not provided

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antiretroviral drugs. (Nine of the 15 studies being conducted outside the U.S. were funded by the U.S. government.) Despite Public Citizen's call to halt the unethical trials, many of the studies proceeded without alteration, and dozens of infants in the placebo group of one study in Thailand were needlessly infected with HIV.

In another case, in January 2001, the FDA internally circulated a memorandum of a presentation entitled "Use of Placebo-Controls in Life Threatening Diseases: Is the Developing World the Answer?" The presentation concerned the proposed design of a study that would have explored the effectiveness of the drug Surfaxin in the treatment of Respiratory Distress Syndrome, a sometimes-fatal disease of premature infants, in hundreds of infants in four Latin American countries.

Although four similar surfactant drugs had already been approved in the U.S. and had been shown to reduce mortality rates by about one-third, the company proposed giving half of the patients a placebo, reasoning that in those countries people did not receive surfactant anyway. (Another study planned by the company in Europe gave all infants either the company's surfactant or another surfactant known to be effective. That study did not use placebos.)

In February 2001, Public Citizen wrote to then-Health and Human Services (HHS) Secretary Tommy Thompson, urging him both to prevent the FDA from endorsing the study as designed and to require the company to give all subjects effective treatment with surfactant therapy. Three months later, the company agreed to alter the trial protocol and administer effective surfactant therapy to all subjects.

An analogous historical case from the West is found in the infamous Tuskegee syphilis experiments conducted in the early 20th century, in which African-American men infected with syphilis were followed for decades to document the natural progression of the disease.

Penicillin therapy, discovered to be effective in eradicating the disease after the trial was started, was withheld from the men for years. These men were largely poor and marginalized, similar to the study populations predominant in the developing world, which made it easier for the unethical study to continue for so long under the radar.

### **Lax regulatory oversight enables dubious trials in the developing world**

Current U.S. law allows placebo-controlled trials, such as in the Surfaxin and HIV cases discussed above. In addition, enforcement of existing regulations also is notoriously lax, increasingly so with the proliferation of foreign trials.

The FDA is responsible for overseeing the operations of clinical trials, both domestic and foreign, that are conducted in support of a future application for a new drug approval in the U.S. Though companies are required to report such trials to the FDA before they begin, the agency has virtually no capacity to follow through with inspections once the trials are under way. In fiscal year 2008, the FDA inspected only 0.7 percent of all foreign clinical trial sites. (The rate of inspection was only marginally greater, 1.2 percent, at U.S. sites.)

Regulatory agencies in developing countries are even less equipped to deal with the flood of new trials, meaning that virtually all trials conducted in the developing world effectively operate in a vacuum of regulatory oversight, with no governmental review until after the trial is completed (and then, usually only in cases in which the trial is successful and presented to American or European regulatory agencies as part of a marketing application).

In the absence of governmental oversight, institutional review boards (IRBs, which are frequently associated with academic medical institutions) are almost always the only independent entities capable of ensuring ethical integrity in clinical trials by declining

to approve those trials not meeting accepted ethical standards. Established in the 1970s in response to revelations of past human study scandals, such as the Tuskegee experiments, IRBs are expert panels tasked with affirming that studies involving human subjects are ethically designed and implemented.

A recent investigation by the Government Accountability Office (GAO) suggested potentially glaring gaps in IRB oversight. In 2009, the GAO created a fictitious medical company that proposed a clinical trial for a risky, unapproved medical device to three IRBs in the U.S. One of the three approved the trial, with few questions asked and without verifying the credentials or even the existence of the fictitious company. The GAO's investigation revealed the potential for dubious clinical trials to proceed within the U.S.

The globalization of clinical research raises additional questions regarding oversight and accountability. Foreign clinical trials can be overseen by a U.S.-based or local IRB in the study country. U.S.-based IRBs, located far from study sites, may be less able to monitor the conduct of an ongoing trial, while IRBs located in the developing world may face staffing or financial barriers, or they may lack the organizational capacity to provide adequate oversight. One 1999 survey found that U.S. and foreign researchers reported that in their experience, developing countries' IRBs were less likely to raise procedural and substantive issues with studies than were U.S. boards.

### **Conclusion**

There is currently no regulatory or legal mechanism in place to prevent more unethical trials, like the Surfaxin and antiretroviral trials, from going forward. As more trials are outsourced overseas, increasingly by for-profit corporations, a dearth of oversight leaves millions of vulnerable patients in the developing world at the mercy of drug companies' interests. ♦

# Buying Drugs Online Presents Hidden Risks

At first glance, the Internet may appear to be an attractive source for prescription drugs, and sales have continued to grow as more and more Americans fill their prescriptions online. The reasons for this trend may be understandable: Online pharmacies offer the prospect of convenience and reduced prices on prescription drugs. But these appealing promises may come at a price, as online pharmacies present a number of dangers to consumers. Many pharmacies use the Internet to skirt the law, and some customers are cajoled into taking risks shopping online that can lead to serious harm.

Any pharmacy can break regulations protecting consumers from dangerous drugs, but online pharmacies are far more likely to do so. In fact, a recent review by the National Association of Boards of Pharmacy (NABP) found that a staggering 97 percent of these websites violate pharmacy laws and practice standards. Prosecuting those that violate the law can be difficult, as online sellers of drugs may evade authorities by either concealing their location or moving it outside the U.S. Likewise, consumers who use these websites engage in a high-risk behavior, often knowing that some online pharmacies break laws but choosing to shop anyway.

Customers who shop online for drugs can reduce some of the risks by only visiting the very few websites that have been approved by trustworthy sources (see box on this page). Even after careful research, it may be difficult to guarantee that drugs purchased online are identical to the drugs being sold at the local pharmacy.

## Flaunting safety laws

All pharmacies in the U.S. are regulated under a system of state and federal laws designed to ensure that the drugs they sell are safe, effective and appropriately labeled with instructions and warnings to prevent misuse and injury. Pharmacies must receive licenses from state boards, comply with safety

### Organizations that help mitigate consumer risk

It is hard to guarantee that drugs purchased online will be the same as those dispensed in your local pharmacy, but the websites of the following organizations can help you avoid the most serious risks if you choose to purchase drugs online.

**National Association of Boards of Pharmacy (NABP)**  
[www.nabp.net](http://www.nabp.net)

The NABP's Verified Internet Pharmacy Practice Sites (VIPPS) accreditation program works to ensure and consistently monitor, on an ongoing basis, the legitimacy of the few businesses it approves. For a list of VIPPS-accredited online pharmacies, visit [www.nabp.net/programs/accreditation/vipps/find-a-vipps-online-pharmacy](http://www.nabp.net/programs/accreditation/vipps/find-a-vipps-online-pharmacy).

**LegitScript**  
[www.legitscript.com](http://www.legitscript.com)

LegitScript is recommended by the NABP because it applies evaluation standards comparable to NABP's standards. On its home page, LegitScript states that only .6 percent of the websites it monitors have been deemed legitimate.

standards, undergo inspections and obtain specialized training. Pharmacists cannot dispense prescription drugs without a valid prescription from a licensed health care professional, and they must take additional steps to prevent fraud or abuse when dispensing controlled substances.

With a few exceptions, pharmacies also must only sell drugs approved by the Food and Drug Administration (FDA) that are made in manufacturing facilities registered by that agency. The FDA inspects these facilities and imposes strict manufacturing and quality-control standards that require all makers of a given approved drug, brand name or generic, to ensure the same purity, potency (amount of active ingredient) and labeling. The FDA also routinely double-checks manufacturers' quality-control practices by independently testing the products the agency approves. This system seems to be generally working: Fewer than 2 percent of products fail the FDA's tests, and fewer than 0.1 percent fail the tests because they contain the wrong amount of active ingredient.

However, even some brick-and-mortar pharmacies break federal, state and local regulations. For example, a compounding pharmacy, a type of pharmacy specializing in individually tailored medicine, recently made headlines for manufacturing and distributing contaminated steroid injections that had not been approved by the FDA. These incidents are limited to a particular kind of pharmacy practice, however, and most traditional brick-and-mortar pharmacies abide by the applicable laws and sell FDA-approved products made by registered drug manufacturers.

In contrast, the vast majority of online pharmacies make evading the laws part of their business models by selling expensive, high-risk or addictive drugs without prescriptions and without complying with regulatory standards. These dangerous practices allow them to offer drugs at artificially low prices. When the NABP recently reviewed more than 10,000 online pharmacies, it found that 97 percent of these websites violate pharmacy laws and practice standards. Half offered drugs that

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were foreign or not FDA-approved, and approximately 87 percent did not require a valid prescription from a health care provider. Some online pharmacies pretend to offer medical services by asking patients to fill out a questionnaire prior to dispensing a prescription drug, a practice that is illegal and allows the website to collect confidential personal and health information about its customers.

### **Risky consumer behavior**

Some consumers use websites in the same way they would use an ordinary brick-and-mortar pharmacy. They visit a doctor, obtain a diagnosis and a prescription to treat it, and place an order at a trusted website. People who engage in this type of online shopping can reduce their risks by taking steps to identify whether the website is operating legally and selling FDA-approved drugs (see box on page 7).

Other online shopping behaviors are far riskier in that they involve websites that do not comply with state and federal laws; for example, they dispense drugs without a doctor's prescription, or they sell a controlled substance without the usual safeguards. Online shoppers sometimes know or suspect that the websites operate in a legal gray area, but they choose to take the risk because they feel that the laws are expensive, unnecessary or overly restrictive.

Customers' motivations for risky online shopping are reflected in the sales figures of the top illegal online retailers: Many illegal online pharmacy purchases are for drugs that are easy to abuse, such as painkillers, weight-loss drugs, sleeping pills or controlled substances. Others are for drugs that people may be reluctant to discuss with their doctor, such as male enhancement products or drugs to treat mental illness. A small but troubling number of illegal online pharmacy sales are for drugs to treat serious acute or chronic illness, such as HIV or other infections, diabetes, or heart disease. Cost — and lack of adequate health insurance — is

probably the main factor driving some of these questionable website purchases.

### **Hidden health risks**

Unfortunately, it is almost impossible for consumers to assess the risk of purchasing from an online pharmacy. Qualified federal and state regulators do not test the drugs dispensed from online pharmacies. Studies addressing the quality of these drugs have tended to use crude techniques designed to pick up blatant counterfeits but not to evaluate handling or labeling or to detect impurities, degraded products, potency issues or the potential for drug abuse.

In 2004, the U.S. General Accounting Office (GAO, now called the Government Accountability Office) ordered 68 samples of 11 different drugs from online pharmacies and tested them for authenticity, appropriate handling and labeling, and FDA approval status. The GAO found that 4 of the 68 samples, close to 6 percent, were either total counterfeits or had "significantly different chemical composition" than the product that had been ordered. The GAO also identified handling errors: Several samples of a drug requiring temperature-controlled handling arrived in envelopes without insulation.

The GAO report also showed that many drugs sold online did not have adequate instructions for use or safety warnings. For example, 2 out of 3 orders of isotretinoin (Accutane), obtained without a prescription, included no warning labels informing patients of serious safety risks. Accutane is a prescription acne medication that can cause severe side effects, including birth defects and serious mental disturbances leading to suicide among some users. The FDA requires doctors prescribing this drug to participate in a special program to help ensure that patients know about the risks, take appropriate birth control, avoid giving blood and have access to psychiatric help should side effects arise. Accutane is an expensive drug, and numerous websites tempt patients with low-cost versions that do not require a prescription.

When patients obtain a drug without a prescription, they also run the risk of taking an inappropriate dosage that will lead to side effects. This is particularly true with addictive drugs. A recent study compared those who obtained a prescription for their pain medication to those who purchased it on the web without a prescription. More than half of patients who bought their drugs online did so to obtain higher doses of the drug than their physicians would allow. That freedom came at a price: The online shoppers were significantly more likely to report severe side effects, including life-threatening seizures, than those who bought painkillers after obtaining a prescription from a doctor.

### **Getting scammed**

A final prominent risk for many online shoppers, especially those using sites that are not accredited, is getting scammed. Often the scam is simple: The ordered drugs never arrive. Yet the risk of a financial scam does not end when drugs are delivered. Illegal businesses may also be less careful with a customer's private information, which can remain in databases for years and be vulnerable for use in future scams.

The FDA recently warned consumers of a scam by criminals who had obtained the records of hundreds of people who since 2008 had made purchases of drugs online or over the phone. The perpetrators were making phone calls pretending to be FDA agents, threatening prosecution and seeking bribes.

More such scams may be on the way. Leaked information has recently revealed several large-scale hacking incidents involving prominent online pharmacies GlavMed, SpamIt and RX-Promotion. Hackers broke into the sales databases of these companies and stole customers' private information, potentially including credit card numbers, Social Security numbers, dates of birth and contact information. The hackers shared data from more than a million orders on various underground forums and file-sharing sites,

**see ONLINE, page II**

# Product Recalls

## January 2, 2013 – February 5, 2013

This section includes recalls from the Food and Drug Administration (FDA) Enforcement Report for drugs and dietary supplements ([www.fda.gov/Safety/Recalls/EnforcementReports/default.htm](http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm)), and Consumer Product Safety Commission (CPSC) recalls of consumer products.

### DRUGS AND DIETARY SUPPLEMENTS

#### Recalls and Field Corrections: Drugs – Class II

Indicates a problem that may cause temporary or reversible health effects; unlikely to cause serious injury or death

**Levothroid (Levothyroxine Sodium Tablets), USP, 50 mcg.,** 100-count bottles. Volume of product in commerce: 37,441 bottles. Subpotent: nine-month stability interval. Lot #:s: 1093992 and 1094095, expiration date 9/2012. Lloyd Inc. of Iowa.

**Levothroid (Levothyroxine Sodium Tablets), USP, 75 mcg.,** 100-count bottles. Volume of product in commerce: 16,548 bottles. Subpotent: nine-month stability interval. Lot #: 1094098, expiration date 9/2012. Lloyd Inc. of Iowa.

**Levothyroxine Sodium Tablets, USP, 175 mcg** in 90-count bottles. Volume of product in commerce: 7,432 bottles. Subpotent: 15-month stability interval. Lot #: 11T7011A, expiration date 12/2012. Alara Pharmaceutical Co.

**Lisinopril Tablets, USP, 40 mg**, packaged in: (a) 100-count tablets per bottle; (b) 1,000-count tablets per bottle. Volume of product in commerce: unknown. Presence of foreign substance: Uncharacteristic black spots identified as a food-grade lubricant with trace amounts of foreign particulates and stainless steel inclusions have been found in the tablets. Multiple lots affected. Westward Pharmaceutical Corp.

**Lisinopril and Hydrochlorothiazide Tablets, 20 mg/25 mg**, packaged in: (a) 100-count tablets per bottle; (b) 1,000-count tablets per bottle. Volume of product in commerce: 43,478 bottles. Presence of foreign substance: Reports of gray smudges identified as minute stainless steel particulates were found in the recalled tablets. Multiple lots affected. Westward Pharmaceutical Corp.

**Mylan, Tacrolimus Capsules, 0.5 mg**, 100-count bottle. Volume of product in commerce: 15,181 bottles. Failed USP content uniformity

requirements: Out-of-specification result reported on retained samples. Lot #:s: 3027684, expiration date 5/13; 3027688, expiration date 6/13; and 2002157, expiration date 9/12. Mylan LLC.

**Prednisone Tablets, USP, 10 mg**. Volume of product in commerce: 86,616 bottles. Presence of foreign substance(s): Sub-recall due to tablets contaminated with trace amounts of food-grade lubricant, as well as stainless steel inclusions. Multiple lots affected. L. Perrigo Co.

**Prednisone Tablets, USP, 20 mg**, packaged in: (a) 100-count tablets per bottle; (b) 500-count tablets per bottle; and (c) 1,000-count tablets per bottle. Volume of product in commerce: 60,289 bottles. Presence of foreign substance: A complaint was received for black specks identified as stainless steel inclusions and cellulose with trace amounts of aluminum and iron-rich inclusions. Multiple lots affected. Westward Pharmaceutical Corp.

**Propylthiouracil Tablets, USP, 50 mg**, packaged in: (a) 100-count tablets per bottle; (b) 1,000-count tablets per bottle. Volume of product in commerce: 43,075 bottles. Presence of foreign substance: Uncharacteristic spots identified as steel corrosion, degraded tablet material and hydrocarbon oil with trace amounts of iron were found in tablets. Lot #:s: 68478A, 69059A, 69059B, expiration date 1/16. Westward Pharmaceutical Corp.

**Synthroid (Levothyroxine Sodium) Tablets, 150 mcg (0.15 mg)**, 90 tablets per bottle. Volume of product in commerce: 28,524 bottles. Labeling: Error on declared strength. Product labeled to contain 150-mcg tablets actually contained 75-mcg tablets. Lot #: 18262A8, expiration date 09/13. Abbott Laboratories.

### CONSUMER PRODUCTS

Contact the Consumer Product Safety Commission (CPSC) for specific instructions or return the item to the place of purchase for a refund. For additional information from the CPSC, call its hotline at (800) 638-2772. The CPSC website is [www.cpsc.gov](http://www.cpsc.gov). Visit [www.recalls.gov](http://www.recalls.gov) for information about FDA recalls and recalls issued by other government agencies.

#### Name of Product; Problem; Recall Information

**2013 Polaris Ranger® 400 Recreational Off-Highway Vehicles.** The recreational vehicle's throttle can fail to operate properly, which can cause the vehicle's rider to lose control, posing a crash hazard. Polaris, at (888) 704-5290 or [www.polarisindustries.com](http://www.polarisindustries.com).

**Air Mister.** The Air Mister can shatter during use, posing an injury hazard. Target, at (800) 440-0680 or [www.target.com](http://www.target.com).

## CONSUMER PRODUCTS (CONTINUED)

**Amana Packaged Gas/Electric Heating and Cooling Units.** The serial plates on the units have inaccurate information that could result in installers and servicers using undersized wiring, posing a fire hazard. Goodman, at (800) 394-8084 or [www.amana-hac.com](http://www.amana-hac.com).

**Bicycles and Frame Sets.** The steerer tube in the front fork can break, posing a fall hazard. Specialized Bicycle Components, at (877) 808-8154 or [www.specialized.com](http://www.specialized.com).

**Bugaboo Cameleon and Bugaboo Donkey Model Strollers.** A button on the stroller's carrycot/seat carry handle can become disengaged and cause the handle to detach, posing fall and choking hazards to young children. Bugaboo International, at (800) 460-2922 or [www.bugaboo.com](http://www.bugaboo.com).

**Bunk Beds.** The openings between the metal rails of the end structures are greater than allowed in the standards and pose a risk of entrapment or asphyxiation hazard. World Imports, at (855) 473-9992 or [www.worldimportsltd.com](http://www.worldimportsltd.com).

**Burien Floor Lamps.** The on/off foot switch on the lamps can fail and melt, resulting in shock and fire hazards. Dolan NW LLC, at (888) 213-5758 or [seattlelighting.com](http://seattlelighting.com), [globelighting.com](http://globelighting.com), [builderslighting.com](http://builderslighting.com) or [destinationlighting.com](http://destinationlighting.com).

**Can-Am® Commander Side-by-side Off-road Vehicles.** Debris such as leaves, hay and grass in wet-terrain areas can collect in the vehicle's exhaust pipe area in a short period of time. A hot exhaust pipe and accumulated debris that has dried poses a risk of fire. Also, improper assembly of the steering column to the rack and pinion can result in the loss of steering control, posing a risk of serious injury or death to the user, passenger or bystanders. BRP, at (888) 638-5397 or [www.can-am.brp.com](http://www.can-am.brp.com).

**Children's Two-piece Pajama Sets.** The children's cotton or cotton/fleece pajamas sets fail to meet the federal flammability standards for children's sleepwear because they do not meet the tight-fitting sizing requirements. This poses a burn hazard to children. Target, at (800) 440-0680 or [www.target.com](http://www.target.com).

**Egg Incubator.** The base can ignite during use, posing a fire hazard to the consumer. Brower Division of Hawkeye Steel Products Inc., at [www.hawkeyesteel.com](http://www.hawkeyesteel.com).

**Enduro Motorcycles.** During use, the pre-formed fuel hose can develop small holes or cracks at the ends of the hose, allowing fuel to leak. This poses a fire and crash hazard to the rider and/or others. KTM North America Inc., at (888) 985-6090 or [www.ktmusa.com](http://www.ktmusa.com).

**Game Winner® Crossbow Cocking Ropes.** The hooks attaching the cocking rope to the crossbow string can break and cause it to recoil, posing a laceration hazard. Academy Sports + Outdoors, at (888) 922-2336 or [www.academy.com](http://www.academy.com).

**Girls' Circo Fleece Blanket Sleepers.** These fail to meet the federal flammability standards for children's sleepwear, posing a risk of burn injuries. Target, at (800) 440-0680 or [www.target.com](http://www.target.com).

**High-Pressure Scuba Diving Air Hoses.** The diving hose that connects the regulator to the tank's pressure gauge can separate, reducing the available air supply to the diver and posing a drowning hazard. A-Plus Marine, at (800) 352-2360 or [www.aplusmarine.com](http://www.aplusmarine.com).

**Magnet Balls® Manipulative Magnet Sets.** When two or more magnets are swallowed, they can link together inside a child's intestines and clamp onto body tissues, causing intestinal obstructions, perforations, sepsis and death. Internal injury from magnets can pose serious lifelong health effects. SCS Direct, at (888) 749-1387.

**Mattresses and Mattresses with Foundations.** The mattresses fail to meet the mandatory federal open flame standard for mattresses, posing a fire hazard. The Mattress Cloud Inc., at (855) 622-4233.

**MegaFood One Daily Supplement Bottles.** The packaging is not child-resistant as required by the Poison Prevention Packaging Act. The supplement tablets inside the bottle contain iron, which can cause serious injury or death to young children if multiple tablets are ingested at once. FoodState d/b/a MegaFood, at (866) 234-2668 or [www.megafood.com](http://www.megafood.com).

**Men's and Women's Heated Jackets.** The heated inner wrist cuff can overheat, posing a burn hazard. Columbia Sportswear Company, at (866) 201-9073 or [www.columbia.com](http://www.columbia.com).

**Million Dollar Baby Dressers.** If a young child climbs up open dresser drawers, the dresser can tip over and pose the risk of entrapment. Million Dollar Baby, (888) 673-6652 or [www.themdbfamily.com/safety2](http://www.themdbfamily.com/safety2).

**Nanospheres Magnetic Desk Toys.** If two or more magnets are swallowed, they can link together inside a child's intestines and clamp onto body tissues, causing intestinal obstructions, perforations, sepsis and death. Internal injury from magnets can pose serious lifelong health effects. Kringle Toys and Gifts, at (888) 801-1649 or [www.kringletoysandgifts.com](http://www.kringletoysandgifts.com).

**Natart Chelsea Dressers.** If a young child climbs up open dresser drawers, the dresser can tip over and pose the risk of entrapment. Gemme Juvenile, at (855) 364-2619 or [www.chelseawallanchors.com](http://www.chelseawallanchors.com).

**Newborn Rock 'n Play Sleeper™.** Mold can develop between the removable seat cushion and the hard plastic frame of the sleeper when it remains wet/moist or is infrequently cleaned, posing a risk of exposure to mold to infants sleeping in the product. The CPSC advises that mold has been associated with respiratory illnesses and other infections. Although mold is not present at the time of purchase, mold growth can occur after use of the product. Fisher-Price, at (800) 432-5437 or [www.service.mattel.com](http://www.service.mattel.com).

## CONSUMER PRODUCTS (CONTINUED)

**Omni-Heat™ Lithium-Polymer Rechargeable Batteries.** The batteries have a cell defect that can cause overheating, posing a fire hazard. Columbia Sportswear Company, at (800) 622-6953 or [www.columbia.com/recall](http://www.columbia.com/recall).

**Perfect Resistance Bands.** The bands can detach from the mesh cloth loops, posing an injury hazard to the user and those in the vicinity. Implus Footcare, at (800) 446-7587 or [www.perfectonline.com/recalls](http://www.perfectonline.com/recalls).

**Q-Series Temperature and Humidity Sensors.** The sensors can overheat, posing a fire hazard. Siemens, at (800) 516-9964 or [w3.usa.siemens.com/buildingtechnologies](http://w3.usa.siemens.com/buildingtechnologies).

**Reclining Chair.** The chair can tip over backwards when used in its fully reclined position, posing a fall hazard to consumers. American Signature Inc., at (800) 743-4577 or [www.vcf.com](http://www.vcf.com) or [www.asfurniture.com](http://www.asfurniture.com).

**Royal Prestige 9-Ply Thermal Wall Cookware.** The cookware can collapse, crimp or severely deform when exposed to heat, posing a burn and fire hazard to the consumer and nearby property. Hy Cite Enterprises, at (800) 609-9577 or [www.royalprestige.com](http://www.royalprestige.com).

**Sportspower BouncePro 14' Trampolines.** The enclosure netting surrounding these trampolines can break, allowing children to fall through the netting and be injured. Sportspower, at (888) or [www.sportspowerltd.net](http://www.sportspowerltd.net).

**Triaminic® Syrups and Theraflu Warming Relief® Syrups.** The child-resistant caps can fail to function properly and enable the cap to be removed by a child with the tamper-evident seal in place, posing a risk of unintentional ingestion and poisoning. These products contain acetaminophen and diphenhydramine which are required by the Poison Prevention Packaging Act to be sealed with child-resistant packaging. Novartis Consumer Healthcare, at (866) 553-6742 or [www.novartisOTC.com](http://www.novartisOTC.com).

**Utility Vehicles.** The fuel line can separate, posing a fire hazard. Deere and Company, at (800) 537-8233 or [www.johndeere.com](http://www.johndeere.com).

**Weight Workbenches.** The weld on the backrest adjustment brackets of the weight workbench can break, posing an injury hazard to consumers. Powertec, at (877) 525-5710 or [www.PowertecFitness.com](http://www.PowertecFitness.com).

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and it remains to be seen how the data may be used for criminal purposes over the next several years.

#### Shopping safely

Consumers can identify the very few legitimate online pharmacies by first visiting the websites of trustworthy groups that vet such businesses to identify the ones that comply with local laws (see box on page 7). One of the best is the NABP website, which accredits those online pharmacies that comply with U.S. laws and pharmacy-practice standards. The NABP requires an application and charges a fee for accreditation, and only a small fraction of online pharmacies have been accredited through this process. Consumers looking for more options also can visit [www.LegitScript.com](http://www.LegitScript.com), which is recommended by the NABP because it applies similar standards in evaluating websites.

It remains risky to buy drugs from online pharmacies claiming to be based in Canada. Foreign businesses

commonly pose as "Canadian" pharmacies while actually being based in other countries, and they dispense drugs manufactured in India or South America under dubious quality standards. Unfortunately, there is no legal, risk-free way to buy Canadian drugs, because the FDA has been reluctant to develop a legal framework for importing Canadian drugs into the U.S., despite pressures from consumers and members of Congress to encourage this type of competitive importation. Drug companies have worked to prevent such importation by lobbying to keep Canadian drugs out of U.S. markets and threatening to raise Canadian prices or stop selling to Canada if importation were to be legalized.

The laws preventing re-importation prevent the NABP and LegitScript from accrediting or verifying pharmacies located in Canada. However, the Canadian International Pharmacy Association, a trade association of Canadian pharmacies, does provide a list of certified websites that comply with Canadian drug safety laws. Although these

drugs all meet Canadian standards — in some cases being identical copies of FDA-approved drugs — patients must still exercise caution when buying Canadian drugs, because there is no system to ensure bioequivalency with FDA-approved products. As a result, there will always be a risk that people who switch from an FDA-approved drug to a Canadian drug will not experience the same effects.

Ultimately, the Internet presents many tempting opportunities to shop for drugs that would be more expensive or harder to obtain through traditional channels. Yet these opportunities come with a hidden price tag, as unpredictable risks force some shoppers to pay more than they bargained for in terms of damage to their health and finances. You can reduce these risks by going to your doctor for a prescription and shopping only at the websites that have been verified by a trustworthy source. Ultimately, however, the surest and simplest way to buy safe, quality drugs is to shop at your local pharmacy. ♦



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## Outrage of the Month! Modeling For Ads Promoting a Diabetes Pill

As a potential adult model, aged 45 to 60, would you like to earn \$1,000 for a half day of posing for ads promoting a widely prescribed diabetes pill, Victoza — generic name liraglutide? A talent search agency in South Carolina recently announced a casting call for such people, requesting that interested people send two to three recent snapshots, including a full-length shot, as well as measurements, via e-mail. It was OK, the casting call specified, to be plus size.

The talent search agency described itself as “a development and placement company that connects potential models and talent with regional and national industry professionals.” There was no requirement that the potential models actually have diabetes, but they would be paid well to be part of an ad campaign to convince readers — be they patients with diabetes or doctors — that

Victoza was a good choice for treating their diabetes. (Full disclosure: Public Citizen’s Health Research Group petitioned the Food and Drug Administration last year to ban this drug because our research has found that its benefits are greatly outweighed by its risks.)

It is possible, though not very likely, that the models were told about the connections between the drug and serious side effects, quoted below from the company’s Patient Medication Guide:

1. **Possible thyroid tumors, including cancer.** ...It is not known if Victoza® will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people. ...If medullary thyroid cancer occurs, it may lead to death if not detected and treated early.

2. **Inflammation of the pancreas (pancreatitis),** which may be severe and lead to death.

If potential models were informed about this, it might allow those with ethical concerns to opt out of a campaign that could well lead to more risks than benefits for people subsequently prescribed Victoza, despite the temptation of \$1,000 for a half a day of posing.