Commentary

Who "Lost" Opioids?

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Google "opioid abuse deterrence" and you'll find a lot of hits from lawyers and elected officials. What you won't find is a lot of expert thinking from the FDA.

That needs to change.

FDA Commissioner Hamburg's March 13, 2014 testimony in front of the Senate HELP Committee) hopefully represent a more aggressive stance by the agency. That's good. But there needs to be more. The FDA must be the leading voice on the issue of abuse deterrence and the safe use of opioids.

At present, politicians and pundits (not to mention trial lawyers) own the conversation. They're the ones talking about it. They're the ones the media goes to when they write about it. Have a look at a sampling of the press coverage surrounding Zohydro and see who's quoted and what they're saying.

The struggle over control of the opioid abuse deterrence story is, shall say, not going the right way for the FDA.

The Commissioner got it right when she testified (per Zohydro), "We recognize that this is a powerful drug, but we also believe that if appropriately used, it serves an important and unique niche with respect to pain medication and it meets the standards for safety and efficacy."

In short—not all opioids are the same and not all patients respond to all opioids in the same way. Further, it's important to remember that "safe" doesn't mean 100% safe. Never has. Never will. Not for any medicine. It's always about the benefit/risk balance.

This is not a new topic. Americans woke up the morning after the Vioxx recall and were amazed to discover that drugs have risks. Good lord. Who let that happen! Avandia, in that respect, was Son of Vioxx. And, like any sequel, new actors were brought in to spice up the story. Now it's about opioids.

Relative safety is an important conversation. It's an opportunity for the FDA to help educate the public about the *safe use of drugs*.

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The foundational proposition of the FDA's "Safe Use" initiative is that the way to make a drug "safer" is to better educate prescriber, dispenser, and user about the product. And nowhere is "safe use" a more important issue than opioids.

Dr. Hamburg's testimony continued, "It doesn't do any good to label something as abuse deterrent if it isn't actually abuse deterrent, and right now, unfortunately, the technology is poor."

As with safety, "abuse deterrent" doesn't mean that an opioid can't be abused. "AD" doesn't mean "100% abuse deterrent" just as "safe" doesn't mean 100% safe.

As the saying goes, everything you read in the paper is true except for those things you know about personally. Such is the case for the drug safety imbroglio currently surrounding opioids.

The FDA must take the lead. And that means more than finessing the label. It means working with the providers of Continuing Medical Education (CME) to develop better curricula. It means more targeted Risk Evaluation and Mitigation Strategies (REMS). It means enhanced and validated reporting tools for post-marketing surveillance. It means using that data for better social science in developing tools that can assist prescribers in determining which patients are likely to abuse. "Abuse deterrence" isn't just a formulation question—it's a systems question.

One of the most promising of the FDA's initiatives on abuse deterrence is a study (to be conducted by the National Institute for Pharmaceutical Technology and Education) to evaluate opioid product formulations and in vitro performance characteristics for solid and oral dosages.

The study will investigate the effect of physiochemical properties of the active ingredient, excipient, composition, and manufacturing technology of an opioid product on potential manipulation of the active ingredient for abuse. The study is projected to take at least two years to complete—and it is not likely the FDA would issue any guidance (draft or otherwise) in the interim. This doesn't mean the agency "isn't doing anything," but "inaction to an important issue" is how many will nonetheless view it.

Unfortunately complex systems make for bad media coverage, while simplistic, dramatic demagoguing makes for sexier headlines. And when Bloomberg reporter Drew Armstrong notes that "FDA pain drug czar Bob Rappaport has already said the agency would consider jerking Zohydro from the market if an abuse-resistant version become available," it reinforces the erroneous concept of "100% abuse deterrence."[1] Dr. Rappaport understands this. The general public does not.

As the saying goes, everything you read about in the news is true—except for those things you know personally. Case in point: coverage of the FDA's advisory committee on Zohydro.

At an FDA advisory committee, the agency is asked to defend its scientific thinking in public, before a panel of experts who can dissect results, challenge conclusions, and ensure no clinical stone goes unturned. Seldom reported, however, is that advisory committee votes are recommendations. They aren't binding on the FDA.

An analysis of advisory committee recommendations compared to agency actions shows FDA followed committee advice 74% of the time. Interestingly, the agency overruled "no" votes only three times: (*Tarceva* for maintenance therapy in lung cancer, *Avastin* for breast cancer, and *Micardis* to lower blood pressure.) Since their approval, these medicines have saved, extended, and improved hundreds of thousands of lives.

So, what about the Zohydro decision? The soundbite is that the vote was against approval of the drug. That's true. But what the general public doesn't know is that, by a vote of 11-2, the experts affirmed that there was no evidence to suggest Zohydro had greater abuse or addiction potential than any other opioid.

When the committee voted, the aforementioned Dr. Bob Rappaport (Director of the FDA's Division of Anesthesia, Analgesia, and Addiction), asked members to explain their votes. All but two said that while Zohydro had met their requirements for approval, their votes were meant to call greater attention to the agency's regulation of opioids in general—not Zohydro specifically.

The FDA decided to approve Zohydro based on the agency's judgment (and the advisory committee's concordance) that the medicine is safe and effective. But the FDA also heeded the expert panel's advice for better *post-approval* regulation of opioids. Shortly before Zohydro's approval, the agency strengthened opioid labeling and post marketing requirements to address the concerns raised by the advisory committee.

There's an apt Japanese proverb that bears repeating, "Don't fix the blame. Fix the problem." Unfortunately, the recent bashing of opioids (and the FDA's regulatory decision-making and oversight thereof) isn't helping. It's time for the grown-ups to step forward and take charge of the debate on drug safety.

Former Canadian Prime Minister Pierre Trudeau once said, "There's no place for the state in the bedrooms of the nation." But what's the appropriate place for the state in our nation's pharmacies and medicine chests—particularly for opioids?

Until now, the FDA had said the drugs were appropriate for the treatment of "moderate-to-severe" pain. The new class label drops the word "moderate" and says it should be used only to manage "pain severe enough to require daily, around-the clock, long-term treatment." Additionally, FDA is adding a boxed warning on the risk of neonatal opioid withdrawal syndrome.

Manufacturers must now conduct one or more post-marketing studies to quantitatively estimate the risks of misuse, abuse, addiction, overdose and death associated with long-term use, as well as a clinical trial to evaluate the risk of developing increased sensitivity to pain with long-term use of extended-release and long-acting opioids. Companies also must conduct a study of "doctor/pharmacy shopping"—a practice in which patients visit multiple doctors and pharmacies to obtain prescriptions—and whether it is "suggestive of misuse, abuse and/or addiction." The FDA also wants companies to work together on the development of post-marketing studies. But is the agency willing to lead? And, if so, are they willing to commit the time and resources required for a serious effort?

Once the FDA's labeling changes are finalized, the agency has said it will modify the class-wide REMS for extended-release and long-acting opioids. The REMS, which the agency approved in 2012, requires companies to make educational programs available to prescribers at no or nominal cost but does not require prescribers to participate and does not include a prescriber registry.

What about Prescription Drug Monitoring Programs (PDMP) and the intended and unintended consequences thereof.

How wide a net should PDMPs cast before they begin to have the unintended consequence of restricting legitimate patient access? To infinity and beyond may make for good soundbites, but makes no practical sense. Most patient-centered thought leaders and patient advocated believe PDMPs should include Schedules 2-4.

What about e-standards for inter-operability with electronic health records? Big Data is certainly part of the answer. Knowledge is Power.

This raises the prospect of doing something that Indiana started doing with its PDMP a couple of years ago—and that a lot of other states want to do. The Hoosier State made it possible for prescribers to communicate

1 http://www.bloomberg.com/news/2014-03-12/purdue-pill-may-force-zogenix-s-rival-drug-off-market.html?cmpid=yhoo

with other prescribers about patients—so, if prescriber B sees a patient and discovers that Prescriber A has prescribed before, B can contact A and make arrangements for which one of them is going to follow the patient. Notes also can be left behind for other providers, for instance, if an ER doc gets a doctor shopper, he can leave a note about it so others are forewarned.

What about pharmacists? What's their role? Should they have broader access to patient data? Beyond being deputized by the DEA, the pharmacy community must be able to play a more appropriate role as a healthcare professional.

Beyond the debate over whether the FDA should insist that all generics be abuse deterrent (and the related IP debate), how should PDMPs instruct physicians and pharmacists? And what about formularies? Can we trust physicians to make the right call? Do all patients need abuse deterrent formulation? And, if not, what are the decision criteria? What about dose and duration limitations?

What about the issues surrounding opioid *misuse*—at present the poor public health stepchild of *abuse*? And how can better physician education defer or deter the prevalent "opioids first" prescribing philosophy of many practitioners?

In the United States, the use of opioids as first-line treatment for chronic pain conditions doesn't follow either label indications or guideline recommendations. 52% of patients diagnosed with Osteoarthritis receive an opioid pain medicine as first line treatment as do 43% of patients diagnosed with Fibromyalgia and 42% of patients with Diabetic Peripheral Neuropathy.[2] Payers often implement barriers to the use of branded, on-label non-opioid pain medicines, relegating these treatments to second line options. The result is a gateway to abuse and addiction.

This places both education (of the CME variety) and best practices (developed not just by PDMPs but also by physicians, pharmacists, and patient organizations) front and center. What about REMS training? And what about more precise criteria for what "pain specialist" or "pain clinic" even mean? As the saying goes, "if you can't measure it, then it doesn't count."

What about take-back programs? Should they only be limited to opioids? And who should pay for them?

Lastly, amercement. On a state-by-state level, does the punishment fit the crime? Should there be national standards on criminal and civil penalties?

Many tough questions—but they deserve thoughtful and timely answers. It's time for a focused national dialogue that recognizes the need for effective oversight through the use of Big Data and broader constituent alliances.

Joshua Lederberg, the Nobel Prize Laureate once observed that the failure of regulatory, legal and political institutions to integrate scientific advances into risk selection and assessment was the most important barrier to improved public health.

Lederberg noted that in the absence of such changes, "the precedents affecting the long-term rationale of social policy will be set, not on the basis of well-debated principles, but on the accidents of the first advertised examples."

Policies and regulations that seek to limit risk are often shaped by the immediate fear of sensational events. This perspective is commonly called "The Precautionary Principle" which in various forms asserts that unless innovators can demonstrate that a new technology is risk free, it should be not allowed into the marketplace. Moreover, any product that could possibly be dangerous at any level should be strictly and severely regulated.

But precaution is not always safer than the alternatives.

Some current examples of precaution and the public health:

- The National Action Plan for Adverse Drug Event Prevention, announced in a September 4, 2013 Federal Register notice, outlines a comprehensive strategy to reduce AEDs for opioids. Much of the research actions called for by the plan seem designed to decrease prescribing. For instance, the plan calls for research by CDC, NIH and, public-private collaborations to look into adopting adjunctive and behavioral modalities to augment and reduce opioids use for chronic pain;
- Upscheduling and the relabeling of medicines to treat depression, diabetes, chronic and acute pain;
- And, finally, the role of tamper-resistant technologies in the appropriate management of pain medicines (both innovator and generic).

On April 3rd, 2014 the agency's approved EVZIO™ (naloxone hydrochloride injection) for the emergency treatment of known or suspected opioid overdose. Smartly, the FDA used the approval to speak, more broadly, to the topic. In the immortal words of Don Draper, "*If you don't like* what is being said, then *change* the *conversation*.

2 IMS data

During the stakeholder teleconference the Commissioner laid it all on the table. It turns out that the FDA is doing a lot to mitigate opioid risk after all! Most importantly, they are doing so while understanding the need to ensure appropriate access for the tens of millions of Americans suffering from chronic pain.

She got specific:

Combatting the serious public health problem of misuse, abuse, addiction and overdose from opioid analgesics is a high priority. Since 2001 the FDA has taken a number of actions designed to help address prescription opioid abuse and to encourage the development of new drug treatments for pain. These actions include:

Revising the labeling for opioid medications to foster their safe and appropriate use, including recent changes to the indications and safety warnings of extended-release and long-acting opioids.

Requiring that manufacturers conduct studies of the safety of long-term use of prescription opioids.

Improving appropriate prescribing by physicians and use by patients through educational materials required as a part of a risk mitigation strategy for extended-release and long-acting opioids.

Using the agency's expedited review programs to advance development of new non-opioid medications to treat pain with the goal of bringing new non- or less-abusable products to market.

Working with other federal agencies and scientists to advance our understanding of the mechanisms for pain and how to treat it, including the search for new non-opioid medications for pain.

Recommending that hydrocodone-containing combination products have additional restrictions on their use by rescheduling them from Schedule III to Schedule II.

Strengthening surveillance efforts to actively monitor the changing nature of prescription opioid abuse and to identify emerging issues.

And, importantly, encouraging the development of medications to treat opioid abuse, such as buprenorphine for use in medication-assisted treatment, and to reverse opioid overdoses, such as naloxone.

Not all of these actions are without negative unintended consequences (upscheduling impacts appropriate access), but it's a pretty powerful list.

The Commissioner returned again and again to the role the FDA must play in facilitating physician education, not only through labeling language but physician education. She specifically mentioned CME and working to develop (with a broad constituency) validated tools for physicians to use in determining which patients may be more prone to slide into abuse so they can choose their therapeutic recommendations more precisely.

"It all comes back to provider education," she said. Amen.

That's not regulatory mission creep; it's the appropriate application of the agency's Safe Use of Drugs initiative. The way you make a drug "safer" is to ensure that it is used by the right patient in the proper manner.

Importantly, the Commissioner regularly referred not to "abuse" but to "misuse and abuse." That's more than a rhetorical flourish since it recognizes that misuse is a gateway to abuse.

Provider education—the Hamburg Manifesto.

The take away message was loud and clear—misuse and abuse of opioids is a serious issue that must be addressed in an appropriate manner.

It's also important to consider the DEA's "Thug Regulation" strategy that results in a decline in appropriate patient access; an increase in regulatory time and cost and, ultimately, a decline in innovation.

The California Medical Association has received reports from physicians that Walgreens pharmacists are refusing to fill controlled substances prescriptions without additional information from the prescriber.

Per dictates from the DEA, Walgreen's pharmacists are now demanding that physicians provide information on diagnosis, ICD-9 codes, expected length of therapy and previous medications tried and failed.

In other words, tighter restrictions for patients who really need the medications, more paperwork for physicians and a heavier workload for pharmacists. Abusers and criminals rarely follow regulations.

When you have a hammer, every problem looks like a nail. The DEA sees opioid abuse and seeks to minimize access to them. That's a law enforcement solution. They mean well—but are behaving like a bull in a china shop

Arbitrarily limiting choice is not generally associated with the Scientific Method.

Should regulation be shaped by factors other than science or should advances in medicine and digital information be used to right-size regulation, reduce the excessive reductionism that leads to regulatory overreaction and promote resilience rather than ever increasing restrictions?

Consider the program recently instituted by CVS (and detailed in a recent *New England Journal of Medicine* perspective piece[3]) where, via the use of "Big Data" the chain pharmacy identified "outlier prescribers" and took appropriate and responsible actions.

The DEA's attempt to deputize pharmacists on the one hand and the CVS program on the other raise some interesting questions:

- What will the role of the 21st century pharmacist be in improving drug safety and medication adherence via more proactive (and remunerated) patient education?
- How can pharmacists become better integrated (beyond Med Guides) into the FDA's Safe Use of Medicines initiative?
- When will pharmacy synchronization programs really kick into gear, and how will states help to jump-start these important initiatives?

To paraphrase the American political scientist Aaron Wildavsky, we need a strategy of resilience based on experience. We must learn from adverse consequences in order to develop a capacity to advance the public health. Variability is the key to survival.

According to the CDC in 2008, there were 14,800 opioid overdose deaths. Half of those, the CDC has claimed, involved opioids and other illicit substances, whether it's cocaine or heroin, or alcohol. They also mentioned that alcohol was involved in many of those deaths but they don't actually tell us the numbers. So conservatively, half or 7,400 deaths occurred in 2008 from opioid overdose. The same year from CDC's own statistics, there were 36,500 suicides. There also were 24,000 alcohol-induced deaths and that doesn't count other related alcohol deaths like drunk driving. The bottom line is that the opioid numbers do not even come up in the CDC's list of the top 15 causes of death of Americans

It's important to add to this "epidemic" perspective, the fact that people suffering fromchronic pain are under-served by existing therapies. A recent IOM report that was issued in June of 2011 found that 100 million Americans are now living with chronic pain. That's a third of the U.S. population. Ten million of those have pain so severe that they are disabled by the pain. The report also said that pain costs the U.S. economy about 600 billion dollars a year in lost productivity and healthcare cost.

The vast majority of people who use opioids do so legally and safely. A subset, approximately four percent use these medications illegally. In fact, from 2010 to 2011, the number of Americans misusing and abusing opioid medications *declined* from 4.6% to 4.2%.

And the FDA's Zohydro decision was "controversial?" Really?

What ever happened to "politics has no role at the FDA?"

Joe Manchin (D, WVA) introduced a bill to overturn the FDA's approval of the opioid Zohydro ER. That certainly *sounds* like legislating science.

As a part of his rationale, Senator Manchin noted that the agency approved the drug last year over the objections of an advisory committee that had voted 11-2 to recommend rejection of the drug.

Yes, Senator, that's why it's called an *advisory* committee. Would he make such votesbinding on the agency? That's a pretty radical shift in regulatory policy. Alas, Senator Manchin isn't alone in his well-meaning but misguided attempts to legislate science. Senator Charles Schumer (D, NY) is urging Health and Human Services Secretary Kathleen Sebelius "to overturn the government's approval of a new powerful prescription opioid, Zohydro ER" (hydrocodone), "until it has been made abuse-proof."

According to reports, Schumer "believed there was a 'decent chance' that" Sebelius would revoke the FDA approval.

In addition to Senator Manchin's call for legislation and Senator Schumer's call for Secretarial interference, this careful balance is also being called into question by 28 state attorneys general who, in a letter to FDA Commissioner Margaret Hamburg, ask the agency to "reconsider its controversial approval of the powerful new narcotic painkiller known as Zohydro." The attorneys general are concerned that the medicinelacks "an abuse-limiting formula." And Massachusetts Governor Deval Patrick wants to ban Zohydro from the medicine chests of the Bay State.

Was the approval "controversial?" Well, it depends what you mean by "controversial." It's controversial because the issue of opioid abuse is controversial. And that's an important difference. Nobody said the FDA's job was easy.

Whatever your position on the issue of opioids, the proper venue for this decision is not the office of the Secretary of HHS or the halls of Congress or the courts—but rather the office of the FDA Commissioner.

Rather than dealing with the problem of abuse with sledgehammer solutions, Senators' Manchin and

3 Mitch Betses, R.Ph., and Troyen Brennan, M.D., M.P.H, "Abusive Prescribing of Controlled Substances," *New England Journal of Medicine*, August 21, 2013 DOI: 10.1056/NEJMp1308222

Schumer, and the various state AGs should focus on potential solutions such as:

- The role of the 21st century pharmacist in improving drug safety and medication adherence via more proactive and remunerated patient education? How can pharmacists become better integrated beyond Med Guides into the FDA's Safe Use of Medicines initiative? When will pharmacy synchronization really kick into gear, and how will states help to jump-start these important initiatives?
- Government and legislative initiatives such as the Stop Act (H.R. 486), which focuses on tamper-deterrent formulations and the continued development of those. Also, Senate Bill 1277 (sponsored by Senator Barbara Boxer, D/CA) which would establish a commission to bring all of the stakeholders together to have discussions about how to approach this issue so that law enforcement, providers, patients, and pharma can debate the issues and reach common ground.
- The appropriate role of tamper-resistant technologies. They are part of the solution, but they're not the *whole* solution. We need to develop policy options that focus on the prescriber/patient relationship, and a professional assessment of what's the risk involving this patient. Is the patient is going to tamper with the medication and potentially expose themselves or others to some danger. We have to do a better job (via CME and other methods) of training physicians and other prescribers on how to do these kinds of assessments.

In "Personalized Medicine and Responsible Access to Pain Medication" (a white paper based on the Center for Medicine in the Public Interest's September 2013 Capital Hill conference), Dr. Douglas Throckmorton, CDER's Deputy Director, for Regulatory Programs and the FDA's point person on opioids, writes,

> *We understand that for the millions of Americans experiencing an acute medical need or living with chronic pain, opioids, when prescribed appropriately, can allow patients to manage their pain as well as significantly improve their quality of life. However, we have also become increasingly concerned about the abuse and misuse of opioids. We are challenged with determining how to best balance the need to ensure continued access to patients who need these medications while addressing concerns about abuse and misuse.*

The FDA must walk a difficult public health tightrope, balancing patient need, medication safety, and (in the case of opioids), the dangers of abuse. And, most importantly, we need to keep the needs of patients front and center.