Chapter 2: Drugs are Still Unsafe

According to *BioCentury*, "Americans take it for granted that government ensures foods are safe, and medical products are safe and effective. But that wasn't always the case." The FDA is charged with ensuring that all medicines we Americans consume are safe, a role that many support. Has it succeeded?

If you, like most people, support the FDA's safety policing, you are probably assuming that it is obvious which drugs are safe and which ones aren't, and that safety is a clear concept with clear measurements, providing unambiguous signals. Further, you are probably assuming that the FDA is doing the job you would do if you had the training and were put in that position—that if you pored over the data, both you and the FDA would come to similar conclusions. But what if safety isn't that black or white? What if the FDA has biases and is employing judgments and values that don't coincide with yours? What if the FDA is using flawed techniques? What if the FDA is just guessing?

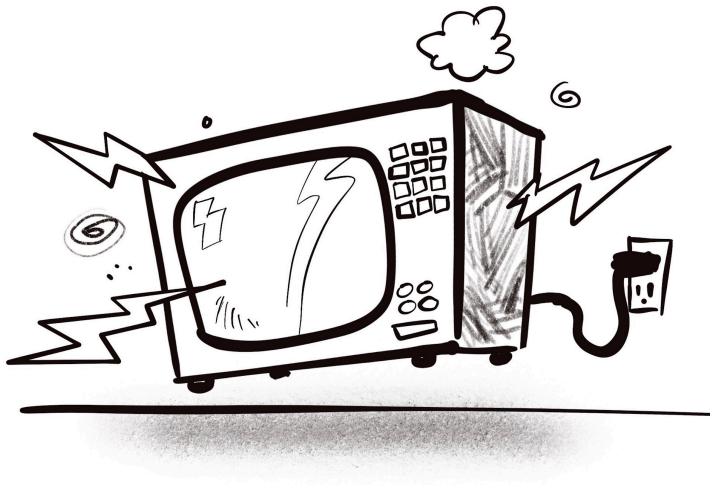
What if there are "safe" drugs that are really unsafe and "unsafe" drugs that are really safe?

What Does Safety Mean?

Consider the definition of safety. Safe is defined as not likely to cause or lead to harm or injury; not involving danger or risk. Safety is defined as the condition of being protected from or unlikely to cause danger, risk, or injury.

Does drug "safety" mean that no one will ever be hurt by a medicine? Or is there a threshold of harm below which a drug is considered safe? If so, is that threshold one percent of patients? Five percent? Ten percent? How badly do they need to be hurt? Do they need to die, or would a headache count? How about a swollen purple tongue?

A microwave oven is considered safe if it doesn't short circuit and burn down your house while you are at work, render your leftover Thai food toxic, or shower you with harmful electromagnetic waves. Even a product considered safe can be dangerous if used improperly, either inadvertently ("Wow! Look at the cool colors the aluminum foil on my soup bowl gives off in the microwave!") or purposefully, if, for example, you override the safety features.



The FDA works hard to ensure that the foods and medicines that we Americans consume are safe. But what does safe mean in the context of medicine? Many would assume that it means—as with the microwave oven—that if not abused or used in crazy ways, the foods and medicines approved by the FDA will not directly hurt us. Anyone holding this belief will be disappointed.

Are FDA-Approved Drugs Safe?

Since the passage of the Food, Drug, and Cosmetic Act in 1938, all pharmaceutical companies have been required to test their drugs for safety, and safety is the most important product attribute the FDA considers before approving new drugs—more important than efficacy,

tolerability, and dosing. Every new drug marketed during the last eight decades has been certified "safe" by the FDA.

Would it surprise you to learn that some patients who have taken FDA-approved drugs for osteoporosis have had the unfortunate aftereffect of a rotting jawbone? It's called Dead Jaw Syndrome and it has happened, albeit rarely, when the jawbones of patients on osteoporosis drugs have failed to heal after a minor injury, such as getting a tooth pulled. Patients can end up with a rotted, soft jawbone, unable to speak clearly or even eat solid foods. Can we consider these drugs, which otherwise help millions by slowing the deterioration of their bones, "safe"?

Cyanide is one of the metabolites of Nitropress (nitroprusside sodium)—used to treat conditions such as congestive heart failure—creating the risk of cyanide poisoning with longer-term use, particularly in patients with liver dysfunction. You might be interested in the symptoms: an almond odor to the breath, acidosis, tachycardia, mental status changes, and the ultimate of all adverse events, death. Is Nitropress safe?

Sometimes safety warnings can be unexpected and startling. The FDA reported that "Viberzi (eluxadoline), a medicine used to treat irritable bowel syndrome with diarrhea (IBS-D), should not be used in patients who do not have a gallbladder. An FDA review found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death."[1] This strange result was discovered *after* the FDA approved Viberzi based on clinical trials involving nearly three thousand patients.

Consider Adriamycin (doxorubicin), a chemotherapeutic agent green-lighted by the FDA in 1991. Approximately 11 percent of patients taking Adriamycin develop acute cardiotoxicity and 1.7 percent develop chronic cardiotoxicity.[2] Cardiotoxicity can lead to cardiomyopathy, for which there is no treatment and carries a 50-percent mortality rate. Should we consider Adriamycin "safe"?

Shine a light on Pfizer's Norcuron (vercuronium bromide), a muscle relaxant that the FDA has approved as "safe and effective." Norcuron is used, against Pfizer's wishes, to carry out lethal injections for executions of

condemned prisoners. With convoluted logic suitable for Alice in Wonderland, lawyers for inmates on death row sometimes question whether the drugs to be used in executions are safe and effective.[3] If you are going to kill someone, you should make sure the drug you use is safe! Can we judge Norcuron safe if it is proficient at killing people?

Consider another drug, Reglan (metoclopramide)—used to treat such issues as nausea, vomiting, and heartburn—approved by the FDA in December 1980 and saddled with a "black box warning" on its label in 2009. Is metoclopramide safe? The FDA-approved label for metoclopramide tells us in bold lettering: "**Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.**"

The side effects of metoclopramide include repetitive, involuntary muscle movements, such as lip-smacking, lip puckering, pursing of the lips, excessive eye blinking, grimacing, tongue movements, and an urge to be constantly moving (extra-pyramidal effects). In a more extreme form, the side effects are termed tardive dyskinesia and include irreversible, uncontrollable body or facial movements. But that's not all. Here is a list of metoclopramide's adverse reactions—reactions that can occur, even if rarely—according to the FDA-approved label, in the order presented:

- Restlessness
- Drowsiness
- Fatigue
- Lassitude
- Insomnia
- Headache
- Confusion
- Dizziness
- Mental depression with suicidal ideation
- Acute dystonic reactions
- Parkinsonian-like symptoms
- Tardive dyskinesia
- Neuroleptic malignant syndrome
- Galactorrhea

- Amenorrhea
- Gynecomastia
- Impotence
- Hypotension
- Hypertension
- Supraventricular tachycardia
- Bradycardia
- Fluid retention
- Acute congestive heart failure
- Nausea
- Bowel disturbances
- Hepatotoxicity
- Urinary frequency and incontinence
- Neutropenia
- Leukopenia
- Sulfhemoglobinemia
- Rash
- Uticaria
- Angioneurotic edema
- Visual disturbances
- Porphyria

I'm not sure that I even want to know what some of those adverse reactions, such as sulfhemoglobinemia, are. Is metoclopramide "safe"? To truly make an informed choice, we would need to know the rates for each of these adverse events. But, on the surface, metoclopramide appears to be anything but safe. Imagine if your microwave oven had such a long list of possible problems, including:

- Explosions
- Fires
- Broken glass
- Electrocution
- Molten metal
- Pealing lead paint
- Chipping plastic
- Effluvium

- Ear-piercing noises
- Mushroom clouds
- Conflagration
- Tumult
- Hazardous flashes of light
- Toxic fumes
- Skin discoloration
- Pandemonium
- Lawlessness
- Shrapnel
- Etc.

Would you consider such an oven safe? Few would. Has the FDA succeeded in ensuring that all drugs are safe? Clearly not. According to Glaxo's former chairman and chief executive officer, J.P. Garnier, "The notion that drugs are perfectly safe 'is Wonderland.'"[4] And metoclopramide is still on the market today, categorized as "safe and effective" by the FDA.

Consider epilepsy. A close relative of mine suffers from epilepsy, and his family can attest to the fact that it is a life-stealing disease, party from the seizures and partly from the nasty treatments. Drugs used to treat or control seizures are responsible for the following side effects:

- Difficulty thinking clearly (66 percent of patients)
- Drowsiness (67 percent)
- Lethargy (66 percent)
- Clumsiness (61 percent)
- Depression (57 percent)
- Weight gain (42 percent)

And the sad list goes on and on. Fifty-three percent of epilepsy patients found their medication side effects to be "extremely frustrating," while 36 percent found them to be "debilitating."[5] Identify people with a bad disease and then hobble them with bad treatments. It's barbaric, really.

Are epilepsy treatments "safe"? No. Are the treatments literally killing people? Scientists aren't sure. But they do know that epileptics suffer from an increased incidence of sudden and unexplained death, perhaps due to the treatments or to the disease itself.

There are two broad actions that the FDA takes regarding drugs that have safety issues. The first consists of drugs that have such imposing problems that they are pulled from the market. The diabetes drug Rezulin (troglitazone) was pulled from the market in 2000 after it was linked to dozens of cases of fatal liver damage. Propulsid (cisapride), a heartburn drug, was pulled from the market in March 2000 after 80 users died. Baycol (cerivastatin), Seldane (terfenadine), Vioxx (rofecoxib), and "Fen Phen" (fenfluramine and phentermine) are well-known examples of FDA-approved drugs that their manufacturers voluntarily withdrew after they were found to be dangerous to some patients. In the case of Vioxx, a non-steroidal anti-inflammatory drug (NSAID), Merck discovered that patients on therapy for 18 months or more faced a doubled risk of heart attack and stroke and promptly pulled its blockbuster product from the market.

The second action regards drugs that have some problems, but whose benefits still outweigh their risks, so they remain available. Xalatan (latanoprost) for glaucoma has caused ten to 20 percent of people's blue and green eyes to permanently turn brown. This amazing side effect was uncovered only after the drug was green-lighted by the FDA.

Just watch any television ad for any drug and you'll hear a long list of potential side effects, some worse than others. For instance, due to repeated advertisements, we have learned that if you take Viagra (sildenafil) for erectile dysfunction, you could develop sudden vision or hearing loss or an erection that won't go away. The more common—but still not very common—side effects of Viagra include headache, flushing, upset stomach, abnormal vision, changes in color vision, blurred vision, stuffy or runny nose, back pain, muscle pain, nausea, dizziness, and rash. "I don't know, honey, I took my Viagra, but I'm just not in the mood tonight. It must have something to do with this headache, upset stomach, blurred vision, and rash."

Taking too much of the popular drug Tylenol (acetaminophen) can poison your liver. Serious liver damage is rare, but of the 100 million people a year who take acetaminophen, 56,000 end up in emergency rooms due to acetaminophen overdoses, and about 100 people die after unintentionally

taking too much. Liver toxicity from acetaminophen poisoning is by far the most common cause of acute liver failure in the U.S.

Years ago, I talked to a family friend who nearly died from bleeding due to the analgesic Naprosyn (naproxen). This was especially upsetting to me because at the time I worked for the company, Syntex, that invented and made Naprosyn. Even with her close call and, perhaps, many others that we don't know about, naproxen is still available and widely used today, frequently as Bayer's over-the counter (OTC) drug Aleve.

Vioxx and all the COX-2 inhibitor drugs, such as Celebrex (celecoxib), were specifically designed to be safer than drugs such as aspirin, ibuprofen, and naproxen, all of which are non-steroidal anti-inflammatory drugs that can cause gastrointestinal bleeding. Experts have estimated that in the United States, NSAID-induced gastrointestinal complications result in more than 100,000 hospitalizations and 16,500 deaths per year. This is what happened to the aforementioned family friend who took naproxen and ended up in the hospital.

Safety is an important issue; however, it is vital to realize that safety fears can be overblown. For instance, in clinical trials, children on antidepressants were 1.8 times as likely to have so-called suicidal tendencies as equally depressed children taking placebos. That sounds bad. Is it? Not really. An analysis of 27 studies of young people being treated with antidepressants showed that only 0.7 percent of patients had increased suicidal thoughts—so, that 0.7 percent is 1.8 times an even smaller number (0.4 percent).[6]

How many of the 4,000 children on eight different antidepressants actually committed suicide in these studies? None.[7] Not a single one. While there were no completed suicides in *any* of the studies, there *was* a measured increase in the rate of teen suicides after the FDA, in response to these studies, required pharma companies to put "black box" warnings on all antidepressants' labels, scaring patients and reducing SSRI usage.[8] Moreover, a separate study among teenagers suggests that, as we would expect, antidepressant usage *reduced* suicides.[9] "Many experts credit a rise in use of Paxil, Prozac and other antidepressants known as SSRIs for a 25% reduction in teenage suicides in the past 10 years—to about eight per

100,000 teenagers per year."[10] This makes sense because if you are no longer depressed, you are less likely to take your life.

Many of us, when we hear a statement such as "antidepressants cause suicidal tendencies," imagine that all patients experience these thoughts, which is far from the truth. Also, the relationship identified is correlational —that is, no cause and effect has been established. Information can be scary. Pharmaceutical companies generally provide far more information for their products than do other companies, and some of that information is, frankly, frightening.

Despite all the frightening information, we need to retain perspective and learn what this information really means; people can worry too much about the side effects of drugs. While there has been much press about the muscle pain and weakness problem resulting from statins such as Crestor (rosuvastatin), Lipitor (atorvastatin), Mevacor (lovastatin), and Zocor (simvastatin), we should temper those worries with the startling results from a paper published in the *New England Journal of Medicine.* This paper, published in 2016, examined the results of 12,705 people from 21 countries with "intermediate risk" for cardiovascular disease. After 5.5 years, the statins in the study reduced the risk of heart attack and stroke by a whopping 24 percent, and, surprisingly, more patients on placebos discontinued therapy due to adverse events than did the patients on statins.[11] If more patients on placebos complained of adverse events than did those on the actual drugs, and the statins were so beneficial, how can that not be a ringing endorsement for statins?

Safety is Ambiguous

It's not just the drugs themselves that can be dangerous. Too large a dose, taken either inadvertently or on purpose, can be dangerous. That individual sleeping pill might be safe, but the whole bottle certainly isn't. There isn't much the FDA can do to prevent this danger.

The Dose Makes the Poison

Making the FDA's job that much harder, and complicating the discussion of the FDA's proper powers, is the fact that, as wise people have known for

centuries, the dose makes the poison. "All things are poison and nothing is without poison; only the dose makes a thing not a poison," said Paracelsus. A substance can be benign or harmful, depending on your exposure.

For detrimental agents, low doses generally produce no adverse effects, but at a higher dose, the negative effects can be seen. For beneficial agents, the benefit rises as the dose rises and then, at some point, the relationship reverses, and even the beneficial agent can cause serious adverse reactions. Alcohol is one example of such a beneficial agent. Based on a 1995 study of 85,000 women, having one drink every three to four days led to a 17-percent reduction in the death rate. One drink each day led to an 11-percent reduction in the death rate; thus, in that study, alcohol's benefits were already in decline at the higher dose. With *more* than one drink per day, the death rate was higher than with abstinence from alcohol, moving alcohol from the beneficial into the detrimental category at a higher dose.

Is drinking alcohol beneficial? Is it deleterious? Repeat after Paracelsus: it depends on the dose. The dose makes the poison.

> *Even nectar is poison if taken in excess.*
> **Hindu proverb**

Consider something as ubiquitous and essential as water.

Without water, we die relatively quickly. But water can also kill people. We can drown, of course, but there are other risks. In 2002, a runner collapsed and died at the Boston Marathon. Medics later determined that she suffered from hyponatremia, or water intoxication. In common terms, she drank too much water while not getting enough electrolytes during the endurance event. "You can get too much of a good thing," said Arthur Siegel, of McLean Hospital. "With prolonged, strenuous exercise, the combination of too much water plus the muscle injury that shuts down the ability of the kidney to excrete the water produces this dangerous, life-threatening problem."[12]

As noted in the Introduction, Jennifer Strange died just hours after drinking water for a radio station contest.[13] She, too, suffered from hyponatremia.

Should water be outlawed or restricted by the FDA? What would the rules be and what would that accomplish? Is water "safe"? Is it "unsafe"? It is both.

As was covered in the Introduction, a large dose of warfarin may have killed Joseph Stalin and yet a smaller dose successfully manages my friend's blood clots. Thalidomide is dangerous for fetuses but safe enough to treat people with multiple myeloma. Mustard gas is very dangerous, but mustard-gas-derived chemotherapy is safe enough to treat cancer patients.

Repeat after Paracelsus: safety depends on the dose.

Finally, if the most dangerous toxin known to humans—the neurotoxin produced by the bacterium *Clostridium botulinum*—can pass the FDA's tests as a safe drug (see Allergan's Botox), then really, anything can pass. We could, somewhat facetiously, simplify the FDA's safety tests to this:

- Rule 1: if it's not more toxic than botulinum toxin, then it can be used safely
- Rule 2: nothing is more toxic than botulinum toxin

Risk Everywhere

The discussion of water highlights the problem with blanket statements about water being safe and thalidomide being unsafe. When people choose treatments for conditions, they try to choose the best treatments within the context of their situations. Blanket statements about thalidomide being unsafe don't help. Instead, the question should be: given what we know, is thalidomide the best therapy or not? At what dose? What is the risk?

We incur a risk whenever we consume a pharmaceutical. But there's also the risk we incur by *not* taking beneficial medicines. Members of Debby Demaree's family in Bethesda, MD were, for years, taking drugs that were