Congress Moves Toward Opioid Response 2.0

Bills Are Wide Ranging and Well Intentioned but Mostly Lightweight

Stephen Barlas

The Food and Drug Administration (FDA) approved Flexion Therapeutics' Zilretta (triamcinolone acetonide extended-release injectable suspension) in October 2017. The short-acting corticosteroid is indicated for the management of osteoarthritis pain of the knee. Triamcinolone acetonide has been around for years. It is used in ointments for poison ivy and in nasal sprays to relieve sneezing, runny, stuffy, or itchy nose, and itchy, watery eyes caused by hay fever or other allergies.

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There is nothing new chemically about Zilretta, but the same is true for almost all the new pain relievers recently approved by the FDA and those in phase 3 clinical trials, opioid and nonopioid. And that's a problem given the opioid crisis that now has the U.S. in a tight grip. It might be easier to relieve the national infection if there were a nonopioid new molecular entity (NME) for pain relief that worked as well as hydrocodone and oxycodone, the abusable and abused prescription opioids that dominate the market for prescription pain relief.

Kerry Wentworth, Chief Regulatory Officer at Flexion Therapeutics, admits that had Flexion attempted to develop its first commercial product based on an NME, investment backing would have been hard to come by. "Yes, we do believe the fact that our lead development program used an already approved active ingredient helped to attract investment dollars because it did not carry the risk associated with a novel molecular entity for an analgesic indication," Wentworth states. "The lack of investment dollars in novel nonopioid analgesics is a major issue and the subject of a lot of discussion amongst those in this space."

With Congress readying a second iteration of massive legislation to address the opioid crisis, one would think that the lack of pharmaceutical industry research into effective nonaddictive substitutes for hydrocodone and oxycodone would be a leading concern for members of the House and Senate. But none of the evolving legislative proposals expected to be included in the second iteration of a Comprehensive Addiction and Recovery Act (CARA 2.0) (version 1.0 passed in 2016) provides incentives to drug companies along the lines of the 2012 Generating Antibiotic Incentives Now Act, which extended by five years the exclusivity period during which certain antibiotics—those that treat serious or life-threatening infections—can be sold without generic competition.

The House Energy and Commerce Committee and the Senate Committee on Health, Education, Labor, and Pensions held half a dozen hearings in the first four months of 2018 and are considering at least 30 different bills on opioids between them. Stoking the drug industry pipeline would seem to make sense, but none of the potential legislative components of CARA 2.0 would appear to do that. The flock of diverse bills featured at the February, March, and April House and Senate hearings are a grab bag of proposals that seek to both bolster current programs and initiate new ones. They parallel many of the proposals in the White House agenda, which was announced in general terms, without many specifics. But in a broad outline, a CARA 2.0 would address physician prescribing of opioids, prescription drug monitoring programs (PDMPs), FDA standards for clinical trials and drug approval, National Institutes of Health (NIH) research, Health Insurance Portability and Accountability Act barriers to the sharing of a patient's abuse history, broad-based treatment centers, the viability of electronic health records with regard to an individual's prescription drug/abuse history, and Medicare and Medicaid's ability to use such things as utilization reviews and pharmacy "lock-in" to restrict addicts' access. This is a short list of what the proposals would do and does not include a host of actions that would give the U.S. Customs Service and FDA inspectors more authority to inspect packages coming into international mail facilities (IMF), where illegal fentanyl arrives in huge quantities. The FDA says it or Customs only inspect one-tenth of 1% of the 2.4 million packages that arrive from overseas at an IMF daily. FDA Commissioner Scott Gottlieb, MD, estimates that 9% of those 2.4 million packages contain drugs, legal and illegal.

It is hard to avoid the impression that both Democrats and Republicans are simply throwing proposals at a wall in an election year hoping something will stick. Many of the proposals advocate "education," "guidance documents," and "voluntary actions." There are no tough measures that, for example, would mandate electronic prescribing of controlled substances or mandate physician and pharmacist use of state PDMPs, with stiff penalties for noncompliance. At House hearings on April 11, 2018, U.S. Representative Frank Pallone (D-New Jersey), the top Democrat on the House committee, said, "A lot needs to be done to address this epidemic, but we should focus our time on what is most meaningful and impactful. While I support addressing this crisis through a bipartisan process, I am concerned that the sheer quantity of bills before the Committee today and the Chairman's extremely ambitious timeframe will not leave us much time to get these policies right. At times, to me, this process feels more like an opioids media blitz than a thoughtful discussion about our national public health crisis."[1]

Congress isn't the only player in Washington rushing to come up with new opioid addiction solutions. President Trump announced a menu of prospective actions on March 19.[2] At the FDA, which has a major role to play in enforcing proper use of prescription opioids, an opioid policy committee is considering making changes to its risk evaluation and mitigation strategies

Mr. Barlas is a freelance writer in Washington, D.C., who covers issues inside the Beltway. Send ideas for topics and your comments to sbarlas@verizon.net.

(REMS) program to incorporate, for the first time, all opioid analgesics that are intended for use in the outpatient setting, including the immediate-release formulations. The NIH is upping its funding of opioid research. In early April, NIH Director Francis S. Collins, MD, PhD, announced the launch of the Helping to End Addiction Long-Term (HEAL) initiative with nearly a doubling of funding to $1.1 billion in fiscal year 2018.[3]

Need for a Stronger Federal Response

Here is the question, though: Are these efforts going to be another pinky in the dike? The fact that Congress is rushing to pass a big CARA 2.0 would seem to indicate that CARA 1.0 didn't have as much of a positive impact as hoped. Statistics on the continuing damage done by opioids are incontrovertible. The Centers for Disease Control and Prevention (CDC) reports that, in 2016, more than 63,000 deaths resulted from drug overdoses. More than 42,000 of those deaths involved opioids. According to the most recent provisional data, there were 67,344 drug overdose deaths in the 12-month period ending August 2017. This is an increase of nearly 8,000 deaths attributed to drug overdose compared to the 12-month period ending August 2016. The CDC's data indicate that these increases were primarily driven by synthetic opioids, including illicitly manufactured fentanyl, which, unlike prescription opioids, has not been proven to be addictive.[4]

The Role of Pharmacy and Pharmaceuticals

The opioid problem is multifaceted, starting with physician overprescribing, lack of effective, new, nonadditive pain killers, a leaky distribution system, timid health plan policies that result from balancing real need for analgesics with the risk of excess access, and a certain amount of pharmacist blindness to a customer's panoply of pain killer prescriptions. That is just the "pharmaceutical" component of the problem, and some of its aspects, such as physician overprescribing, have lessened in the past few years. Beyond the pharmacy lies the growing problem of imports of illegal fentanyl.

There are a number of offensive plays for the pharmacy sector in terms of reducing the impact of the prescription opioid crisis. One of the current problems is the holes in PDMPs, which exist in every state but differ to some extent. These PDMPs are important because they allow physicians and pharmacists to plug into data repositories prior to issuing or dispensing an opioid prescription. That theoretically makes it harder for addicts or scammers to game the system. However, pharmacists often do not check the database when filling an opioid prescription, even when a state mandates it.

In states with voluntary use of PDMPs, usage is typically up to 25%. Forty states now mandate provider use of PDMPs, but even with a mandate, use of PDMPs is typically 75% to 80%, according to Brad Bauer, Senior Vice President at Appriss Health, which worked with the National Association of Boards of Pharmacy (NABP) to create PMP InterConnect in 2011. The best way to increase provider usage of PDMPs is through integration that creates "one-click" or in some cases "no-click" access, he explains.[1]

But Bauer says there is still a gap in usage of the PDMP by prescribers and pharmacists due to ease-of-use issues. "To resolve this, PDMP data should be incorporated directly into the electronic health record, pharmacy dispensing system, and health information exchange to allow one-click, near-instantaneous access to PDMP information," he told the House committee. "Tremendous progress has been made in this area in the last two years, but much work remains. Today approximately 20% of prescribers have access to PDMP data and information in their EHRs, and additional funding is needed to increase that number."[1]

There have been improvements over the past half-decade as states have begun to share patient drug-use data, making it more comprehensive, and therefore more useful. Today, 45 PDMPs share data across state lines. For the remaining states, state-level policy issues, not technology, are the only barriers preventing them from joining PMP InterConnect and sharing PDMP data with other states, according to Bauer. Florida and California do not share data although there is legislation in both state legislatures that would remedy that situation.

But physician and pharmacy data integration will be costly, and it is not clear where the money will come from. One of the discussion drafts featured at the March 21–22 hearings[5] would provide the CDC with authority to carry out certain controlled substance overdose prevention and surveillance activities in order to improve data collection and integration into physician clinical workflow so that timely, complete, and accurate information will get into the hands of providers and dispensers. Additional funding to the CDC for this purpose is included in the bill. But whether that funding is sufficient or whether it will be appropriated even if the provision stays in any final bill is unclear. No money would go to physicians and pharmacists for software integration. Nonetheless, Bauer says, "The PDMP discussion draft from Representative Griffith would be very beneficial for incentivizing these activities and enabling more states to take advantage of the latest developments in PDMPs."

Asked about its position on the PDMP bills and drafts, a spokeswoman for the NABP responded, "NABP does not have information pertaining to the bills or legislation."

However, pharmacy groups such as the National Association of Chain Drug Stores (NACDS) think there needs to be "a nationwide PDMP solution to harmonize state PDMPs." Such a solution could take many forms, pulling information from several data sources, including clinical data extracted from insurers, pharmacy benefit managers (PBMs), and state PDMPs; and aggregated data via a commercial market solution. This solution could be supported and housed within a federal agency, or it could be built and delivered entirely outside government through commercial market forces.

None of the bills authorize a national PDMP. One bill makes a feint toward helping pharmacists better police customer opioid prescriptions: the Empowering Pharmacists in the Fight Against Opioid Abuse Act, authored by U.S. Representatives Mark DeSaulnier (D-California) and Earl "Buddy" Carter (R-Georgia). That is a relatively toothless bill that would enable the FDA to distribute educational materials to pharmacists to help them determine when to reject a prescription for pain killers "because the pharmacist suspects the prescription is fraudulent, forged, or otherwise indicative of abuse or diversion." There is no federal funding attached to that program.[6]

Involvement of P&T Committees?

Pharmacists will be more directly impacted by changes in the Medicare Part D drug benefit meant to give health plans and their PBMs more ammunition with which to slow down unnecessary opioid use. Medicare established an opioid deterrent policy in 2013 and has been tightening it a little bit every year. The evolution in this area continues unabated for Part D Prescription Drug Plans in 2019, based on a rule the Centers for Medicare and Medicaid Services (CMS) issued last fall and the Call Letter it issued on April 2, 2018.[7,8] The final rule will set legal parameters. The Call Letter essentially provides guidance. They parallel one another in places related to utilization management.

The major initiative for Part D plans stems from Section 704 of CARA 1.0. It *permits*—but does not require—Part D sponsors to establish drug management programs (DMPs) for at-risk beneficiaries under which Part D sponsors may limit such beneficiaries' access to coverage for frequently abused drugs to certain prescribers and pharmacies. This is referred to as the "lock-in" provision. The final rule will also allow Part D plans to establish utilization controls for patients at high risk for opioid abuse.

For prescription drug plans that want to establish a DMP, their P&T committees will use clinical guidelines to select participants based on use of opioids with an average daily morphine milligram equivalent daily dose (MME) greater than or equal to 90 mg for any duration during the most recent six months, and either four or more opioid prescribers and four or more opioid-dispensing pharmacies OR six or more opioid prescribers, regardless of the number of opioid-dispensing pharmacies. Medicare recipients who qualify under these clinical guidelines would be subject to either a pharmacy lock-in or limited access to coverage of opioids through a point-of-sale claim edit.

The Call Letter, which provides guidance for Part D plans in 2019, had proposed some stiff measures when it came out as a draft in February. The two measures that prompted an uproar of disapproval from both plans and patients were a 90 MME-per-day hard edit and a seven-day supply allowance. Because of patient and industry complaints, the CMS dropped both proposals in the final Call Letter published on April 2. Instead, the CMS expects plans to implement a real-time opioid care coordination safety edit at the time of dispensing based on a cumulative MME threshold of 90 MME per day. Pharmacists would have to use an override code signaling they have discussed the patient's prescription with his or her physician if the edit is overridden. Notably, even if the pharmacist confirms intent, consultation with the prescriber does not supersede what is ultimately the pharmacist's decision to fill or not fill the prescription based on professional judgment.

Are Drug Manufacturers Doing Enough?

Maybe health plans and PBMs would have to spend less time and money on drug utilization programs related to opioids if there were better nonaddictive pain control options. But the search for even more effective pain medicines with low- or no-addiction profiles has not taken place at breakneck speed. Cartier Esham, Senior Vice President of Science and Regulatory Affairs at the Biotechnology Innovation Organization, states that less than 4% of total venture investment in the biopharmaceutical sector is being directed into companies whose lead product is a novel pain therapy. In addition, over the last decade, companies working on novel pain therapies have received 17 times less funding than companies working on oncology drugs, with even less investment for the development of novel therapies for addiction.

Flexion's Wentworth says there are a number of reasons why investments for pain medication discovery are hard to come by. At a high level, the contributing factors can be summarized into four buckets:

1. The underlying pain phenotypes are poorly understood, which translates into lack of good efficacy "biomarkers" to follow to prove that the intended target is resulting in a direct effect on a pain outcome.
2. There is typically a very high placebo response in pain trials due to the high variability in pain reporting in patients. For small companies innovating in this space, failure in a randomized trial is usually very difficult to recover from, yet the failure could very well be related to the study design and not a reflection of the product lacking efficacy.
3. The regulatory hurdles in developing analgesics in the chronic pain space are quite high, and we know that the FDA is looking at whether its current requirements are setting insurmountable barriers to innovation.
4. The pain market is highly genericized, and it seems as if there's little appetite for payers to cover higher-priced products.

FDA Throws Some Weight Around

The proposals being discussed might spur pain medication research by giving the FDA greater authority to approve pain medication under its accelerated approval and breakthrough therapy pathways. The FDA, according to Dr. Gottlieb, is already using its administrative authority to widen the intake lane for new pain medications seeking expedited approval. Any additional statutory (granted by Congress) authority to quickly approve additional NMEs for pain would certainly be useful. Strengthening the FDA's authority to consider the misuse and abuse of a controlled substance when determining if its overall benefits outweigh the risks also makes sense and is the subject of another bill under consideration.

The FDA already has the right to restrict how opioids are distributed under its REMS authority, and it already does so under its Extended-Release and Long-Acting Opioid Analgesic Risk Evaluation and Mitigation Strategy (ER/LA REMS), which is expected to be extended to all immediate-release opioids.[9] The FDA's Opioid Policy Steering Committee is in the midst of considering recommendations that could, in many respects, mirror the standards being inaugurated for Medicare Part D programs in 2019 related to overutilization.

Many of the shortcomings of what appear to be the many components of CARA 2.0 are of the same ilk as the shortcomings of CARA 1.0: too many "educational," "guidance," and "voluntary" measures and not enough muscular measures, such as forcing integration of physician and pharmacy software systems with electronic health records and PDMP data, at least for controlled substances, and limiting opioid access for high-risk Medicare and Medicaid enrollees. Medicare has already run into resistance from physicians and patients when

it suggested those kinds of strict limits; so Congress may have gotten the message that significant measures are fraught with political peril.

REFERENCES

1. Committee on Energy and Commerce Subcommittee on Health. Combating the opioid crisis: improving the ability of Medicare and Medicaid to provide care for patients. April 11, 2018. Available at: https://energycommerce.house.gov/hearings/combating-opioid-crisis-improving-ability-medicare-medicaid-provide-care-patients. Accessed April 17, 2018.
2. The White House. President Donald J. Trump's initiative to stop opioid abuse and reduce drug supply and demand. March 19, 2018. Available at: www.whitehouse.gov/briefings-statements/president-donald-j-trumps-initiative-stop-opioid-abuse-reduce-drug-supply-demand. Accessed April 17, 2018.
3. National Institutes of Health. NIH launches HEAL Initiative, doubles funding to accelerate scientific solutions to stem national opioid epidemic. April 4, 2018. Available at: www.nih.gov/news-events/news-releases/nih-launches-heal-initiative-doubles-funding-accelerate-scientific-solutions-stem-national-opioid-epidemic. Accessed April 17, 2018.
4. Centers for Disease Control and Prevention. Opioid overdose. October 23, 2017. Available at: www.cdc.gov/drugoverdose/index.html. Accessed April 17, 2018.
5. Committee on Energy and Commerce Subcommittee on Health. Combating the opioid crisis: prevention and public health solutions. March 21, 2018. Available at: https://energycommerce.house.gov/hearings/combating-opioid-crisis-prevention-public-health-solutions. Accessed April 17, 2018.
6. DeSaulnier M, Carter EL. H. R. 4275—Empowering Pharmacists in the Fight Against Opioid Abuse Act. 115th Congress (2017–2018). November 10, 2017. Available at: www.congress.gov/bill/115th-congress/house-bill/4275/text. Accessed April 17, 2018.
7. Centers for Medicare and Medicaid Services. Medicare program; contract year 2019 policy and technical changes to the Medicare Advantage, Medicare Cost Plan, Medicare Fee-for-Service, the Medicare Prescription Drug Benefit Programs, and the PACE Program. *Fed Regist* 2017;82(227):56336–56527. Available at: www.gpo.gov/fdsys/pkg/FR-2017-11-28/pdf/2017-25068.pdf. Accessed April 17, 2018.
8. Centers for Medicare and Medicaid Services. 2019 Medicare Advantage and Part D rate announcement and call letter. April 2, 2018. Available at: www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2018-Fact-sheets-items/2018-04-02-2.html. Accessed April 17, 2018.
9. Food and Drug Administration. Risk evaluation and mitigation strategy (REMS) for opioid analgesics. February 27, 2018. Available at: www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. Accessed April 17, 2018. ■