PIONEER HEALTH

The Left-Hand Doesn't Know What the Right-Hand is Doing:

The Federal Government and Opioids

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Introduction

The opioid epidemic in the U.S. has been devastating, with hundreds of thousands of overdoses. For decades, the federal government has encouraged the use of non-opioids for pain and also incentivized the research and development of non-opioid therapies that might replace opioids. If biopharmaceutical research labs could discover effective pain therapies that were less addictive than opioids, it would be an enormous step in mitigating the terrible epidemic of opioid abuse and overuse.

Then, in 2022, the federal government reversed course with passage of the Inflation Reduction Act (IRA). The IRA provides strong disincentives for research and development into potential small molecule drugs because it imposes price controls on these therapies four years earlier than so-called large molecules or biologics. The IRA significantly reduces the return-on-investment for small molecule drugs, and there is considerable evidence to suggest that venture funds and biopharmaceutical companies will pull back from small molecule research, given the reduced future profitability of these products. Since most potential replacements for opioids fall into the small molecule category, we wanted to take a look at the pipeline for non-opioid drugs and then estimate how the new IRA might impact that pipeline.

The Opioid Epidemic

According to the Congressional Research Service (CRS), between 1999 and 2020, 565,000 Americans died of opioid overdoses.[1] Opioid abuse grew four-fold from 1999 to 2010, by which time opioid prescriptions had been given to 81.2 out of every 100 Americans.[2]

The opioid crisis unfolded in three phases.

The first phase was related to prescriptions for opioids written by doctors. Prescription opioid sales quadrupled from 1999 to 2010. As CRS indicates, "between 1999 and 2010, the rate of opioid-involved overdose deaths in the United States more than doubled from 2.9 to 6.8 per 100,000 people."[3]

By 2010, policymakers began reacting to the crisis. Efforts were made to limit opioid prescribing through a variety of programs, including prescription drug monitoring programs (PDMPs) in which the authorities tracked opioid prescriptions. As the crisis expanded, policies grew harsher, with penalties against physicians, limits on pain clinics, and limits on the duration of prescriptions.

Because of these policies, prices increased for prescription opioids (POs), and they became more challenging to obtain, either from a doctor or illegally. At about this time, retail heroin prices began to drop significantly. This led to the second wave of the opioid crisis as abusers of opioids turned to heroin to replace the POs that were now too expensive or unavailable. As CRS has chronicled, "from 2010 to 2016, heroin-involved deaths increased from 1 to 4.9 per 100,000."[4]

By 2016, the nation had entered the third phase of the opioid epidemic, the fentanyl phase. That year, fentanyl overdose deaths surpassed those of heroin and prescription drugs. The U.S. still finds itself in this terrible third phase.

Due to the strength and addictive properties of fentanyl, by 2020, the rate of opioid overdose deaths more than doubled from 10.4 to 21.4 per 100,000. Through the three phases of the opioid crisis, overdose deaths have risen steadily with less than 3,000 opioid overdoses in 1999 and more than 80,000 in 2021.

Data from the National Institute of Drug Abuse indicate that we are firmly in the third phase of the epidemic, as overdose deaths from prescription opioids peaked in 2017, with 17,029 deaths. That figure dropped to 16,706 in 2021.[5]

To put these numbers in perspective, 7,050 American soldiers died in the post-9/11 wars in Iraq, Afghanistan, Syria, etc.[6] The nation is losing 10 times that amount of people to opioid overdoses each year.

The Continuing Role of Prescription Opioids (POs) in the Opioid Epidemic?

Policymakers may conclude that the measures taken to limit POs have been successful, and we should now turn our focus to fentanyl. This may be a mistake as there are some data to suggest that POs continue to play a prominent role as a "gateway" drug, with many people still getting their first exposure to opioids through a prescribed product, then later turning to heroin or fentanyl when POs become difficult to obtain.

In a 2022 study, researchers interviewed 148 opioid abusers in three states in an attempt to discover how these people found their way to heroin, fentanyl, and other more dangerous opioids. The study concluded, "a large majority of participants (134/140, 90%) started with prescription opioids, used either medically or non-medically. Roughly half of the participants started with opioids that were prescribed to them (64/134, 48%). The majority of those who started with POs (111/134, 83%) switched to heroin, fentanyl, or some combination over time…"[7]

For those who obtained POs for non-medical reasons and did not get a prescription from their doctor, the study concluded that individuals obtained POs "through friends or family members or, less frequently, by buying them illicitly."

Study interviews indicated that opioid abusers slowly came to realize that policy changes were limiting their access to POs. "Participants described a gradual process starting about 2010 to 2016 by which POs became more difficult to acquire as doctors became less likely to prescribe them, which in turn, led to greater scarcity and higher prices of POs on the street."

It is one of the tragic ironies of this epidemic that measures taken to limit the prescribing and availability of POs likely led users to turn to heroin and fentanyl, more dangerous drugs.

While we cannot draw firm policy conclusions from one small study, there is some other evidence that POs continue to have a role as a gateway drug to more serious opioids such as heroin and fentanyl. A study of Massachusetts toxicology reports during the 2013–2015 period concluded that POs were no longer the leading cause of opioid deaths. But the study also concluded that, "prescribed opioid exposure appeared to have a 'more distal' effect on overdose risk by acting as a gateway drug."[8]

Another older study from the National Institute of Drug Abuse found that 86 percent of injected heroin users "had used opioid pain relievers non-medically prior to using heroin."[9]

There are not enough data to definitively say that POs are the most important gateway drug for those who later initiate heroin or fentanyl use, but there is enough evidence to suggest that POs serve as a gateway for some who later become heroin and fentanyl users. Therefore, it makes considerable policy sense to continue the research on non-opioid pain therapies and to incentivize this type of research.

Federal Government Creates Programs to Develop Non-Opioid Alternatives for Pain

Perhaps because they are aware of the continuing role of POs in the opioid epidemic, federal policymakers created two significant programs to foster the development of non-opioid pain drugs or therapies that could replace opioids.

In 2022, the Food and Drug Administration announced a program that provides guidance and recommendations to drug developers on generating data on pain drugs and argues that such therapies could be eligible for "fast track" approval and priority review by the FDA.

A second program, funded by the National Institutes of Health (NIH), is even more robust than the FDA program as it provides funding to develop non-opioid therapies. NIH's Helping to End Addiction Long-Term Initiative, or HEAL, "supports new clinical trials and the expansion of existing programs to help establish evidence-based guidelines for treating pain with non-opioid therapies."[10]

The HEAL initiative was announced in 2018 by then-NIH Director Francis Collins, and funding for research on this category of non-opioid pain drugs nearly doubled from $600 million in 2016 to $1.1 billion in 2018.[11]

Numerous other federal agencies have encouraged the use of non-opioid pain relievers. The Centers for Medicare and Medicaid Services (CMS), for example, created an "Action Plan" in 2021 to stem "Opioid Use Disorder."[12]

Among other things, the Action Plan recommended that "CMS review and modify rate-setting policies that discourage use of non-opioid treatments, particularly those options for treating immediate post-surgical pain." In other words, the federal government should consider paying more for non-opioid pain drugs.

Likewise, the Centers for Disease Control and Prevention (CDC) encouraged patients to consider "non-opioid therapies". They asserted that such therapies "may actually work better for some conditions and have fewer risks in side effects."[13]

Congress has recently gotten into the act to encourage the development and use of non-opioid pain therapies. In 2022, it passed the "The Non-Opioids Prevent Addiction in the Nation Act ("NOPAIN Act")." The bill would require more generous reimbursement for non-opioid pain relievers in the Medicare program and require a report to Congress on "limitations" and "gaps" in Medicare coverage for these non-opioids. An advocacy group, "Voices for Non-Opioid Choices," supported the passage of this legislation and is monitoring its implementation.[14] It is a supreme irony that this law was passed in the same year as the Inflation Reduction Act (IRA). We will discuss this inference later in this paper.

The only conclusion that can be reached about federal policy in this area is that policymakers have encouraged and funded the development and use of non-opioid therapies and that a broad bi-partisan consensus exists in Washington that non-opioid therapies, capable of replacing opioids, could offer a solution to the raging opioid epidemic.

The Challenge of Discovering Pain Therapies

Some public support for research into non-opioid pain therapies seems appropriate, given the severity of the opioid epidemic and the genuine difficulty in discovering new pain treatments. Despite years of research by industry and government, there are essentially still only two types of pain medications on the market: opioids and anti-inflammatory analgesics (the latter are generally sold over the counter).

A 2023 study by the Biotechnology Industry Organization (BIO) provides insight into why physicians have limited choices in treating pain: the attrition rate for pain research projects is much higher than most other therapeutic areas. BIO's report states, "(C) clinical success in pain drug development remains extremely difficult for novel drugs, with only a 0.7% probability of FDA approval from Phase 1, compared with an overall 6.5% success rate for novel drug programs across all diseases."[15]

For obvious reasons, investors tend to avoid the risk inherent in pain research programs, and venture capitalists have shown a distinct disinterest in investing in pain research. "Venture capital

into U.S. companies with novel drug programs in pain totaled $0.86 billion over the last ten years. By comparison, oncology venture investment raised during the same ten years was $35.7 billion."[16]

The BIO study looked at pain research projects operating in 2017. By 2022, researchers found that of 65 projects that were in Phase 1, none had achieved FDA approval, and 55 of those 65 Phase 1 projects had been canceled. Overall, of the 220 active projects in 2017, only 21 made it to FDA approval. Moreover, "of the 21 approved drugs, seven target CGRP (Calcitonin Gene-Related Peptide, a new target for migraine), and 14 programs work through well-established targets for pain (*e.g.,* opioid receptors, cyclooxygenases, and sodium channels). It appears that even in the new potential crop of pain therapies, many do not represent profound innovations that might replace opioids. (More on the 2017 data later in this report.)

The BIO report also points out that, in addition to this challenging attrition in the pipeline, far fewer pain research projects are being launched. "Clinical programs for pain with novel chemical entities declined 40%, with 125 back in 2017 to just 75 in 2022. There was also a larger decline (48%) in the clinical pipeline for reformulated and repurposed drugs, from 95 to 49."

The BIO report's conclusion about potentially finding a replacement for opioid pain drugs is grim: "With an overall success rate of just 0.7%, the odds suggest a challenging environment for the next wave of non-opioid, non-addictive medications."

The Right-Hand Doesn't Know What the Left Hand is Doing: The Inflation Reduction Act (IRA) and the Future of Non-Opioid Pain Drugs

The IRA contains many complex provisions that will shape biopharmaceutical R&D for decades. However, one of the most important and controversial provisions was permitting the federal government to impose price controls on "small molecule drugs" four years earlier than large molecules or biologics.

Ironically, and contradicting every other federal policy initiative on opioids, this provision of the IRA will discourage the development of small molecule non-opioid pain drugs. As was discussed above, non-opioid pain research projects are markedly more complicated than most other drug therapies. The IRA will make those discoveries nearly impossible because the number of R&D projects that need funding will shrink considerably.

Small molecule drugs are essential treatments for conditions that might originate in the body's central nervous system. This is because the human body contains an important filter — the blood-brain barrier — that is necessary to prevent foreign substances from infiltrating the delicate central nervous system.

Therapeutic areas in which medicines are needed to cross the blood-brain barrier include "diseases of the aging," such as people who suffer from diseases like cancer and Alzheimer's."[17]

So, when the IRA limits the amount of time a drug therapy can be on the market without federal price controls, it also limits the potential return on investment in those drugs and, therefore, discourages their development. Hence, one can predict that, in the future, there will be fewer small-molecule drugs in development for cancer and neurological conditions.

One patient advocate and biotech researcher, Dr. Steven J. Potts, was concerned about the damage the IRA might do to small molecule research, so he surveyed 100 venture capital firms that invest in biopharma research. He found that 85 percent of those firms were "pivoting away from small molecule drug development."[18] A healthy majority of biotech executives and biotech employees also saw diminished interest in small molecule drug development, as the IRA would significantly reduce these drugs' return on investment.

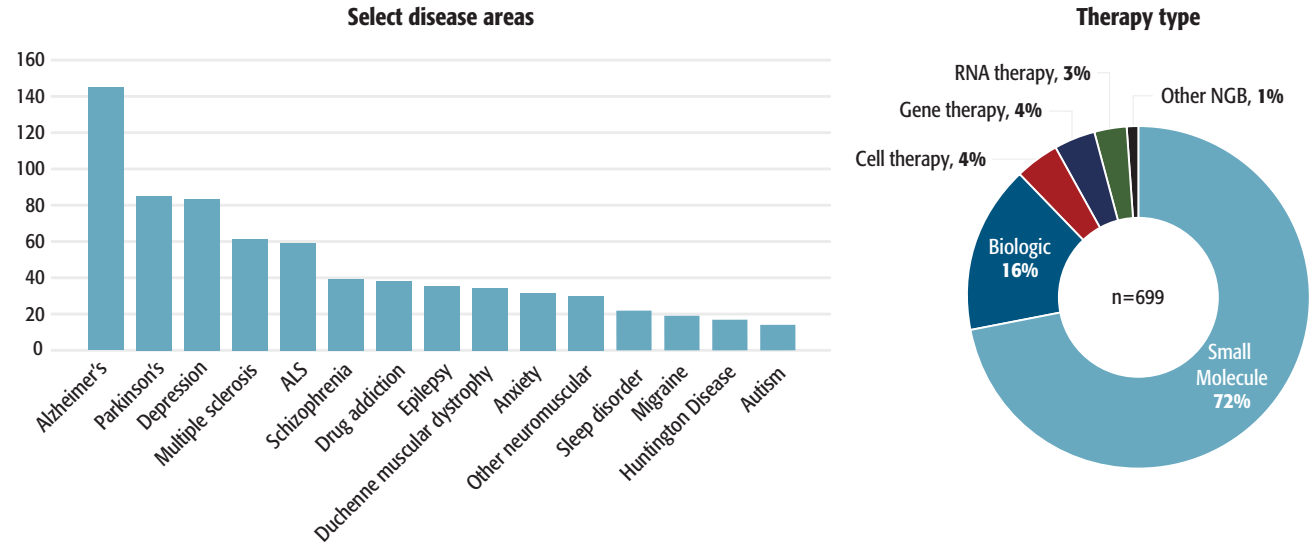
One life sciences venture capital expert pointed out that "50% of the recouping of investment in all drugs happens in years 9 through 13 — a reminder that the early years of drug approval rarely

yield financial windfalls."[19] Post-IRA, revenues for small molecules in years 9 through 13 will barely exist.

Pharmaceutical giant Pfizer recently announced its strategy for declining sales of COVID-19 therapies. Pfizer executives indicated they would turn to oncology treatments to replace shrinking revenues from COVID therapies. Pfizer will not, however, focus on small-molecule cancer therapies. Pfizer's head of oncology R&D told CNBC that their oncology plan would shift its focus from small molecule treatments to biologics. Pfizer's oncology pipeline was previously only 6 percent biologics, and Chris Boshoff hopes biologics will comprise 65 percent of the pipeline by 2030. Here is how CNBC reports the shift to biologics: "Boshoff said biologics represent 'a more durable revenue potential' based on several factors. That includes upcoming patent expirations and potential pressure from President Joe Biden's Inflation Reduction Act."[20]

The IRA has the potential to adversely impact research in other therapeutic areas. Very recent data from IQVIA indicates that 72 percent of the clinical trials for neurology drugs to treat Alzheimer's, Parkinson's, depression, and multiple sclerosis involve small molecule therapies.[21] According to the IQVIA figures, there are about 503 small molecule neurology projects in all. If 85 percent of venture firms back away from these small molecule projects, hundreds of neurology clinical trials will be canceled.

Neurology research is focused on Alzheimer's, Parkinson's and depression, with a range of other often rare diseases



Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Jan 2023.

Another study from the University of Chicago concluded that the IRA would cause an overall reduction in "R&D investment of almost 12.3% or $232.1 billion over 20 years. Over the same time frame, we conclude that there will be 188 fewer small molecule treatments, including 79 fewer small molecule drugs and 109 fewer post-approval indications for these drugs."[22]

The impact of the IRA on post-approval research on small molecule drugs is thought to be significant. After all, what incentive is there for manufacturers to launch new clinical trials in hopes of obtaining an additional pain indication if that drug will be subject to price controls in a few short years?

And post-approval research on small molecules has, until the IRA, been quite robust. According to a study funded by The Pharmaceutical Research and Manufacturers of America (PhRMA), of the small molecules approved by the FDA between 2006 and 2012, 52 percent of the indications for these medicines were secured post-approval.

Of this same group of drugs approved between 2006 and 2012, 25 percent of the post-approval indications were "for a different disease or disease subtype than the initial approval."[23] The perfect example of such an outcome is that many therapies approved to treat a neurological condition were found to be effective pain medicines years later.

Finally, very few observers have pointed out the tremendous costs of the opioid epidemic and the tremendous savings that an effective opioid replacement pain drug would generate. "The Society of Actuaries estimates the total economic burden caused by the opioid epidemic from 2015 to 2018 was $631 billion, with other estimates that included the statistical value of life ranging up to $2.5 trillion during this time frame."[24]

In contrast to the massive $631 billion in four-year costs arising from the opioid epidemic, the Congressional Budget Office (CBO) estimates that savings from the price control provisions of the IRA will generate savings of only $129 billion during the ten-year period of 2022–2031.[25] It seems the height of policy folly to disincentivize research on possible opioid replacements that might generate far more massive savings than the entirety of the IRA price control provisions.

The IRA and Opioid Replacement Therapies

While the most important therapeutic areas that will be impacted by a reduction in small molecule drug development will undoubtedly be cancer, neuroscience, and certain orphan diseases, one therapeutic area that has not received the attention it deserves is small molecule non-opioid pain therapies because of the potential for an effective therapy to mitigate the opioid epidemic.

There are certain types of pain where small molecules might be indispensable in mitigating that pain and where non-opioid therapies might replace opioids. With a limited number of projects for pain in 2022, the number of non-opioid pain projects is quite small, as migraine drugs and other traditional pain targets comprise the majority of such projects.

The IRA creates enormous uncertainty for drug development as the law creates tremendous disincentives for certain types of research. It also may portend worse disincentives, as some politicians have proposed placing price controls on all therapies only five years after FDA approval. This proposal would decimate drug R&D projects across the board.

Finding a therapy that can replace opioids is even more challenging because opioids are a terribly effective remedy for pain. There are no reliable options in some therapeutic areas, so discovering a therapy that partially mitigates a disease may be easier. For a replacement to opioids, drug discovery would need to produce a therapy that is more effective at pain reduction than opioids — a challenging task.

The R&D Pipeline for Non-Opioid Therapies

Pioneer contacted the Biotechnology Industry Organization (BIO), which released a report on the R&D pipeline for pain drugs in February of 2023.[26] BIO provided Pioneer with a list of all the R&D pain projects during 2022. To narrow the focus to small molecules that might serve as replacements for opioids, we excluded R&D projects that were targeting conditions in which opioids typically would not be prescribed since not all pain drugs could serve as replacements for opioids as they may target conditions, such as migraine or neuropathic headache, for which opioids are neither recommended nor commonly prescribed. We also excluded three trials for cyclooxygenase, which, from a therapeutic perspective, are probably not strong enough pain relievers to replace opioids. The only COX-2 inhibitor on the market, Celebrex, is only indicated for mild to moderate pain. These products generally have the same mechanism of action as over-the-counter pain relievers such as Advil.

We therefore focused on R&D projects that are seeking the following Indications for their product label:

- Acute Pain
- Cancer Pain
- Chronic Pain
- Moderate to Severe Pain
- Osteoarthritis Pain
- Pain Indications
- Post-Surgical Pain

Of the 88 small molecule research projects on the BIO list, nine were seeking the above indications and could produce drug candidates that might replace opioids. (We obviously excluded opioid pain projects.) Those nine programs entailed the following mechanisms of action:

1. Glycine Transporters
2. P1 Adenosine Receptors
3. P2 Adenosine Receptors
4. Protease Activated Receptor
5. Reformulation, ND
6. Sodium Channels
7. Vanilloid Receptors

Potential Opioid Replacements

Drug Name	Lead Company	Indication Name	Sep 2022 (BIO IA changed)	Target
CNTX-6970	Centrexion Therapeutics Corporation	Pain Indications	II	Chemokine receptors
VVZ-149	Vivozon, Inc.	Postsurgical Pain	III	Glycine transporters
NTM-006	Neumentum	Pain Indications	II	PI adenosine receptors
AK1780	Eli Lilly and Company	Chronic Pain	I	P2 adenosine receptors
MEDI0618	AstraZeneca PLC	Osteoarthritis Pain	I	Protease activated receptor
SL-1002	Saol Therapeutics	Osteoarthritis Pain	II	Reformulation, ND
PCRX-301	Pacira Biosciences, Inc.	Postsurgical Pain	I	Sodium Channels
ST-2427	SiteOne Therapeutics, Inc.	Postsurgical Pain	I	Sodium Channels
VX-548	Vertex Pharmaceuticals Incorporated	Acute Pain	II	Sodium Channels

These data suggest the number of R&D projects that could yield a therapy that would replace opioids is very small and, by some biopharmaceutical standards, minuscule. For example, the number of CAR-T cancer R&D projects (a subset of oncology research) during 2022 totaled 377.[27]

The BIO report on pain also looked at the "fate of the 2017 clinical pipeline for pain."[28] BIO found that of the 220 clinical projects for pain in 2017, less than 10 percent (21) had yielded an approved drug (although 13 percent, or 29 projects, were "still in the clinic"). See chart on the next page.

Fate of the 2017 Clinical Pipeline For Pain

2017 Status		2022 Status		
Phase	Count	Remains in Clinic	Approved	Suspended
I	65	10	0	55
II	88	11	1	76
III	53	7	11	35
NDA/BLA	14	1	9	4
Total	**220**	**29**	**21**	**170**
Percent	**100%**	**13%**	**10%**	**77%**

BIO's data from 2017 suggest that R&D projects for pain have an attrition rate of at least 77 percent. If that attrition rate applies to the nine small molecule projects that could serve as opioid replacements, we estimate that seven of the nine R&D projects will not succeed. That leaves only two R&D projects that might lead to a replacement for opioids.

However, BIO's more extensive view of the attrition rate for pain R&D projects was far higher than the 77 percent figure in the 2017 data. Overall, BIO concluded that pain R&D projects have an attrition rate of 99.3 percent. If that percentage is applied to the nine projects that could yield an opioid replacement, those projects will likely produce no viable therapies.

Please note that this estimate does not consider the rush away from small molecule research projects instigated by the IRA, as indicated by Pfizer and the survey of venture capitalists. Pain projects are among the riskiest in the entire biopharma portfolio, and the reduced return on investment caused by the IRA will likely lead to substantial attrition in pain R&D projects for financial reasons, not therapeutic ones. In short, we can only conclude that the disincentives for small molecule research in the IRA and the difficulty of pain research generally will very likely snuff out any hope of finding an effective non-opioid pain therapy.

Non-Opioid Therapies and Reimbursement

One strategy being discussed in Washington is to reimburse for non-opioid pain therapies more generously and to remove barriers to patient access to these therapies. A D.C.-based advocacy organization, Voices for Non-Opioid Choices,[29] is supporting bi-partisan congressional legislation, the Alternatives to PAIN Act, which would lower patient cost-sharing in Medicare Part D plans for non-opioid therapies and ban step therapy and prior authorization requirements for patients to obtain these therapies.

This approach has some merit as more generous reimbursement and access could make the return-on-investment in research on these therapies more attractive for companies and investors. However, one challenge to this approach is that there are a small number of effective non-opioid therapies that can compete with highly effective opioid therapies. If the pipeline for non-opioid pain therapies suddenly becomes robust, this reimbursement/access strategy could be highly effective. However, as discussed, there are serious obstacles to creating a robust pipeline for non-opioids.

One study[30] developed a somewhat comprehensive list of alternatives to opioids, including drugs, devices and injections. As the reader can see from the list, alternatives of exercise and Tylenol may not be as attractive as highly effective opioids to patients with serious post-surgical pain. This reimbursement/access approach should be combined with strong incentives for research into non-opioid therapies and elimination of the IRA's disincentives for small molecule research. In order to discover an effective non-opioid pain drug, there would likely need to be upwards of 100 clinical trials, many "shots on goal," that might yield an effective therapy.

Conclusion

To Americans suffering under the crushing burden of the opioid epidemic, these data offer little hope. But as we know from numerous scientific discoveries, sometimes long-shot research yields a discovery.

In January, the very innovative biotechnology company Vertex reported that its experimental non-opioid pill, VX-548, had reduced post-surgical pain in clinical trials and that they plan to file for FDA approval for the pill.[31]

However, the news on the Vertex drug was not perfect. As reported by BIOPHARMA DIVE: "VX-548 didn't prove superior to a combination of the widely prescribed opioid hydrocodone bitartrate and Tylenol, falling short on a key secondary goal Vertex had set in both trials."[32] In other words, the Vertex pill did not prove more effective at reducing pain than traditional opioids.

Real-world use will provide a better picture of whether the Vertex therapy is an adequate substitute to opioids for patients and their physicians, and relieves pain effectively enough to become an opioid replacement therapy in common usage.

As those who know drug development are aware, the first drug in a therapeutic class is rarely the best drug to emerge. With a robust pipeline, follow-on drugs typically emerge that are more effective and have fewer side effects. Yet, with only nine projects for opioid replacements, an attrition rate of 99.3 percent, and huge disincentives in the IRA to conduct research on opioid replacements, the prospect of a robust pipeline of non-opioid therapies is greatly diminished. Left unchecked, the IRA was probably the final nail in the coffin for small-molecule non-opioid replacement therapies.

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About the Authors

Dr. William S. Smith is Senior Fellow & Director of Pioneer Life Sciences Initiative. Dr. Smith has 25 years of experience in government and in corporate roles. His career includes senior staff positions for the Republican House leadership on Capitol Hill, the White House Office of National Drug Control Policy, and the Massachusetts Governor's office where he served under Governors Weld and Cellucci. He spent ten years at Pfizer Inc as Vice President of Public Affairs and Policy where he was responsible for Pfizer's corporate strategies for the U.S. policy environment. He later served as a consultant to major pharmaceutical, biotechnology and medical device companies. Dr. Smith earned his PhD in political science with distinction at The Catholic University of America.

Dr. Robert Popovian is Visiting Fellow with Pioneer Institute's Life Sciences Initiative. He is the Founder of the strategic consulting firm Conquest Advisors, and previously served as Vice President, U.S. Government Relations at Pfizer. Dr. Popovian has published extensively and has delivered briefings, and expert reviews for the U.S. Congress, state legislatures, and at national and global conferences. He was recently appointed as the Chief Science Policy Officer for Global Healthy Living Foundation. He completed his Doctorate in Pharmacy and Master of Science in Pharmaceutical Economics and Policy degrees at the University of Southern California with honors; and a residency in Pharmacy Practice/Adult Internal Medicine and Infectious Diseases at the Los Angeles County-USC Hospital and fellowship in Pharmaceutical Economics and Policy at USC.

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