HEALTH & MEDICINE

Two Thalidomide Disasters

Myths about the FDA's role in the thalidomide tragedy have resulted in decades of it obstructing many beneficial drugs.

BY CHARLES L. HOOPER AND DAVID R. HENDERSON

Most people have heard of the thalidomide tragedy. Few people have heard that that tragedy led lawmakers to cause an even bigger tragedy. In short, there were two thalidomide disasters.

In the first one, babies were born with severe deformities after their mothers took the drug. The second tragedy was more serious and damaging. Lawmakers used thalidomide as an excuse to pass legislation that would have done little or nothing to prevent the first tragedy but has led to six decades of lost lives. Those lives were lost because the legislation led to fewer beneficial drugs being developed and sold.

THE FIRST THALIDOMIDE TRAGEDY

Many people know there was a tragedy in the early 1960s in which more than 10,000 babies, mainly in Europe and Australia, were born deformed after their pregnant mothers took a sedative called thalidomide. It was seen as a promising treatment for anxiety, sleeplessness, and morning sickness, but after it became available to a large number of users, researchers found it can cause phocomelia, "a disorder that prevents the growth of arms and legs *in utero*, leading in extreme cases to 'flipper limbs': hands and feet attach directly to the shoulders and hips" (Kean 2024).

Many people also know that the US Food and Drug Administration reviewer of thalidomide, Frances Kelsey, never approved the drug, sparing countless American babies from its effects, although there were still, unfortunately, 12 victims here. In August 1962, Kelsey was hailed as a heroine and President John F. Kennedy presented her with the President's Award for Distinguished Federal Civilian Service.

THALIDOMIDE MYTHS

The facts in the above section are true. But there are also many myths about thalidomide.

For instance, it's often said that the FDA had already *rejected* thalidomide when its negative effects came to light. But as noted above, the drug was *in the middle of* the FDA's review process, and there's no reason to think that, given its approach and the technology of the time, the agency wouldn't have eventually approved it. Experts have asserted that the FDA would probably have approved thalidomide *even if new legislation had been in place*. Write drug researchers William Kennedy and Lionel D. Edwards:

> Amazingly enough, the 1962 amendments would still not have kept thalidomide off the market in the United States. The precise strain of rodent that would have been required to identify the lesion was not in common use, and the adverse event frequency in neonates [newborn babies], in the average-sized NDA [new drug application] of the day, might not detect adverse events of such low frequency. (Kennedy and Edwards 2007)

If that's true, then the FDA would certainly have approved thalidomide *before* the 1962 rules, when less testing was required.

It's also often said the drug company that tried to market thalidomide in the United States, William S. Merrell Co., prioritized profits over people's health, resulting in the birth defects.

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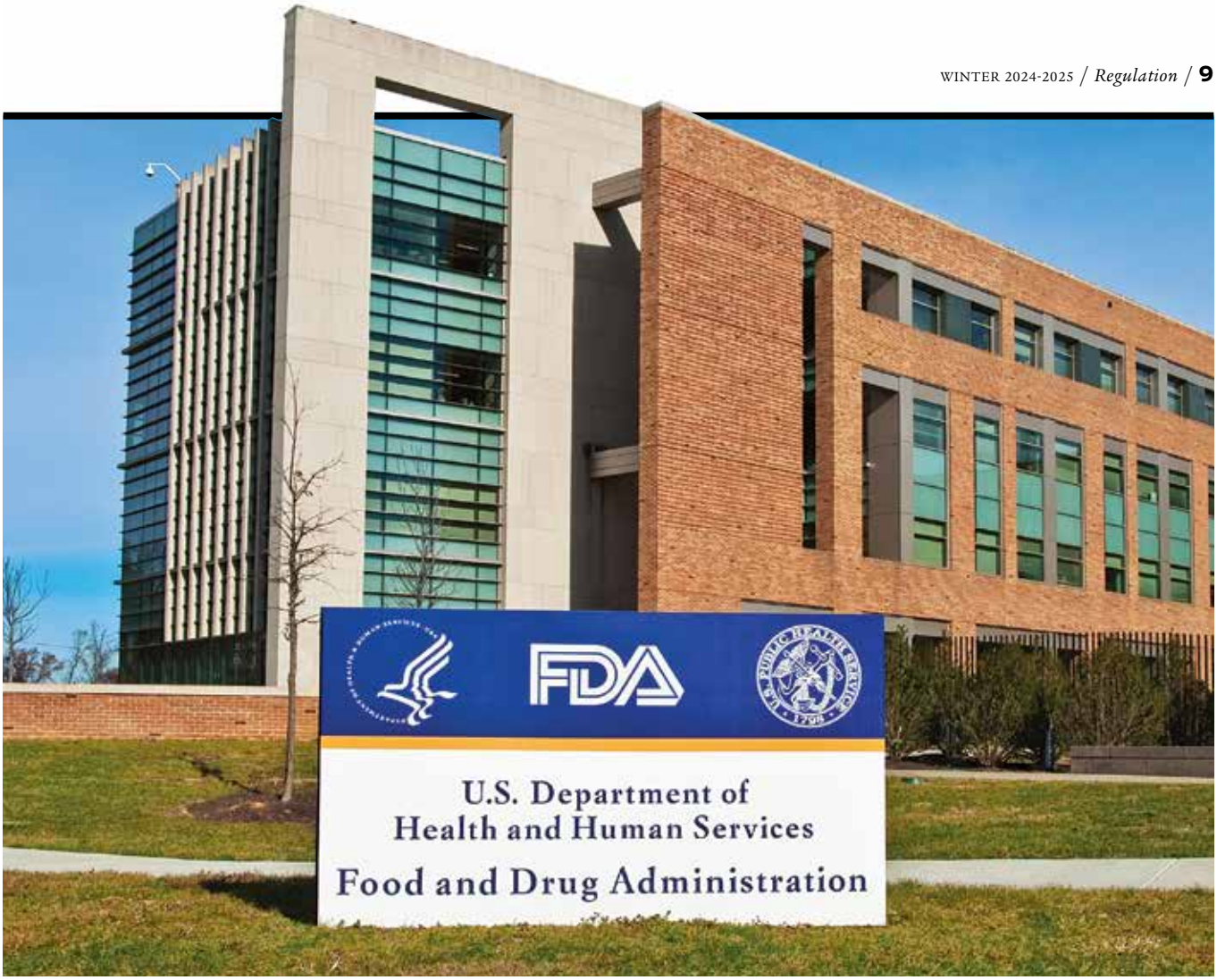

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But in fact, no one, including Merrell (which was not the drug's developer), was aware of the linkage between thalidomide and birth defects when it submitted the drug for review. The firm voluntarily withdrew the new drug application when the risks of thalidomide became apparent.

Another myth is that, at least in the thalidomide era, the FDA usually uncovered problems with new drugs before they became obvious. The truth is the FDA learned about the problems with thalidomide at the same time as the public. It was only after the tragedy was exposed in Germany and Australia that the FDA became aware of the issue, obviating an FDA review.

Another myth is that thalidomide is an awful drug that has been forever banished from the market. In fact, it and some close variants are available and widely used today, though with the guidance that it not be used by pregnant women. The drug is effective in adults for treating several serious diseases, including some skin conditions arising from leprosy and certain cancers, such as multiple myeloma. Bristol Myers Squibb's Revlimid (lenalidomide), a slightly tweaked version of thalidomide, was the second largest selling drug in the United States in 2019 and it is helping thousands of people. US revenues for Revlimid peaked at $12.9 billion in 2021, the year before its patent expired.

People also commonly think that FDA rules were changed in the wake of thalidomide to give the agency more power to prevent subsequent drug safety problems. But in fact, the main changes to federal law and regulations following the tragedy addressed drug *efficacy*, i.e., effectiveness, not drug *safety*. The FDA had been charged with ensuring that new drugs were safe more than two decades *before* the thalidomide tragedy. No published study we know of shows that drugs today are safer than they were in the thalidomide era, even with the new FDA rules.

Another common belief is that the FDA, itself, discovered the linkage between thalidomide and the birth defects. In fact, given the available data on thalidomide at the time, FDA reviewers had no reason to suspect the drug's dangers. The linkage between it and the birth defects first became apparent in Germany, where the drug was developed by the firm Chemie Grünenthal, and Australia, where it was marketed by the British firm Distillers.

Another common myth is that, without aggressive FDA regulation of the profit-seeking pharmaceutical industry, drug companies would forever try to launch new dangerous drugs. In short, without strict regulation, we would have more "thalidomide babies." But in fact, drug companies have strong incentives to avoid marketing dangerous drugs. Consider the problems with the arthritis drug Vioxx that led to lawsuits that nearly sunk Merck & Co., its originator and marketer. The

challenge for the FDA and, really, everyone is that drug safety problems are relatively rare and are often discovered long after the problematic drugs have been on the market and used by enough people to make the problems statistically apparent. Drug companies don't want to market products that have safety problems because such problems can lead to expensive lawsuits, penalties, and adverse public relations. This doesn't mean the drug companies always catch problems, but rather that they try to identify those problems before the drugs go to market.

One final myth: Kelsey acted heroically by delaying thalidomide from reaching the market. In fact, the delay was simply because she was awaiting additional information from Merrell. According to the American Society of Health-System Pharmacists:

> She noted the submitted file contained mostly anecdotes, and testimonials of company employed physicians. She also noted ... there were gaps in the data supporting safety and efficacy. Although the submitted rodent data showed a wide safety margin, she noted there were no tests conducted to determine if the rats were able to absorb thalidomide.
>
> Dr. Kelsey decided to declare the application as incomplete (rather than rejecting the application) proving herself to be an expert at working under the Washington Bureaucracy. (Fotis 2015)

Indeed, we have learned the cause of the delay was even less flattering than this account. According to Dr. Solomon S. Steiner, who was a colleague of Kelsey's at Lederle Labs, a drug maker in Pearl River, NY, where she worked after her long career at the FDA, she was disinclined to take a stand on the approval or rejection of *any* drug. That is a significant flaw for an FDA reviewer. Concerning thalidomide specifically, she had misplaced some of the material Merrell had sent her, resulting in the approval's delay. This being the era before email, FedEx, and fax machines, she wrote a letter to the company asking it to resend the information, and the manufacturer took time to respond because, invariably, Kelsey asked for additional information, partly to avoid confessing her loss of the original material. So, yes, the Merrell application was factually incomplete and its approval delayed, but that was because Kelsey had lost key parts of it.

THE SECOND THALIDOMIDE TRAGEDY

Given these misconceptions, we can see how most people consider thalidomide to be a great FDA success story. However, as we wrote above, there were two thalidomide tragedies: In the first, babies were harmed. In the second, almost all Americans were harmed.

It is no exaggeration to say that the hefty powers of the FDA and the current drug regulation scheme were built on the thalidomide backlash. The modern FDA is, essentially, the house that thalidomide built, here to protect us from future drug tragedies. No drug before or after thalidomide has had even a fraction of the effect it has had on our beliefs about the proper level and role of drug regulation. For example, the author of the afore-cited American Society of Health-System Pharmacists writes:

> Of course there are many unnecessary, frivolous, and probably useless government regulations. However every time I listen to a politician rant against federal regulations I think of Dr. Kelsey, and how fortunate so many parents and children are that we had this regulation, and that we had the right person in the job at the right time. President John Kennedy awarded her the Distinguished Federal Civilian Service Medal for her work on thalidomide. In 2010 the annual Drug Safety Excellence Award was established in her honor. Oh and its [sic] not a coincidence that her guidelines for FDA approval require at least two adequately powered randomized placebo controlled trials which of course we now consider as the minimum requirement for Level 1 Evidence. (Fotis 2015)

In a nutshell, the belief among people both inside and outside the pharmaceutical industry is that if the FDA doesn't protect us in the way it has since 1962, we will have more thalidomide babies. This belief lies just below the surface of any discussion of FDA powers. Yet it doesn't comport with the facts. Our current drug regulation framework was built on concepts incorrectly and opportunistically drawn from the thalidomide disaster.

KEFAUVER–HARRIS AMENDMENTS

Around 1960, Sen. Estes Kefauver (TN) held hearings and wrote bills that were, essentially, populist swipes at big business. One industry that caught his attention because of its high profits was the pharmaceutical industry. To solve some perceived problems, he wanted to dramatically shorten patent lives, curtail marketing practices, substantially reduce drug prices, and require drug companies to prove that drugs were both safe and efficacious before they were marketed. At that time, drug companies needed to prove only safety.

He wasn't getting much traction.

And then the thalidomide disaster hit. The issue might have blown over given that the drug never came to market in the United States, but Kefauver persuaded the press to focus on it and, subsequently, the issue blew up. With the press and public focused on this tragedy, something had to be done. And it was. In just a few weeks, President John F. Kennedy went from opposing Kefauver's bill to saying it was too weak.

The FDA's rules were altered with the Kefauver–Harris Amendments of 1962. They required drug companies to prove both safety and efficacy before a new drug could be marketed.

Note the irony. What kind of problem did thalidomide have? An efficacy problem? No; it did what it was supposed to do: treat anxiety and morning sickness. A safety problem? Yes. The FDA already had rules in place to prevent unsafe drugs. *The FDA could have rejected thalidomide based on rules that had been on the books since 1938*.

Anticipating by nearly half a century Rahm Emanuel's maxim that "You never want a serious crisis to go to waste," Congress and President Kennedy didn't waste this one and the Kefauver–Harris Amendments were passed. The opportunist Kefauver got his bill because of the thalidomide tragedy, even though his bill had almost nothing to do with the thalidomide tragedy.

The primary difference between our attitude toward thalidomide now and pre-1962 doesn't necessarily have to do with the FDA. Rather, it's what we have learned through experiences that have been deposited, just like sedimentary layers, throughout our society. Give thalidomide to a pregnant woman? No way! Everyone knows that. We have little doubt that if doctors who prescribed thalidomide and patients who used thalidomide had heard reports of its teratogenic effects in 1960, sales of the drug would have dropped to zero. That is, after all, what we have witnessed with other drugs that have had real or perceived problems.

FDA DRUG REGULATION

The thalidomide episode demonstrates that if the only objective of a drug regulation agency is to prevent the marketing of dangerous drugs, a failsafe strategy is delay, delay, delay. Make sure that every box is checked and take as much time as possible; meanwhile, consumers in other countries will act as our coal mine canaries, letting us know if there is a problem. But new drugs, in addition to potential health risks, also have potential health benefits, and delaying those benefits harms people. What if people had not had access to BMS's Revlimid? They would have suffered more than they already have.

FDA regulation of new drugs has benefits and costs. The benefits include potentially avoiding future thalidomide-like safety problems. The costs include delaying potentially safer and better drugs. Americans can have serious problems because of dangerous drugs, but they can also have problems because of a *lack* of better lifesaving and health-improving drugs. Further, past situations show that while the presence of dangerous drugs can hurt a certain number of people, that number is often limited, while the number of people hurt by a lack of good, new drugs is often orders of magnitude larger.

Columbia University's Frank Lichtenberg has estimated that three quarters of the increase in life expectancy that we've enjoyed in recent decades is the sole result of our adoption of modern drugs (Lichtenberg 2014). New pharmaceuticals are more friends than foes; they are more lifesavers than killers. Because new drugs are typically beneficial, we *all* suffer—friends and loved ones (not to mention ourselves)—when the availability of new drugs is limited. People need to be aware of the potential benefits and costs of FDA actions.

THE EFFECTS OF EFFICACY REGULATION

UCLA economist Sam Peltzman compared the number of new chemical entities—not just drug reformulations—approved by the FDA before and after the law was changed. (Peltzman 1973). He found that approvals post-1962 were a shocking 61 percent below what he projected they should have been. There were fewer beneficial drugs available for patients than there would have been had the rules not changed.

Part of the reason for this slowdown is the much higher cost of drug development after Kefauver–Harris. In the subsequent decades, capitalized drug development and approval costs per approved drug have increased at 7.5 percent per year in real terms: $179 million in the 1970s, $413 million in the 1980s, $1.04 billion in the 1990s through early 2000s, and $2.56 billion in the 2000s through early 2010s (all in 2013 dollars).

If this 7.5 percent annual growth rate were to persist, costs would more than double every 10 years. But the cost increase seems to be *accelerating*: The annual growth rate over the last decade has been 8.5 percent. The cost today is probably already at least $8 billion (in 2024 dollars).

In short, we have fewer drugs and the cost per drug has exploded. Is this attributable only to the bad drugs that were weeded out by the new rules? Multiple researchers have concluded that the answer is no. Peltzman came to this same conclusion, seeing the culling as if "an arbitrary marketing quota ... had been placed on new drugs after 1962." The adjective "arbitrary" isn't something a supposedly scientific organization strives for.

With the post-1962 rules, based on the results of these studies, we may well have about 60 percent fewer good new drugs to help us fight cancer, cardiovascular disease, infections, osteoporosis, pain, and a thousand other conditions.

No one knows the exact number of missing drugs attributable to Kefauver–Harris because the drugs for which development was ceased all met their fate in portfolio review meetings behind the closed doors of drug companies. However, one of us has participated in such meetings and has recommended to pharmaceutical management teams to cease development on drugs that were being developed to treat brain cancer, ovarian cancer, melanoma, hemophilia, and other important conditions. It's better to cut the losses than to lose even more.

Ultimately, the problem Peltzman uncovered was unnecessary. One could make an argument that a federal government agency *should* check drugs for safety before marketing, realizing that some safety problems are rare and won't show up in clinical trials because of the limited numbers of test subjects. Making that argument for efficacy is much more tenuous

because an FDA certification of efficacy simply doesn't add much value.

The biggest holdup in getting drugs to market is not how long it takes to demonstrate that they're safe but, rather, the time and expense to show, to the FDA's satisfaction, that they are efficacious for particular uses. An FDA drug efficacy imprimatur is duplicative. Doctors and patients participate every day in a similar process of drug testing, making FDA certification neither necessary nor sufficient. If 60 percent of people got better during a clinical trial, that doesn't guarantee that a *particular* individual will get better. The only way to discover if a particular drug works for a particular person is for that person to try it. And even then, if the patient gets better, we still won't *know* that the drug was responsible.

Moreover, doctors often prescribe, and patients often use, drugs "off label," meaning for uses other than what the FDA has found efficacious. So, for example, when Eli Lilly introduced Prozac for depression, some doctors wondered if it might be useful for treating pre-menstrual syndrome (PMS). They tried it and, voilà, for many women it worked. But under federal drug laws, Eli Lilly initially could not advertise Prozac for that use or even recommend the use to doctors behind closed doors, preventing important information from reaching doctors and patients. The drug was so successful in treating PMS that Eli Lilly ultimately had it tested, and approved, for treating the condition. But often doctors prescribe drugs, particularly cancer drugs, for treating diseases even though the FDA has not approved the drugs for those uses.

Who would want to take a drug that has not been shown, to the FDA's satisfaction, to be effective? The answer: almost everyone. According to the health information website *WebMD*, "More than one in five outpatient prescriptions written in the U.S. are for off-label uses" (Miller 2009).

There are many prominent examples of drugs being used effectively and safely for purposes outside of their FDA approval. Here are just a few:

- For the first eight months that the mRNA-based COVID-19 vaccines were available to the public, they did not have the FDA's official approval; rather, they were made available under an "emergency use" exception. By the time they received approval, about 160 million Americans had had at least one dose administered.
- Soon after Merck launched Proscar (finasteride) to treat enlarged prostate glands, physicians started sharing stories of men reporting new hair growth. "One of the doctors said that was impossible," recalled Merck spokeswoman Janet Skidmore. It wasn't impossible. Proscar lowers levels of the hormone dihydrotestosterone, making it effective for both shrinking prostate glands and growing hair. Merck turned this off-label usage into a second product, specifically designed for hair growth: Propecia (finasteride).
- Researchers noticed that patients with tuberculosis had lower rates of cancer. This led some urologists to treat cases of bladder cancer off-label by filling patients' bladders with a mixture containing Bacillus Calmette–Guérin (BCG), a live but weakened tuberculosis-causing bacteria that is used as a tuberculosis vaccine. It is now the standard of care to treat some types of bladder cancer and has received FDA approval for that indication.

CONCLUSION

If the FDA didn't require proof of efficacy before marketing, drug approvals would be faster and cheaper. More drugs would be on the market, providing physicians and patients with more choices and more competition, which is the only thing that consistently holds down drug prices.

A misunderstanding of the thalidomide disaster has spurred a different and bigger disaster: the post-1962 drug regulation disaster of ballooning R&D costs, fewer new treatments for patients in need, less competition, and much higher drug costs. And, through this all, there is no evidence that Kefauver–Harris has made drugs any safer.

Is keeping thalidomide off the US market the FDA's greatest achievement? No. Rather, thalidomide is a story of a multifaceted drug with good and bad sides, a lack of information, bureaucratic red tape, a disorganized FDA employee, misplaced materials, bureaucratic delays, dumb luck, incorrect conclusions, an opportunistic senator, a reactive president, subsequent legal non sequiturs, an explosion in the cost of drug development, and fewer beneficial drugs available for patients.

Because of misunderstandings and opportunism, the first thalidomide disaster fed the second thalidomide disaster, from which we suffer every day. It's time the second thalidomide disaster got more attention. *R*

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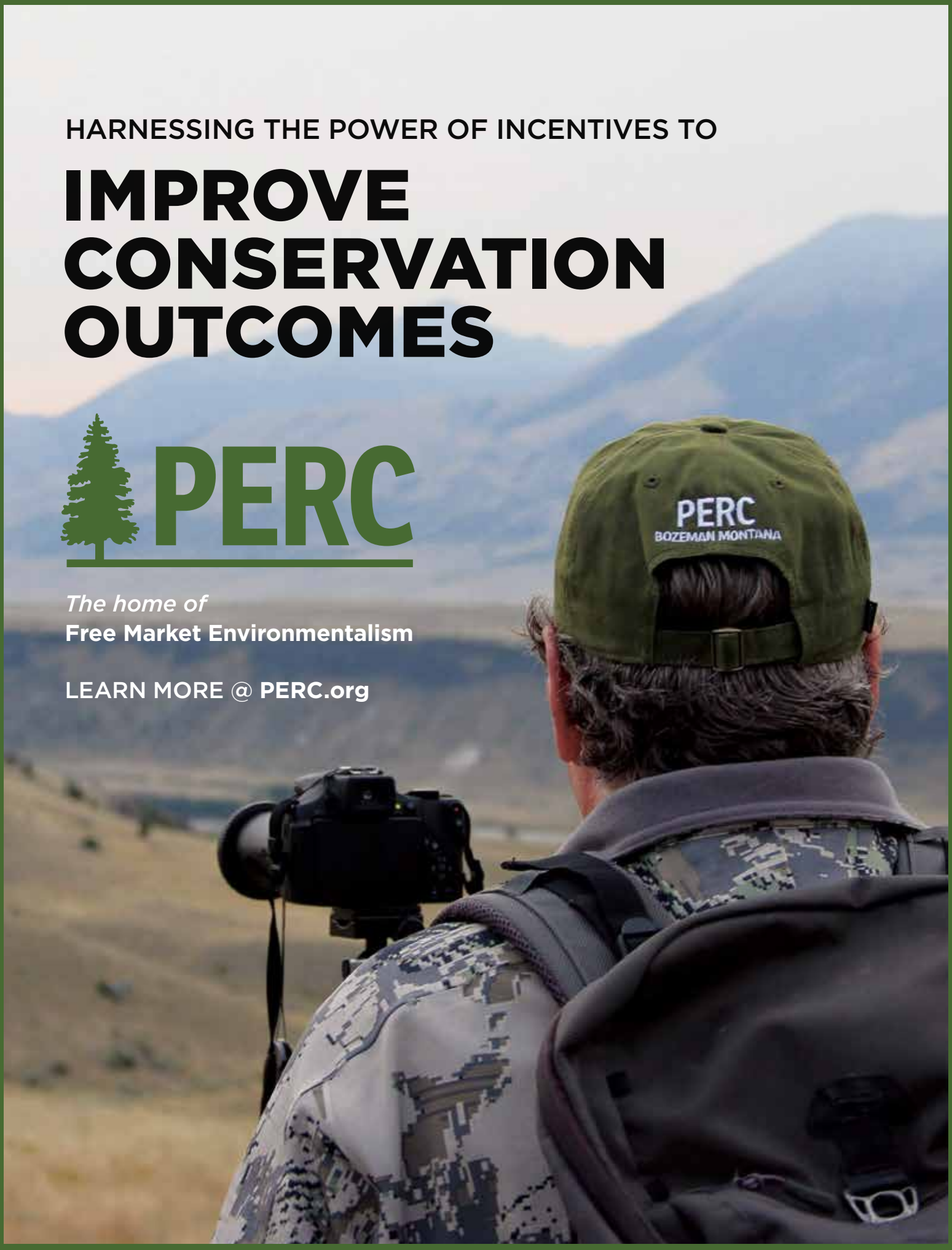

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